Zaheer-Ud-Din Babar
Editor

Pharmaceutical Policy in Countries with Developing Healthcare Systems

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To my grandfather

Foreword

Pharmaceutical policy refers to the implementation of legislation, regulation, procedures, and principles to attain certain objectives. These objectives are usually spelled out in the national medicines policy and, at a minimum, should encompass sustainable and equitable access to affordable quality medicines for the population. The extent of this commitment –whether it includes only essential medicines or also more specialised medicines for example – will vary based on the country's resources and the country context (e.g. industrial policy considerations).

Achieving equitable access to affordable quality medicines through sound pharmaceutical policies is a challenge for countries at all levels of health system development. The challenge is even greater for countries working towards universal health coverage, where some parts of the population still rely heavily on out-of-pocket payments to access their medicines (e.g. Brazil, Ecuador, China, East African Community countries, Pakistan, Philippines, Russia, South Africa, and Vietnam). Affordability issues have become all the more important as the prevalence of non-communicable diseases and multi-morbidity is on the rise globally. Diseases such as diabetes and cardiovascular conditions require continuous access to quality medicines and a responsive health-care system to address the health needs of the patients. Other chronic diseases such as cancer and rare conditions are regularly making the headlines in high-income countries where increasingly active patient advocates lobby for access to new medicines. While a number of high-income countries provide universal access to basic health services and products, this is not always the case. In these countries and others, patients may still need to make potentially substantial co-payments to access health services and medicines. In some countries, national resources have been used to increase access to health services and medicines (e.g. Saudi Arabia, Trinidad and Tobago, and United Arab Emirates).

The 17 country chapters highlight the pluralistic nature of their health and pharmaceutical systems. Building on their respective strengths of public and private sectors and creating synergies within existing systems – which are determined by the history of each country – are likely to be key elements in achieving universal access to essential medicines.

In an environment where new health technologies are launched on a daily basis, deciding how to allocate resources to maximise health benefits for the population becomes crucial to ensure the sustainability of health-care systems. In this context, health technology assessment (HTA) has been proposed by the 67th World Health Assembly as a tool to inform policy decisions on the path to universal health coverage. Individual country's efforts in increasing the evidence base of decision-making processes and transparency through HTA is also addressed in the book, particularly in the chapters on Argentina, Bulgaria, Colombia, Poland, and Russia.

The publication of this book is very timely. The 2016 Lancet Commission on Essential Medicines Policies Report provided many country's examples, concrete recommendations, and an evaluation framework that can be used to improve access to essential medicines. The 2016 United Nations Secretary-General's High-Level Panel on Access to Medicines Report specifically addressed the misalignment between the right to health, intellectual property, and trade. This book provides a wealth of experience to inform policy decisions that countries will need to take to improve access to medicines.

The chapters in this book are written by country experts, who often have had first-hand experience in introducing and implementing policy change, under the experienced editorial guidance of Professor Zaheer-Ud-Din Babar.

This book is therefore a unique asset for policy-makers, health professionals, academics, researchers, and students wishing to learn from the experience of a wide range of countries, which have taken bold steps in trying to improve access to medicines by embarking on the arduous, but potentially rewarding, path of pharmaceutical policy reform.

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Preface

Medicines are the most common health interventions, and the way medicines are dispensed, procured, and used can greatly impact on humans and society. The challenges related to medicines could include medicines compliance, medicines optimization, issues related to high cost, highly specialized medicines, and the funding and access to medicines. Solving these macro- and micro-level issues could improve patient health outcomes and can enhance quality of life.

Pharmaceutical policy deals with many of the issues mentioned above, and the World Health Organization (WHO) recommends that all countries formulate and implement a national pharmaceutical policy. Medicines account for a large share of the health budgets in countries with developing health systems and hence are an integral part of health policy of a country.

In the last 30 years, the successful implementation of pharmaceutical policies has resulted in increasing availability, affordability, and in improving quality use of medicines. However, still challenges lay ahead with increasing aging population, emergence of resistance microbes, development of new expensive medicines, access and funding of high cost medicines, and ethical and legal challenges in providing equitable access to medicines. These challenges are also coupled with fast pace changes in healthcare, technology, and automation.

This book provides an up-to-date account and synthesis of pharmaceutical policy across a spectrum of low-income, middle-income, and high-income countries. Many of these issues are common among countries and perhaps pose variety of challenges. Understanding and documenting these challenges is the key and first vital step towards achieving the goal of "health for all".

Huddersfield, UK
March, 2017

Zaheer-Ud-Din Babar

Contents

Chapter 1
Introduction

Helle Håkonsen, Isabel Emmerick, and Zaheer-Ud-Din Babar

Abstract All across the globe, pharmaceutical policies have undergone significant changes in recent decades to improve availability, access and quality of drugs. This chapter provides examples of policies of low-income, middle-income, and high-income countries that are at different stages of development with regard to their health system. It includes policies implemented in the wake of the Universal Declaration of Human Rightsfollowed by a description of national efforts to increase pharmaceutical production and supply, and measures to harmonize national regulations with international standards. Finally, increased access to affordable drugs is explored with an emphasis on the wider availability of generic drugs. The low-income and lower middle-income countries included are Pakistan, the Philippines, Vietnam, and the East African Community; the upper middle-income examples included are Argentina, Brazil, Bulgaria, Colombia, China, Ecuador, Jordan, Russia and South Africa. Poland, Saudi Arabia, Trinidad and Tobago, and UAE are then presented as examples of high-income countries with developing healthcare systems. The chapter concludes that pharmaceutical policies have played a central role to make drugs more available and accessible and thereby improve social conditions

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and decrease poverty. Still, there are structural developments that present considerable challenges in providing equitable access to drugs.

Pharmaceutical policy deals with the development, provision, and use of drugs within a healthcare system. The need for pharmaceutical policies became urgent after the thalidomide scandal in the 1960s [1] and was reinforced by an overall increase in drug utilization and the establishment of health insurance systems [2]. The World Health Organization (WHO) recommends that all countries formulate and implement a comprehensive national pharmaceutical policy in order to address pharmaceutical sector issues under a common framework [3]. The policy should embrace all drugs which should be available in a market, including original brands and generic drugs, biologics (products derived from living sources, as opposed to chemical compositions), vaccines, and natural health products [3]. It should ensure that people get good quality drugs at the lowest possible price, and that doctors prescribe the minimum of required drugs in order to treat the patient's illness. In four decades, the concept of national pharmaceutical policy has become broadly recognized and implemented in more than 100 countries [4]. Key components of a national pharmaceutical policy are regulation of access (e.g., essential drugs), control of quality, safety and efficacy, economic accessibility (e.g., price regulation and reimbursement systems), publicly available information, and strategies for rational drug use.

All across the globe, pharmaceutical policies have undergone significant changes in recent decades, resulting in improved availability, access, and quality of drugs by better systems for surveillance and support to national industry. This book provides examples of regulatory policies in pharmaceutical markets in a selection of countries that show a great deal of variety in the construction of their healthcare systems. Yet, there are common features in agreement with international treaties on human rights and implementation of national drug policies within a framework of combined public and private healthcare systems.

1.1 Pharmaceutical Policy and the Right to Health

The foundation for the Right to the Highest Attainable Standard of Health (from now on the Right to Health) was laid by The Universal Declaration of Human Rights of 1948. The UN Committee on Economic, Social, and Cultural Rights (CESCR) states in their General Comment No. 14 that the Right to Health includes basic preventive and curative health services and appropriate treatment of prevalent diseases [5]. The Right to Health encompasses the elements of AAAQ (availability, accessibility, acceptability, quality). Availability focuses on the physical aspects of health services such as sufficient quantity, whereas accessibility includes nondiscriminatory, physical, economic, and information accessibility. Acceptability implies that health services must be respectful of medical ethics, culturally appropriate, and gender sensitive. Medical treatment must be explained in an understandable manner. Finally, quality requires that health services are scientifically and medically appropriate and of good quality. Most of the world's countries have ratified the International

Covenant on Economic, Social, and Cultural Rights (ICESCR). One of the few exceptions of countries which has not ratified ICESCR is Saudi Arabia [6].

By the 1970s, effective drugs were developed for nearly all the major diseases. However, large parts of the world's population had little or no benefit of this medical milestone [4]. In 1977, WHO introduced the first Essential Drug List (EDL) to improve the worldwide accessibility to drugs. According to WHO, the essential drugs are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. Today, nearly two-thirds of the world's population have regular access to the essential drugs through a combination of public and private health systems [4].

Besides functioning as a guide for rational drug use, the EDLs form the basis of the reimbursement system in countries with developing healthcare systems. For instance, in Russia, uptake on the EDL goes hand in hand with price regulation and inclusion in the reimbursement system. The listed drugs are provided free of charge for treatment received by individual patients in hospitals and municipal outlets. However, not all countries have managed to utilize its full potential, and this has impacted on the number of essential drugs that is available in the market. There are also marked differences between public and private sectors in many developing countries where the total availability of drugs in public sector in general is considerably lower than in the private [7].

In the 1990s, implementation of a national pharmaceutical policy was one of the first postapartheid health policy actions made by the first democratic government in South Africa. During the apartheid era, the selection of drugs for the public sector was highly fragmented, and rational drug utilization was therefore a key topic in the new policy. This policy became instrumental in guiding a number of important reforms in the pharmaceutical sector. The commitment to an essential drugs approach was described as successfully implemented, although monitoring and evaluation of the impact have been weak. Other areas such as pharmaceutical pricing were presented without a clear policy prescription. In South Africa, the big discrepancy between the access to drugs in public and private sectors is noticeable. The situation in the private sector still reflects the previous fragmentation of the public sector. Seven times more money per capita is spent in the private sector, which serves about one-fifth of the population, than in the public health sector, which serves the remaining 80%.

More recently, the need for an operational EDL has unfolded in Jordan. Due to the humanitarian crisis in the neighboring countries such as Iraq and Syria, Jordan has received hundreds of thousands of refugees. The spread of communicable diseases among the refugees presents a big health problem within the refugee camps and also serves as a severe threat to the whole population of Jordan. This situation requires serious efforts to ensure an uninterrupted availability of essential drugs and vaccines to prevent the spread of infection. Particularly, in the public sector, this has been a challenge for the Jordanian healthcare system.

In several countries, pharmaceutical policies have been a priority of the governments. For instance, in Brazil, a series of policies has been implemented, aiming to

promote and extend access to drugs in the last five decades. However, the pharmaceutical policy systems in many low and middle, and even in upper middle and high, income economies are described as underdeveloped. The implementation of national pharmaceutical policies is hindered by the fragmented and heterogeneous nature of the healthcare systems. Despite being a high-income country, health resources in Trinidad and Tobago are scarce, and decrentralization of the healthcare system is desperately needed for better utilization and implementation of existing policies. The Ministry of Health of the Republic of Trinidad and Tobago is the prime healthcare administration authority. After the Regional Health Authorities Act No. 5 in 1994, the responsibility of the healthcare services delivery was transferred to the Regional Health Authorities that operate independently in their respective regions. However, recent years' increase in the government drug coverage has proved inadequate to meet the rising demand of drugs in the public sector. Another reason for the shortcoming of policy implementation is a lack of reliable health data and IT infrastructure, especially in countries with great geographic and epidemiologic diversity. This hampers the monitoring of the national drug situation and evaluation of how drugs are being used across the countries. However, although some countries do not have a uniform pharmaceutical policy, regulation of access, quality control, pharmacovigilance, and rational drug use are incorporated in different public policies.

Several chapters in this book highlight the progress that has been made in terms of healthcare and drug supply. In the former Soviet bloc countries, significant changes in pharmaceutical policy have been effectuated over recent years. The current healthcare system of Russia is a fusion of features from the former Soviet Union, with changes made by the Russian Federation after the Union's fall in 1991. The system has a centralized structure to ensure maximum efficiency of managerial decisions supported by tight administrative control. The state-funded healthcare system which previously provided uniform access to the entire population has now moved in the direction of more diverse funding including additional voluntary insurance (including private insurance) and corporate finance allocations for employees. A share of the medical expenses is covered by the patients themselves. In Poland, the political transformation in the late 1980s was the start of an extensive development of the pharmaceutical market. The pharmaceutical distribution has undergone major privatization, which has culminated in the development of pharmacy chains and growth of nonpharmacy drug trading. Due to societal changes, there has been an increase in the quantity and diversity of available products. Also, Bulgaria has gradually changed its centralized system into a social health insurance model. At present, the country lacks a cohesive national pharmaceutical policy, and as a result, the development of policy is described as reactive and ad hoc. While the regulatory framework has been largely brought into line with EU standards, existing mechanisms for selection, pricing, and subsidizing of drugs are not promoting value for money, giving rise to a rapid growth in expenditures.

Outside Europe, Vietnam is another country which has experienced health sector reforms which have transformed the publicly funded healthcare system into a combination of public and private systems. Transition from a socialist economy to a

market-based economy has presented a number of challenges for Vietnam's healthcare system. Free access to drugs and other healthcare services has been gradually replaced by a system of direct payment by patients. Increased reliance on market mechanisms has led to substantial increase in out-of-pocket health expenditures and even poorer drug quality and less rational drug use. Moreover, the supply chain is complex and involves a number of intermediaries between manufacturers and consumers. Due to the liberalization of the pharmaceutical markets, Vietnam and Poland have, within their own continent, experienced a considerable increase in self-medication. In Vietnam, it is estimated that as much as two-thirds of the population rely on self-medication when they get sick, with private pharmacies becoming the first, and often only, contact with health services.

The extent of private drug insurance is also prevalent in the United Arab Emirates (UAE). While the government of UAE covers the healthcare expenses of their Emirati residents, expatriates, who represent 85% of UAE's inhabitants, are encouraged to get private insurance to bypass the otherwise out-of-pocket expenditures, if there is not an employer to pay for the health insurance. As the healthcare system of UAE is rapidly growing, development of new policies alongside the implementation of existing ones is highly needed to achieve a more universal healthcare system.

1.2 Pharmaceutical Production and Supply

The pharmaceutical markets in countries with developing healthcare systems are often heavily dependent on drug import. In UAE, as much as 80% of medicines are imported, which puts undue burden on the healthcare sector and ultimately on the government of UAE. Another example is Ecuador, where the pharmaceutical market relies mostly on importation. The national production comprises a basic level of manufacturing technology, which requires the import of pharmaceutical active ingredients, raw materials, and finished products. There is only one public pharmaceutical company in the country. Its scope includes research, production, import, and marketing of medicines (human and veterinary). To lessen the load, some governments are making efforts to expand the local production of pharmaceuticals. The national production can comprise a basic level of manufacturing technology, which requires the imports of pharmaceutical active ingredients and raw materials. This is, for instance, the situation in Pakistan where few of the active ingredients and raw materials which are produced locally meet international quality standards. Therefore, most of the country's pharmaceutical production units are dependent on China, Europe, North America, and India for active ingredients and raw materials. Though a majority of the active ingredients are imported, the national pharmaceutical manufacturing units are able to manufacture finished products following current good manufacturing practices.

However, there are countries where all steps of the pharmaceutical value chain are represented, from small local production of active ingredients to extensive facilities for producing finished pharmaceutical products. Moreover, the domestic

production is increasingly growing, earning more of the market shares. In Brazil, large-scale manufacturing is done, and the country is the sixth largest pharmaceutical market worldwide. In Vietnam, the opening of the country to foreign trade and the liberalization of rules governing pharmaceutical production and supply have led to a 300% increase in drug production and a tenfold import increase. Even some of the former Soviet bloc countries make good examples in terms of increased domestic drug production. In Bulgaria, the pharmaceutical industry is in fact one of the fastest growing sectors of the economy. Bulgaria is today one of the largest producers of pharmaceuticals in Eastern Europe, and exports have increased substantially over the past few years. The main domestic pharmaceutical manufacturers began as former state-owned enterprises that were restructured and privatized. Domestic production accounted for 30–40% of the pharmaceutical market in 2009. Also, in Poland, the growth of the pharmaceutical industry is occurring at a much higher rate than the overall economy. The Polish market contains more than 300 companies that deal with sale of drugs, dietary supplements, and medical devices. Further, Poland is considered an attractive place for establishing pharmaceutical manufacturing sites and outsourcing of expensive stages of research and development, such as clinical trials. Still, the country faces significant supply-side issues with pharmaceutical availability. It is estimated that local production is only able to meet one-third of the societal demand for drugs. In Russia, the share of domestically produced drugs amounted to 55% in terms of the quantities of packs sold in 2014, and more than two-thirds of drugs listed on the Russian EDL are produced within the country's borders. Although some of the domestic production is exported to other countries, this quantity is yet smaller than the amount of imported drugs.

Argentina is one of the world's largest emerging economies with a solid industrial base of pharmaceutical industrial facilities existing mainly of national capital. The country has about 230 laboratories which are engaged in the production of a wide range of products to meet the demand of the domestic and foreign markets. Some of them are certified by health authorities in developed countries. Argentina has taken measures to harmonize national regulations with international standards concerning issues such as the adoption of good manufacturing practices and the regulations of bioequivalence and bioavailability standards and clinical trials.

In the Arabic Peninsula, Jordan constitutes the center for pharmaceutical technology. The country exports approximately 75% of their production to foreign markets in about 70 different countries. The relative success of this industry is explained by the high quality of the manufactured drugs, which conform to international quality standards.

1.3 Access to Affordable Drugs

It is characteristic for low-income and middle-income countries to have high proportions of the direct costs of disease associated with drugs. Pharmaceuticals account for a larger share of the health budgets in poor countries compared to rich.

In lower middle-income countries, drug expenditures make up about 50% of the total healthcare costs compared to 20–30% in wealthier countries. Despite being an upper middle-income country, in Bulgaria, drugs constitute as much as three quarters of all out-of-pocket expenditures on health. Moreover, Bulgaria is experiencing a rapid growth in drug expenditures, but is seeing no obvious improvements in health outcomes. Many of the current policy settings appear designed to limit the National Health Insurance Fund's outlays, rather than ensure financial protection for patients.

For larger economies, challenges often result from the fragmented nature of healthcare systems. In Argentina, drug coverage varies among and within subsectors in relation to the supply and financing of drugs. In the public sector, the coverage of health services and drugs varies greatly depending on the development level and management capacity of the provinces. Although the country has a substantial production capacity, the lack of a pricing regulation impairs the access to drugs. Even in Brazil, a country that on paper provides universal access to drugs and other healthcare services, most people end up paying out-of-pocket for their drugs through the private sector. Overall, it has been estimated by the WHO that 50–90% of the population in low-income and middle-income countries have to pay for the drugs themselves [4]. In Vietnam, for instance, drugs are mainly paid out-of-pocket, accounting for 72% of total drug expenditure. Another example is Trinidad and Tobago, where drugs are freely accessible in the public health system. Approximately 275 private pharmacies are enrolled in the so-called Chronic Disease Assistance Programme, and provide specified drugs and medical devices at no cost. Yet, the net health expenditure covered by households constitutes about 42%. The lack of an active price reporting system and dearth of national and international affordability studies are some of the contributors to the high private spending.

In spite of the presented challenges, the global drug situation has become considerably improved in terms of availability of more affordable drugs. National pharmaceutical policies have encouraged publicly available price information and some sort of price regulation strategy (e.g., reference pricing). Most importantly, however, almost every country has implemented measures to promote increased use of generic drugs. Stimulation of generic competition is one of the most powerful tools for improving access to drugs and bringing down drug prices. Consequently, drug treatment has been made possible for many patients, especially in developing countries, because of low-cost generics. Implemented in the pharmaceutical legislation is either a right or obligation for physicians to prescribe by the International Nonproprietary Name (INN) or for pharmacy personnel to substitute brand-name drugs with generic equivalents. One exception is Bulgaria where there is a theoretical prohibition on generic substitution. Despite this, the generic share is estimated to be 75% of the Bulgarian pharmaceutical market by volume.

High market shares for generic drugs are described as important characteristics of the pharmaceutical markets in several countries. For instance, the Russian Federation prioritizes generic drugs in competitive bidding based on INN for inclusion in the public reimbursement system. In developing countries, generics are

generally more widely available than original brands. The exception is the private sector in Pakistan where original brands are more available than generics. In Pakistan, the treatment cost for chronic illnesses, such as diabetes, hypertension, peptic ulcer, arthritis, epilepsy, and depression, is still unaffordable despite the use of low-cost generics. This is attributed to the expansion of originator brand and ongoing discrepancy and instability of medicines' prices in the country. In low-income and middle-income countries, average prices of generics are 0.5–1.5 times higher than the international reference price and 2–3 times higher for original brands in the public sector [7]. In the private sector, this discrepancy is estimated to be much bigger. The explanation lies in the high wholesale and retail markups which are possible in countries with a lack of regulatory policies for pricing. In Jordan, which after all has a well-developed system for pricing, local manufacturers are allowed to price their products up to 80% from the originator price. It is suggested that the reason behind the high markups is the local generic industry and originator wholesalers' influence on the national pharmaceutical policy. It is certainly one of the world's social injustices that drug prices are high, and sometimes even higher, in developing countries compared to wealthier societies. One example is Vietnam where the pharmaceutical companies are allowed to set prices of their products based on market forces. Adjusted for purchasing power parity, the prices to patients in the public sector are 11 and 47 times the international reference price for the lowest priced generics and brand-name drugs, respectively. Drug prices in Poland make an exception, as they are much lower when compared to prices in other European markets.

Several countries have invested in their own generic drug production. However, it varies to what extent this is accompanied by the implementation of regulatory, incentive-based systems for further development, acceptance, and rational use of generic drugs. Barriers to increasing generic drug use, which are especially present in less developed healthcare systems, include mistrust of generic drugs in terms of quality, efficacy, and safety among patients as well as physicians and pharmacists [8, 9]. This is especially notable in countries with high shares of counterfeit drugs and low educational levels among the general population.

1.4 Conclusion

In many countries, pharmaceutical policies have played a central role to make drugs more available and accessible, and thereby improve social conditions and decrease poverty. However, increased privatization of healthcare systems has increased the out-of-pocket expenses for large population groups. There have been improvements made, in terms of better quality control and drug surveillance, although the fight against counterfeit drugs is far from won.

Still, countries with developing healthcare systems face considerable challenges in providing the population with equitable access to drugs. While parts of the

healthcare systems appear to function well overall, there are still subpopulations at risk of substandard access to healthcare. Many countries' regulatory systems are currently in a transition period, and there are government initiatives to strengthen the pharmaceutical regulatory capacity.

The book is structured with the aim of exploring the policies of low-income, middle-income, and high-income countries that are at different stages of development with regard to their health system. The low-income and lower middle-income countries included in this book are Pakistan, the Philippines, Vietnam, and the East African Community; the upper middle-income examples included are Argentina, Brazil, Bulgaria, Colombia, China, Ecuador, Jordan, Russia, and South Africa. Poland, Saudi Arabia, Trinidad and Tobago, and UAE are then presented as examples of high-income countries with developing healthcare systems. At the end, there are two special chapters: one is on repurposing of medicines, while the last chapter synthesizes the information regarding country case studies included in the book. Numerous country case studies, exhibiting a variety of different policies, are presented in the hopes that this book would facilitate countries learning from each other and enacting useful policy development, with regard to a broad range of medicine issues that impact human health. These issues range from access and affordability of medicines, funding, reimbursement, regulation, and financing, to the rational use of medicines.

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Part I
Low and Lower Middle Income Countries

Chapter 2
Pharmaceutical Policy in the East African Community: Burundi, Kenya, Uganda, Rwanda, Tanzania

Jane Mashingia and Aarti Patel

Abstract This chapter outlines the example of a regional effort to improve access to medicines through regulatory harmonization in the East African Community.

The East African Community (EAC) consists of five Partner States: Burundi, Kenya, Uganda, Rwanda, and Tanzania. The Republic of Southern Sudan was recently admitted to the EAC as the sixth Partner State on March 2, 2016. The East African Community Medicines and Health Technologies Policy is under development to complement provisions of EAC Treaty, Article 118, Chapter 21 on regional cooperation on health and EAC Common Market Protocol in which integration in the health sector is the main policy priority. An assessment of medicines' policies and pharmaceutical legislation was undertaken in all five EAC Partner States in May–June 2015. Key findings indicated that all Partner States have medicine policies, and three Partner States with updated medicine policies. Constitutional changes are driving the policy reform with human rights principles underpinning policies. Implementation planning, together with monitoring and evaluation, are areas requiring support across the EAC. The recommendation for the regional pharmaceutical policy is to guide action in three areas, namely, access, quality, and rational use. The scope of the regional policy needs to include pharmaceuticals for human and veterinary use plus medical devices, health technologies, food, and cosmetics. All Partner States have pharmaceutical legislation in place; however, this is outdated and is in need of reform to align to the regional harmonization initiatives and allow countries to implement their policies in a timely and efficient manner. The slow pace of legislative reform is a barrier to improve access to essential medicines and health commodities across the region. In terms of the medicines' regulatory harmonization

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agenda, legal frameworks for mutual recognition and information sharing are key. Considering the different stages of development across the EAC Partner States and the enablers, together with regional goals and aspirations, a phased approach to implementation of the regional policy and legislation is recommended. First, adopt a stepwise approach to regional collaboration in the pharmaceutical sector starting with implementation of national policies. Second is to establish the East African Community Medicines and Food Safety Commission. Alongside these developments, information sharing activities should increase and continue.

2.1 Background

The East African Community (EAC) is an intergovernmental organization made up of the Republics of Burundi, Kenya, Rwanda, the United Republic of Tanzania, and the Republic of Uganda [1]. The Community was established by the EAC Treaty and has its headquarters in Arusha, Tanzania. At the time of writing this chapter, the terms of admitting another country, Republic of Southern Sudan, is being negotiated. EAC has a combined population estimated at more than 143.5 million people, spanning a land area of 1.82 million sq km and a combined Gross Domestic Product of $110.3 billion [1].

The aim of the EAC is to strengthen cooperation among the Partner States for their mutual benefit, especially in the political, economic, and social fields. The Community plans to become a Political Federation of East African States. It has established a Customs Union and is now working toward a common market.

The organs of the EAC are captured in Box 2.1. These organs oversee the implementation of the EAC Treaty allowing EAC citizens to benefit from a common market, while also sharing in the responsibilities needed to attain the overall goal.

Box 2.1 EAC Organs

- *Summit*: Heads of the Partner States
- *Council*: Ministers responsible for EAC affairs in the Partner States; Attorney Generals of Partner States and any other minister nominated by the Partner States.
- *Coordination Committee*: Permanent Secretaries for East African Community affairs in each Partner State and such other Permanent Secretaries of the Partner States as each Partner State may determine.
- *Sectoral Committees*: consists of nominated representatives from Partner States for thee specific sector, eg. Education, Health etc.
- *East African Court of Justice*: This Court, established under Article 9 of the Treaty for the Establishment of the East African Community, ensures adherence to law in the interpretation and application of and compliance with the EAC Treaty by the Partner States.
- *East African Legislative Assembly*: This Assessmbly, established under the Treaty, is intended as the independent Regional Parliament. It is made up

of nine members elected by each Partner State; ex-officio members consisting of the Minister or Assistant Minister responsible for the East African Community Affairs from each Partner State; the Secretary General and the Counsel to the Community.
- *Secretariat*: The executive organ of the EAC, and consisting of the Secretary General, Deputy Secretaries, General Counsel to the Community, and other offices as may be deemed necessary by the Council.

It is important to acknowledge that while the EAC wants to move toward a common market with the free movement of people, services, and trade, the Community also recognizes the sovereignty of the individual Partner States. This principle guides how the countries work together.

First, areas of cooperation for mutual benefit are identified. This is followed by assessing existing policies, practices, and regulations, with the aim of harmonizing the instruments that will facilitate cooperation and collaboration. In addition, platforms are established to allow for the sharing of information and adopting best practices for strengthening systems and efficiently using limited resources. The EAC Secretariat works closely with the representatives from Partner States and external partners to achieve the agreed objectives.

2.1.1 Focus of This Chapter

With the above background in mind regarding the EAC, this chapter discusses regional harmonization in the pharmaceutical sector focusing on medicines regulation within the overall context of improved access to health. This chapter first presents the Health System of the EAC followed by an overview of pharmaceutical systems, including medicines policies and pharmaceutical legislation, across the EAC Partner States. It goes on to discuss, briefly, the regional intent regarding a regional pharmaceutical policy and medicines regulatory harmonization. This chapter does not extend to other areas of medicines issues including the selection; procurement and use as regional approaches to these areas have not yet been addressed. This chapter ends with a few challenges and recommendations on regional integration and harmonization as an approach to improve access to essential medicines and health commodities.

2.1.2 Health System of the EAC (Health System and Health Indicators)

The EAC does not have one uniform health system. The five Partner States have different systems guided by national policies, legislation, regulations, and delivery structures. As governance systems are being strengthened across the region, Partner States are acknowledging the right to health in their constitutions. There is also a

move toward having a single national health framework with an overarching health policy and development plan addressing key health development goals for the individual countries [1].

EAC Partner States are also at different levels of development. Kenya has recently been classified as a lower middle-income country, while the remaining States are classified as low-income [3]. All Partner States also face many constraints in ensuring adequate access to sustainable, equitable, and affordable healthcare services. In this regard, other nonstate actors like the Churches have become involved with the provision of care. The private sector is growing rapidly across the region. There is a long established system of services provided by the not-for-profit sector driven mainly by Churches. Donors have also played a key role in providing and funding services through different mechanisms. It is beyond the limits of this chapter to describe in detail the individual Partner States and their health systems. The focus of this chapter will be on the regional Community.

Health is a key social sector where the EAC has agreed to collaborate and work together as part of the wider development of the Community. Article 118 of the EAC Treaty spells out the areas of cooperation among the Partner States in this regard. Box 2.2 summarizes these nine areas of cooperation in the health sector.

Box 2.2 EAC Areas of Cooperation in the Health Sector Among EAC Partner States [4]

(a) Disease prevention and control of noncommunicable, communicable, and vector-borne diseases prioritizing HIV-AIDS, cholera, malaria, hepatitis, yellow fever including mass immunization, and other public health campaigns.
(b) Health systems strengthening.
(c) Improved pharmaceutical quality control capacities and good procurement practices.
(d) Harmonize drug registration procedures for medicines.
(e) Information exchange regarding health policies and regulations.
(f) Research and Development of herbal and traditional medicines.
(g) Specialized heath training and health research in areas of reproductive health, pharmaceutical product development, and preventive medicine.
(h) Nutritional standards and popularization of indigenous foods.
(i) Controlling and eradicating the trafficking and use of illicit and banned drugs.

The Partner States of the EAC include four low-income countries and one middle-income country. These countries face many challenges in the development and sustainable delivery of health services. This is reflected in the health statistics of the countries as shown in Table 2.1.

Overall, EAC infant mortality rate and child mortality rate stood at 67% and 89%, respectively, in 2011 [6]. Even with more recent figures unavailable, these rates are higher than the overall infant mortality rate for Africa which stood at 55 in 2015 [7], pointing to weak health systems in the EAC region. However, it is important to note that presently there is no standardized approach to data collection from

Table 2.1 EAC Partner States Statistics [5]

Indicator	Burundi	Kenya	Rwanda	Tanzania (Mainland)	Uganda
Total population (2013)	10,633,00	44,354,000	11,777,000	49,253,000	37,579,000
Gross national income per capita (PPP international $, 2013)	820	2,250	1	1,750	1
Life expectancy at birth m/f (years, 2013)	54/58	60/63	64/67	61/65	57/61
Probability of dying between 15 and 60 years m/f (per 1,000 population, 2013)	312/244	299/250	246/196	312/244	380/307
Total expenditure on health per capita (Intl $, 2013)	62	101	162	126	146
Total expenditure on health as % of GDP (2013)	8.0	4.5	11.1	7.3	9.8

the Partner States regarding health statistics. For this reason, data held at the EAC Secretariat is generally out-of-date.

All EAC Partner States have Ministries of Health [8–12]. The individual Health Ministers constitute the regional Sectoral Council of Ministers. Within the framework of the EAC Treaty, the Sectoral Council on Health will decide on key matters of integration for the health sector.

Secretariat staff, with the support from development partners, facilitate the work of technical working groups consisting of experts from Partner States to develop harmonized frameworks, policies, and regulations supporting regional activities in the health sector. Once proposals, reports, and draft policies are validated by these technical working groups and Partner States, these are presented for decision-making by the Sectoral Council which then advise the relevant organs of the EAC prior to implementation. By understanding the operations of the Community, it becomes clear that processes are inclusive and also lengthy.

2.2 Pharmaceutical Situation of the EAC

The EAC, like other sub-Saharan countries, relies largely on imports for pharmaceuticals. These imports are mainly from China and India. Where pharmaceutical manufacturing does occur, this involves the production of noncomplex, high-volume, essential products such as basic analgesics, simple antibiotics, and vitamins. Kenya has the most developed pharmaceutical manufacturing sector in the region [13].

The regional pharmaceutical sector consists of manufacturers, distributors, wholesalers, retail pharmacies, hospitals, and clinics. Pharmaceutical manufacturers are either local or multinationals. Few multinationals have local manufacturing plants; rather there are local agents who distribute their products. Multinational pharmaceutical companies also have scientific and marketing offices. Multinational firms generally have brand name products in the market, while local manufacturers provide lower priced generics.

Below is a snapshot of the pharmaceutical sector of the EAC Partner States as extracted from the EAC Regional Manufacturing Plan of Action (2012–2016) [13].

Box 2.3 Pharmaceutical Sector Snapshot of EAC Partner States

Kenya

- Biggest and most developed pharmaceutical manufacturing sector in EAC region
- Branded and generic market share is 44% and 56%, respectively
- 28% – the percentage of market share of locally produced pharmaceuticals
- 35–45% of local production exported to neighboring countries
- 15% marginal preference scheme for local products by government tenders
- Local production meeting 30% of the national demand of pharmaceuticals
- Number of registered pharmaceutical manufacturers: 31
- Negative market perception of local manufacturers
- Local production predominantly generic
- Raw materials mostly imported
- Price erosion due to low cost imports

Tanzania

- Most developed semiautonomous regulatory authority within the EAC region
- Branded and generic market constituting 46% and 54%, respectively
- Number of registered manufacturing sites: 8
- Local production meets 31% of national demand
- India is the largest exporter of pharmaceuticals to Tanzania
- State and donor market constitute 85% of total pharmaceutical market
- 15% preferential treatment given to local manufacturers in government tenders
- There is competition from low-cost imports
- Raw materials mostly imported

Uganda

- 13 registered pharmaceutical manufacturers
- 95% of medicines imported to meet local demand
- Only 5% manufactured locally
- Negative market perception of local manufacturers
- Raw materials mostly (over 90%) imported from India and China
- Pharmaceutical plant production technology imported including spare parts
- Tableting lines most developed
- Price erosion due to low-cost imports

Burundi and Rwanda

- Each has one pharmaceutical manufacturing facility
- National Medicines Regulatory Authorities (NMRAs) are currently being established in both countries
- Estimated pharmaceutical market size for each country is US$ 25 million
- Over 95% of medicines consumed locally are imported
- Rwanda has leveraged use of ICT in the management of the medicines distribution and supply systems in the public sector
- Raw materials imported

Source*: EAC Manufacturing Plan of Action, 2012–2016.*

2.3 EAC Medicines Policy, Legislative and Regulatory Environment

All countries, apart from Rwanda, have distinct national medicines policies (NMPs). Rwanda's policy is embedded in the National Health Policy. Burundi, Kenya, and Tanzania (Zanzibar) have updated NMPs. Tanzania (Mainland) has a draft policy that was presented in 2014, but has not yet been approved. Uganda is currently revising its NMP, which is expected to be completed in 2015. Rwanda started work on its NMP in 2009, but this is yet to be approved [14].

The time taken for the review and approval of NMPs is long. Timelines span 24 years, that is, 1991–2015 (Tanzania – Mainland); 13 years, that is, 2002–2015 (Uganda); 6 years, that is, 2009–2015 (Rwanda). Kenya has managed to produce three revisions over the period 1994–2012; Tanzania (Zanzibar) has produced two NMPs from 1991 to 2014; Uganda is on its third revision; and Rwanda is still developing its first policy. These timelines highlight the varying capacities and challenges faced by the Partner States in the development, review, and revision of NMPs.

The scope of existing NMPs of Partner States generally covers pharmaceuticals for human and veterinary use,[1] as well as herbal products. The updated policies of Kenya and Tanzania (Zanzibar's) have extended scopes to also include medical devices and technologies, food products, tobacco products, cosmetics, and emerging health technologies.

Generally, the components of the NMPs in Partner States are based on the WHO-recommended components of NMPs:

- Selection: evidence-based, focusing on morbidity patterns, EMLs
- Supply: local production, procurement mechanisms, distribution and storage, disposal of unwanted or expired medicines
- Rational use: STGs, Medicines Information, rational medicine use for training, education, promotion
- Affordability: taxes or tariffs on essential medicines, pricing, use of generics, TRIPs mechanisms
- Financing: user charges, health insurance, donor assistance
- Human resource development: education, training, continuing education
- Monitoring and evaluation: baseline surveys, indicators for monitoring, periodic monitoring, independent external evaluation
- Research
- Technical cooperation among countries
- Legislative and regulatory framework: Drug Regulatory Authorities, good governance for medicines, legislation and regulation, medicines registration and licensing, quality assurance (inspection and enforcement), regulation of prescription and distribution

All Partner States have legislation in place to support the implementation of their policies. However, such legislation and regulations are often outdated and not enabling; in some instances, the legislation is the bottleneck for implementation. For example, in Uganda, the legislation places the National Drugs Authority as the overall body responsible for both the policy and the regulator. The situation is unique in Uganda, when in most countries the NMPs remain within the policy arm of Ministries of Health, and not with the regulatory authorities [15].

Kenya's Pharmacy and Poisons Act of 1957 (Chapter 244) regulates both the products and the practice, while the policy calls for the separation of these functions. Kenya's Pharmacy Practice Bill, 2012, proposed amendment to the Pharmacy and Poisons Act (Chapter 244). It also allows for the separation of the Pharmacy and Poisons Board from the Ministry of Health. However, current legislation also contributes to confusion regarding the autonomy of the regulatory body as it places the Chief Pharmacist of the Ministry of Health as the Registrar and the Director of Medical Services as the Chair of the Board. Therefore, in Kenya, the provisions in the 2012 policy to elevate the status of pharmaceutical services from under the medical directorate cannot be achieved within the existing legislation.

[1] Normally vaccines, blood products, and other biologicals are considered to be within the framework of medicinal products for human use. This also true for herbal products for human use.

In Burundi and Rwanda, existing pharmaceutical laws have to be changed to ensure semiautonomous status of the regulatory authorities, as these currently are based within Ministries of Health. Rwanda has already enacted a law in 2013 for establishing autonomous institution to regulate medical products; hence, it has not been stated here.

There is a move across the region toward the creation of semiautonomous government agencies to spearhead the national medicines regulatory affairs.

It is only in Tanzania (Mainland), through the Tanzania Food and Drugs Authority, and Uganda, through the Uganda Drugs Authority, that semiautonomous authorities exist. In the remaining Partner States, the regulatory authorities are all within the Ministries of Health. In Kenya, this is the Pharmacy and Poisons Board. In Rwanda, it is the Pharmacy Task Force. In Burundi, no actual structure exists even though registration of medicines occurs under a decree. While changes are being discussed in Partner States to establish semiautonomous structures, progress is slow. In Kenya, the Kenya Food and Drugs Authority Bill remains pending. The Rwanda Food and Medicines Authority (RFDA) Bill was approved in 2013; due to policy changes, this Bill was revoked and a new proposal is being considered where the RFDA will be an institution under the Rwanda Inspectorate and Competitions Authority (RICA) within the Ministry of Commerce.

There are three WHO prequalified drug quality control laboratories in EAC: Tanzania, Kenya, and Uganda. Across the EAC Partner States, there is a shortage of skilled human resource in NMRAs.

Table 2.2 presents an overview of pharmaceutical legislation and the agencies responsible for implementation for the EAC Partner States.

The EAC, unlike the Southern African Development region, does not have a regional mechanism for procurement of medicines. Nor does it have a regional list of essential medicines or regionally standardized treatment guidelines. These are areas for future development. Whereas, the initial focus is on regional harmonization concentrating on policy development and medicines regulation.

2.4 Conclusions: Summary and Way Forward

The pharmaceutical sector of EAC Partner States encompasses research, products, trade, personnel, and services – all linked in a complex and dynamic matrix of health, economics, and politics. There are many stakeholders involved, each with their own agenda, which do not always align with the overall public health goal of improving access to essential medicines and health commodities.

National Medicines Policies (NMPs) have been accepted by all Partner States as the policy instrument to guide the national pharmaceutical sector. In terms of regional harmonization, the existing NMPs of Partner States allow for technical and regional cooperation. This component of the national policies serves as an enabler for the regional regulatory harmonization initiatives.

There is strong support for the regional harmonization agenda by Partner States and partners. Two key gaps present the bottlenecks. First, the Regional Pharmaceutical

Table 2.2 Summary of pharmaceutical legislation and implementing agencies across EAC Partner States

Country	Burundi	Kenya	Tanzania (Mainland)	Tanzania (Zanzibar)	Rwanda	Uganda
Pharmaceutical legislation	Bill regulating the practice of pharmacy in Burundi	Pharmacy and Poisons Act of 1957 (Chapter 244)	Medicines and Food and Cosmetic Act, Pharmacy Council Act, Traditional Medicine Act, Patent Act, Procurement Act, Industrial and Consumer Chemical Act	Zanzibar Food, Drugs, and Cosmetics Act, 2006	2013 law on Inspection of Pharmaceutical Products RICA Bill Pharmacy Law 2013	Drug Policy and Authority Act, 2000
Implementing agencies	Under a Ministerial Decree	Pharmacy and Poisons Board	Tanzania Food and Drugs Authority	Zanzibar Food and Drugs Board (under MoH)	Pharmacy Task Force (in MoH)	National Drug Authority

Policy is long overdue. The Policy is needed to guide the harmonization process as well as providing the platform for collaboration and cooperation in the pharmaceutical sector. Second, the national and regional regulatory and enforcement mechanisms are missing, which has in fact resulted in countries participating in the regional initiatives but not always using the regional decisions into local national policies and in regulatory instruments and frameworks.

At the regional level, the pharmaceutical programme has been strengthened with the appointment of principal technical officers for Medicines and Food Safety as well as for the EAC-Medicines Registration Harmonization project.

At the Partner States level, while progress has been made, the pace is slow and it affects regional harmonization and cooperation. The slow pace is due to some of the following issues:

- Inappropriate institutional structures for policy direction and governance that fail to recognize and address the complexities of the manufacturing supply and also issues related to use of medicines. The Office of the Chief Pharmacist, generally tasked with the NMP, is not supported to fulfill this mandate.
- Outdated medicine laws which fail to provide the NMRAs with the legal instruments to address and adapt to new trends.
- Limited resources or political will to enforce pharmaceutical legislation.
- Policy development and implementation not evolving with other national and regional developments. This has resulted in underperformance and stagnation.
- Conceptualization of pharmaceutical services limited to procurement and supply, and up to some extent to prescribing and dispensing.
- Lack of sustainable strategies for implementation, weak management, and programming of pharmaceutical services.

The directives under Article 118 of the EAC Treaty, the Common Market Protocol, the EAC-MRH project, and the Manufacturing Plan of Action provide opportunities for fast-tracking the harmonization agenda. These directives are also helpful to build technical and management capacity, in building trust through joint activities. These initiatives will definitely benefit the people of the EAC.

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Chapter 3
Pharmaceutical Policy in Pakistan

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Abstract Pakistan is a lower middle-income country, and healthcare in the country is regulated by the Ministry of National Health Services Regulation and Coordination. The overall poor performance in health care is reflected in the form of enormous burden of communicable and non-communicable diseases, and high maternal, neonatal and infant mortality rates. These issues are coupled with a reduced health sector investment and a lack of health insurance schemes. There is no pharmacovigilance system, and there are also problems with counterfeit medications. Nevertheless, Pakistan has a dynamic pharmaceutical sector ranking10th largest in the Asia-Pacific region and fulfilling 70% of the country's medicinal demands. Many finished pharmaceutical products from Pakistan have been deemed acceptable by countries across Asia, Africa and the United States.

Pharmaceutical regulation is governed by the Drug Regulatory Authority of Pakistan (DRAP) which ensures the implementation of the Drugs Act, 1976 (XXXI of 1976). Pakistan's national essential medicine list (NEML) is based on the WHO standards and promotes generic prescribing; however, this list is generally only followed in the public sector hospitals. The majority of prescribers in the private sector health facilities are influenced by pharmaceutical marketing. There are concerns related to underuse and

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overuse of certain medicines reflecting an irrational medicines use in the country. There are also policy concerns related to drug pricing due to an absence of a sound medicine pricing formula. A full range of essential drugs is not available in public sector hospitals, either because of inadequate operational budget or due to lack of efficient management. Many consumers in Pakistan can buy medicines without prescription, leading to poor dispensing practices. However, despite numerous issues, the country has shown signs of improvement with regard to healthcare system. The Prime Minister's National Health Insurance Program initiative, the establishment of drug testing laboratories and the strict punishments for the breach of laws related to medicines' related offences are few examples that show that the government is serious to improve healthcare.

3.1 Pakistan

3.1.1 Country Profile

Pakistan is a lower middle-income country, situated in South Asia at the confluence of Central Asia and the Middle East, with a land area of 770880.0 sq. km [1]. With a population of 199 million, it is the sixth most populous country in the world [2]. The population is expected to grow to an estimated 254.7 million by 2030 and 344 million by 2050 [3]. Approximately, 38% of the population live in the urban areas [4], while the remaining 62% are rural residents [5]. Pakistan is a developing economy in South Asia, with a gross domestic product (GDP) growth rate of 4.24% in 2014–2015 [6]; however, the GDP growth rate has continually fluctuated. Data from the World Bank between 1961 and 2014 show an average GDP growth value of 5.18%,with a minimum value of 0.47% in 1971 and a maximum value of 11.35% in 1970 [7]. The unemployment rate of the country was reported to be 5.2% in 2014 [8].

3.2 Health System of Pakistan

3.2.1 Health System

Between 1947 (the year of country's independence) and 2011, Pakistan followed a health system developed by the British. Historically, the Federal Ministry of Health was responsible for the planning and funding of preventive and curative services. The provincial health sectors managed limited health facilities within their domain. After the devolution of the Federal Ministry of Health in 2011, the allocation of funds and health planning was transferred to the provinces, although some of the health funds are still under the control of the federal government [9].

Presently, the healthcare delivery system is comprised of primary, secondary and tertiary care. Lady health workers (LHWs), the basic health units (BHUs) and the

rural health centres (RHCs) provide primary care. Secondary care is provided by the tehsil headquarter hospitals (THQH) and the district headquarter hospitals (DHQH). Tertiary care is provided by the tertiary hospitals, mainly situated in highly populated and developed parts of the country [10]. There are 1142 hospitals, 5499 dispensaries, 5438 BHUs, and 671 maternity and child health centres in the country. Medicines are either provided by the hospitals or can be purchased from private pharmacies. There are 118,041 hospital beds, 167,759 doctors, 13,716 dentists and 86,183 nurses; and recently over 100,000 LHWs have been deployed in the country. According to estimates, the population to health service ratio is comprised of 1073 persons per doctor, 12,447 persons per dentist and 1593 persons per hospital bed [6].

The government has allocated PK Rs.114.2 billion(0.24%) of GDP for the health sector in the year 2014–2015 [6]; when compared with healthcare needs of the growing population, this amount is low. In response to this need, the Prime Minister's National Health Insurance Program, launched in 2015, aims to serve 3.1 million families in 23 districts, with an aim to improve healthcare delivery services [11].

The majority of medicines are funded out-of-pocket by the population, and this expenditure can be financially debilitating for the consumers [12]. There are many private insurance companies in Pakistan working under the "Insurance Ordinance 2000" [13], and these provide health insurance to the employees working in the corporate sector. However, only 5% of the population have health insurance [14]. These people tend to be the high-income earners of the country. The low-income and middle-income classes seldom have insurance, as they cannot pay the premiums.

3.2.2 Health Indicators

Pakistan is a developing country, and though efforts are being made to improve the overall health status of the country, this is not being achieved. There are issues related to the growing population, scarce resources and low investment in the health sector by the government. These factors have compromised growth when compared to international standards.

In general, life expectancy in Pakistan is 66.2 years of age [15], and the probability of dying before the age of 70 has been recorded in 2012 as 68% in males and 63% in females [16]. The *maternal mortality rate* was recorded in 1978 as 800 per 100,000 live births [17]. This rate reduced to 431 per 100,000 live births in 1990 and 178 by 2015 [18]. Likewise, the *infant mortality rate* has also dropped per 1000 live births, and this was recorded in 1960 as 192 [19], in 1970 as 142 [17] and 66 in 2015 [19]. *Neonatal mortality rate* declined from 64 to 46 per 1000 live births from 1990 to 2015, respectively [20]. In addition, under-5 mortality rate also dropped from 262 per 1000 live births in 1960 to 81 in 2015 [21].

In 1998, the burden of infectious and non-communicable diseases was 38.4% and 37.7%, respectively. Percentage of deaths from non-communicable diseases was 34.1%in 1992 and 54.9% in 2003. The percentage of deaths from communicable

diseases has also declined from 49.8% in 1992 to 26.2% in 2003 [17]; however, recent data on mortality due to communicable diseases in Pakistan are lacking. Diarrhoea and other infectious diseases have declined over time, which has been attributed to increased immunization rates (44% in mid-1990s to 77% in the proceeding decade) [17]. Ischaemic heart disease is the major cause of mortality in the country which resulted in 111.4 thousand deaths in 2012 alone [16]. Lower respiratory tract infections (104.5 thousand deaths), stroke (84.5 thousand deaths), preterm birth complications (77.4 thousand deaths), diarrhoeal diseases (63.7 thousand deaths) and chronic obstructive pulmonary disease (61.6 thousand deaths) continue to be the most common causes of mortality. While in 2013, in children under 5 years old, acute respiratory infections, birth asphyxia, diarrhoea and neonatal sepsis were the most common causes of mortality [16].

Pakistan remains among the top three countries where polio is still endemic. One hundred and seventy three cases of wild poliovirus type 1 (WPV) and 19 cases of circulating vaccine-derived polio virus (cVDPV) were reported in 2014, and 32 cases of WPV were reported in 2015 [22]. The Government of Pakistan has been trying to eradicate the disease by launching dedicated health schemes. The most recent step was taken in August 2015, where the inactivated polio vaccine (IPV) was introduced into routine immunization schedules. Thirty-six districts of the Punjab province have successfully started IPV as a part of routine child immunization schedule [23]. Furthermore, the government is planning to expand immunization of IPV throughout the country specifically at remote and far-flung areas of the country with low immunization rate which has made them high risk areas for polio [24].

Dengue fever has plagued Pakistan over the past two decades, with a total of 21,580 cases being reported. Although, the first confirmed case of dengue outbreak occurred in 1994, it was declared as an epidemic in November 2005 in Karachi. Since 2010, 317 deaths have been attributed to dengue in the country. The government health authorities have taken multiple preventive and curative steps to cope with the current situation and have partially succeeded in this regard [25].

3.3 Pharmaceutical Situation of the Country

3.3.1 Pharmaceutical Industry and Key Statistics

At the time of independence, Pakistan had no pharmaceutical manufacturing plants of its own. The only way to cope with the medicine needs of the country was through import, which was quite expensive. By 1980, the national pharmaceutical industry had grown to a reasonable extent. Between 1980 and 1999, the growth of pharmaceutical industry in Pakistan resulted in the strength to export finished medicinal products. In 2007, the industry was worth US$ 1.2 billion [26, 27]. In 2011, the

pharmaceutical industry in Pakistan was reported to be worth US$ 1.64 billion, with an annual growth rate of 11% [28]. In 2012, the pharmaceutical market in Pakistan was valued at about US$ 2 billion. In 2013, the annual growth rate increased to 17% surpassing the global pharmaceutical growth rate (8%) and becoming the 10th largest pharmaceutical industry in the Asia-Pacific region [29]. The current value of the pharmaceutical market is US$ 2.6 billion, recorded in the fourth quarter of year 2015 [30].

The pharmaceutical industry in Pakistan is comprised of 650 registered companies, of which 31 are multinational companies (MNCs) [27]. The drugs sold are all controlled price products regulated by the Government of Pakistan, and approximately 50,000 drugs and 1100–1200 molecules are registered in Pakistan [28, 31]. Many of the active pharmaceutical ingredients (API) are imported in the country.

The share of the pharmaceutical market is divided between national and multinational companies. In the early 1990s, the country's pharmaceutical market was dominated by MNCs; however, currently it is a different scenario. Today, the national companies have a ratio of 55:45 to MNCs and meet 70% of the country's medicinal need. According to a report by Mohammad Aamir and Khalid Zaman [28, 32], Getz and Sami Pharmaceuticals are among the top national companies, with a high growth rate and market share of 3.76% and 2.79%, respectively. Current sales trend of 2014–2015 shows that Getz and Sami Pharmaceuticals, along with Hilton Pharmaceuticals and Highnoon Laboratories are the top growing national pharmaceutical companies. GlaxoSmithKline (GSK) was the top company among the MNCs having a market share of 11.6% and growth rate of 8.9% in 2008–2009 [28]. Abbott Laboratories, Merck, Bayer, Novartis and Novo Nordisk are also among the top MNCs in the country. Some of the MNCs are showing a negative growth pattern in the country, including Sanofi Aventis, Eli Lilly and Pfizer.

Despite a high growth rate, the national companies are dependent upon the foreign markets for API. Most of the APIs are imported from Europe, North America, China and India [27, 28]. However, some national companies also produce APIs. Army Welfare Pharmaceuticals and Himont Pharmaceuticals are among the local producers of APIs. Nationally produced APIs include analgesics, non-steroidal anti-inflammatory drugs, penicillins, cephalosporins and quinolones. Likewise, the raw materials of ephedrine, ephedrine sulphate, furazolidone, methyl salicylate, magnesium stearate and sulphamethoxazole are also produced in the country.

The quality and effectiveness of locally manufactured APIs meet international standards, and therefore, the locally manufactured APIs have been granted quality certification by the European Union (German Good Management Practice), Canada, United Arab Emirates, Yemen, Uzbekistan, Turkmenistan, Tanzania, Senegal, Sudan and Sri Lanka. The machinery for local production of APIs is imported mainly from the United Kingdom (UK), the United States (US), Japan, Korea, China, Germany, Taiwan and India [27].

The pharmaceutical industry produces the most commonly used pharmaceutical dosage forms, including solid dosage forms (tablets, capsules, suppositories, vitamin sachets), liquid dosage forms (syrups, suspensions, ophthalmic and otic solutions, enemas), injectable solutions (infusions, insulin, vaccines), semisolids (creams, ointments, gels) and modified release dosage forms [27]. Despite a vast array of products manufactured in Pakistan, there are some medicinal products which are imported from other countries. The import totals to approximately 20% of the demand and include biotechnological products, antidotes, immunologicals, anticancer and antidiabetics. These drugs are mainly imported from the United Kingdom, the United States, Germany, Switzerland, Japan, the Netherlands, France, China, Hong Kong, Italy, Belgium and South Korea [29].

3.4 Country's Regulatory Environment

3.4.1 Medicines Regulatory Authority

The Ministry of National Health Services Regulation and Coordination (NHSRC) regulates the healthcare system of the country. It has six major divisions, namely, Tobacco Control Cell, Directorate of Malaria Control, National AIDS Control Program, National Institute of Population Studies, National Tuberculosis Control Program and Drug Regulatory Authority of Pakistan (DRAP). It also regulates the activities of the Pharmacy Council of Pakistan (established under Pharmacy Act, 1967), which supervises pharmacy education and pharmacists' registration in the country [31, 33, 34]. The DRAP was established under the DRAP Act, 2012. The major aim of the authority was to ensure the implementation of the Drugs Act, 1976 (XXXI of 1976) and to regulate the commerce and trade of pharmaceutical products among the provinces (Punjab, Sindh, Khyber Pakhtunkhwa, Gilgit Baltistan and Balochistan) of Pakistan [35].

The Drugs Act, 1976 (XXXI of 1976) is the legislation to govern the import, export, manufacture, storage, distribution and sale of drugs in the country. The federal government of Pakistan formulated this Act. Functions of the federal and provincial governments are distributed in such a way that drug manufacturing, registration, licensing, import and export are regulated by the federal government, whereas drug sale is regulated by the provincial governments. Under this Act, the federal government has defined laws for drug registration, licensing, advertising, labelling, packaging, import and export, and there are also laws to appeal against any decision with regard to licensing and registration board. The duties of federal drug inspectors and the role of federal drug laboratory are also defined under this Act [36].

For the manufacturing of any drug, four types of licences are issued under the Drugs Act, 1976, which are licences for formulation, basic manufacture, semibasic manufacture and repacking. A manufacturer who meets the criteria under the Drugs Act, 1976, to hold a specific licence, can have more than one type of licence after paying a specified fee to the licensing authority [36].

3.4.2 Quality Control

The quality of pharmaceutical products is ensured after analyzing the semifinished and finished products according to pharmacopoeia (United States Pharmacopoeia, British Pharmacopoeia) standards. Each local pharmaceutical company runs an independent quality control (QC) and quality assurance (QA) department which ensure that the product being manufactured meets the standards as described in the official compendia, but unfortunately the QC and QA departments of local pharmaceutical firms are not internationally recognized [31]. These companies are inspected by federal or provincial drug inspectors who scrutinize their compliance with cGMP. Moreover, Provincial Quality Control Board (PQCB) has also been established under the Drugs Act, 1976, which controls the quality of drugs marketed in the country. The drug inspectors employed under DRAP work as federal drug inspectors, and those employed at the provincial-level work as the provincial drug inspectors. Both federal and provincial drug inspectors ensure the quality of drugs manufactured and sold in their respective areas. To ensure the drug quality, samples of drugs are collected by drug inspectors and are sent to the Drug Testing Laboratories (DTLs) for postmarketing surveillance [37].

There are seven DTLs in the country, which are working under the provincial governments. Sindh, Baluchistan and KPK and have one drug testing laboratory in each province, whereas Punjab province has four DTLs. Three laboratories work under the federal government, two are situated in Islamabad, while one is in Karachi. DTLs identify spurious, substandard or misbranded drugs [38]. According to a report published in 2010, about 60,000 samples were sent to these laboratories for quality testing from 2008 to 2010, and 1194 samples failed to comply with the quality standards [37]. Similarly, in a DTL situated in Multan, 55,498 samples of drugs were received from 2009 to 2014, of which 54,565 were tested. A total of 1527 samples failed to meet the standard quality criteria. Out of those samples which failed, 138 were spurious, 183 were misbranded, 699 were substandard and 507 were Unani medicines with allopathic contents in them [39]. Based on over 400 manufacturing units [31], the number of DTLs must be increased, and the laboratories should be accredited by the international drug testing agencies to ensure the standard quality of locally manufactured drugs.

3.4.3 Pharmacovigilance

Detection, identification, assessment, understanding and prevention of adverse effects or any other drug-related problem come under the umbrella of pharmacovigilance (PV). A healthcare system is incomplete without the presence of PV system, as it is vital to ensure patient safety. It is unfortunate that PV has been neglected in Pakistan. In 2011, a locally manufactured drug acting on the cardiovascular system resulted in death of more than 200 patients in the Punjab Institute of Cardiology

(PIC) [40, 41]. In addition, around 450 patients were admitted to hospitals with life-threatening adverse drug reactions (ADRs). The incident jolted the government and healthcare authorities in Pakistan. The provincial assemblies passed resolutions urging the federal government to establish a drug-regulatory authority. Subsequently, in February 2012, the Supreme Court of Pakistan ordered the federal government to establish an independent drug-regulatory authority to monitor the quality of the marketed drugs. The DRAP was then formed, and since then it has been functioning well to maintain the quality of marketed drugs [27]; however, a fully functioning PV division has yet to be established. There is a need to establish an ADR database on national level and also to liaise with the WHO's Uppsala Monitoring Center for monitoring purposes.

3.4.4 Counterfeit Medicines

Counterfeit drugs affect both the local market and the export of locally manufactured drugs in Pakistan. About 50% of drugs sold in Pakistan are considered counterfeit or spurious, as reported by the European pharmaceutical manufacturers and the US trade office [31]. Pakistan's Interior Minister also made a statement in 2010 that a high proportion of drugs being sold in the country were counterfeit [42]. In addition to the PIC incident (discussed above, another medication contamination event led to the death of more than 50 people. This second incident involved a cough syrup, which contained a contaminated excipient. Due to these two incidents, Pakistani manufactured drugs were banned in Sri Lanka [31].

The situation regarding counterfeit drugs has not improved since then. In 2015, a team of DRAP and Federal Investigation Agency (FIA) sealed a factory at the Kahuta industrial area near the capital city [43] where they found that counterfeit drugs were being manufactured. DRAP seems to be ineffective, as this authority is working on a limited budget of only US$ 4.77 million, with only 275 staff members including drug inspectors [31, 44] to regulate a pharmaceutical sector of a country where the GMP malpractices are common [45]. Though, the government is working to improve the situation; however, employment of more drug inspectors, amendment of the Drug Act 1976 and stricter laws are needed to improve the situation [46].

3.5 Medicines Supply System

3.5.1 Procurement

In Pakistan, both centralized and decentralized procurement systems exist. The procurement body performs its duties under the Ministry of NHSRC. In the decentralized procurement system, the public sector hospitals contact the prequalified and registered pharmaceutical manufacturers to bid. Tender notices are published in the newspapers, and the most suitable pharmaceutical company is awarded the contract.

Similarly, medical stores and pharmacy depots (pharmacies) also select the prequalified and approved drug suppliers for their quotations [37]. In terms of centralized purchase, the respective provincial government plays an important role in the drug procurement, which is based on the needs of hospitals in a province. The public sector hospitals can also purchase 20–25% of the medicine needed for the emergency treatment by themselves from the approved distributors or the pharmacy stores. Private sector hospitals, on the other hand, follow their own standards for drug procurement.

The National Drug Policy (NDP) of Pakistan describes the rules regarding systematic procurement practices in the country. According to the NDP, the procurement must be based on generics, and a competitive environment must be created among the drug suppliers to ensure medicines' consistent quality. If there is any doubt regarding the quality of the drugs to be purchased, the licence of the manufacturer must be reviewed or cancelled [47].

3.5.2 Distribution

The distribution process in Pakistan is regulated under the Drugs Act, 1976. According to a WHO report, medicines are distributed in a systematic manner, and the process is well regulated [48]. There are multiple distribution chains present in the country, in the public and private sector hospitals. The medicinal products are distributed directly by the manufacturer, whereas pharmacies and medical stores receive medicines from the distribution companies. These distributors act as a supply source between manufacturers and retailers.

A medicinal distribution process needs reliable storage conditions until the products reach the end user. According to the Drugs Act, 1976, a distributor must maintain the standard storage conditions in terms of area and environment, that is, temperature, humidity and light, to maintain the quality of medicines. The DRAP and provincial health ministries have been playing an active role to maintain the standard storage conditions in the warehouses of distributors, as well as in retail stores. However, despite these efforts, there are still gaps in the country's drug supply management system. A study from Pakistan has revealed that some of the public sector drug facilities do not fulfil the required storage conditions. Approximately, 24% of the storage facilities had adequate temperature control, whereas 40% of the facilities do not even have a suitable refrigeration system [49].

3.6 Medicines Financing

3.6.1 Medicines Expenditures in General

In Pakistan, the government funds the public sector hospitals where the patients are provided with a partial free treatment including medicines and hospital stay. This means that the patients receive free emergency treatment and hospital stay;

however, they have to purchase the medicines not available in the hospital. Moreover, the patients admitted in the hospital acquiring special treatment services have to pay for the hospital stay in private rooms. Overall, on average, the government funds 32% of total health expenditure, whereas 64% is funded by the patients themselves. The government spends only 22% of the operational budget on non-salary items including medicines [50], which is <US$ 2 per capita per year as recommended by WHO [51]. The out-of-pocket payments are huge for the population, where the annual per capita spending is merely US$ 14, much less than US$ 34 recommended by WHO [50, 52]. According to an estimate, a patient has to spend about US$1.91(PKR200) per prescription at a public healthcare facility and more than US$2.39 (PKR250) per prescription at a private sector healthcare facility [53]. In the private sector hospitals, patients have to bear all types of expenses for their treatment [54]. Expensive medical treatment and absence of affordable health insurance schemes further aggravate the health-spending burden for the poor.

3.6.2 Medicines Pricing

In Pakistan, the prices of medicines are regulated by the DRAP. However, there is no transparent price calculation formula mentioned in the Drugs Act, 1976 [50]. The cost and pricing division of the DRAP is responsible for controlling and fixing the price of medicinal products marketed in the country under the Drugs Act, 1976 [55]. Production costs along with the retail mark-up are taken into account when fixing the market price of a medicinal product. In addition, shipping costs are also included in the price of imported medicines. The Government of Pakistan follows either SAARC (South Asian Association for Regional Cooperation) countries (the neighbouring countries) or international market price trends while setting the prices for medicines in the country. In a survey conducted by WHO and Health Action International (HAI) in Pakistan, in 2004, the overall prices of medicines were found to be quite reasonable when compared to international prices, with a few exceptions of some branded off-patent drugs, such as atenolol, ciprofloxacin and acyclovir [27]. However, according to a more recent WHO survey, this has changed. The prices of the originator brand and lowest price generic product were 3.36 and 2.26 times more than the international retail price, respectively [48]. A sudden price hike of 15% in November 2013 further impacted on patients [56]. Although the DRAP has been working quite actively to control the prices at affordable rates, there have been inconsistencies in the price regulation.

3.6.3 Affordability

In Pakistan, 45.5% of the population live below the poverty line [57], which makes healthcare for an average income person unaffordable. Rising inflation (Consumer Price Index (CPI) inflation: 1.3% on year-on-year basis in September 2015) [58] and

low affordability result in underuse of effective medicines. The Ministry of NHSRC has adopted several pro-poor measures to improve the affordability. These include launching of Zakat fund (religious welfare tax), tax exemptions on the import of medicines' raw material and equipment, exemption of general sales tax on medicines and full tax exemption for the medicines funded by the donor agencies [50].

Besides these measures, medicines' affordability is a problem because of expansion of originator brand, and ongoing variation and inconsistency of prices of medicines in the country. The availability of essential generic medicines is only 15% and 31% in the public and private sector healthcare facilities, respectively. Despite using low-priced generics, the cost of treatment for chronic illnesses such as diabetes, hypertension, peptic ulcer, arthritis, epilepsy and depression is unaffordable for middle-income and low-income people of Pakistan [50, 59, 60].

3.6.4 Generic Medicines

In Pakistan, generic medication use dates back to 1972 when the Generic Drug Act was introduced in the country. The main aim was to promote generic medicines and to make them affordable and accessible. The act forbade the use of brand names in the prescriptions and emphasized the use of generic names or international non-proprietary names. It also provided an opportunity to the local industry to become viable, where the other competitors were well-established MNCs. However, the scheme ended in 1975 when 38 local manufacturing companies were found guilty of producing substandard drugs [27]. This led the MNC to dominate the market. In addition, they launched heavily funded marketing schemes targeting prescribers. By 1976, the government revoked the legislation surrounding generic marketing and prescribing [61]. In the hospital setting, the public sector hospitals still have a high rate of prescribing by using generic names.

3.7 Medicines Use (Issues Impacting on Rationale Medicines Use in the Country)

3.7.1 Medicines Use in General (in Community Pharmacies, Dispensing Doctors and General Hospital Sector)

In Pakistan, medicines use patterns differ among gender and age groups. Self-medication and polypharmacy are common among the youth and elderly population, respectively [62–66]. Similarly, the self-use of analgesics and antipyretics is very common in youth [62–64]. According to a study in Pakistan, the average number of drugs per prescription was 2.82 (SD = 1.3), the drugs prescribed by generic name were 56.6%, antibiotics prescribed were 51.5% and the drugs prescribed from Essential Drugs List (EDL) were 98.8%. The average consultation time was 1.2 min

(SD = 0.8), the average dispensing time was 8.7 s (SD = 4.9), the percentage of drugs actually dispensed was 97.3%, the percentage of drugs adequately labelled was 100% and the patients' knowledge of correct dosage was only 61.6% [67]. Another study conducted in Pakistan has reported that approximately 90% of the injections prescribed to patients could be avoided [68].

Standardized dispensing practices are missing in community pharmacies and hospital environments [50, 69]. It is unfortunate that most of the drug dispensing at pharmacies and medical stores is performed by untrained dispensers having no formal pharmacy education. In this context, there is a dire need to ensure the presence of a qualified pharmacist at retail pharmacies to ensure safe dispensing of medicines [49, 69]. Absence of doctors in the rural areas has made the dispensers and quacks sole decision-makers of the medicines used by the people there [70]. Moreover, patients have to travel long distances to purchase essential medicines. Furthermore, the majority of the medicines can be bought from private pharmacies without showing a legal prescription [71–73].

Only few private hospitals such as Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC) and Aga Khan University Hospital (AKUH) follow the internationally approved standard dispensing procedures, and have ideal patient-centred pharmacy environments [74, 75]. Rising cases of counterfeit drugs, consistent lack of available stock in the public sector's health facilities, lack of compliance with the storage conditions and low level of surveillance due to understaffing of DRAP make the performance of the healthcare system questionable [50]. Moreover, low expenditure on health and the pharmaceutical sector is another constraint to the equitable access to medicines.

3.7.2 Essential Medicine List, Selection of Essential Medicines and Standard Treatment Guidelines

The effort to formulate an essential medicines list was initiated in the early 1990s in Pakistan. Prior to 1993, there was a non-uniform system of drug procurement and supply in the country. The provincial and federal governments have had their own medicines' lists, which were followed for the procurement of medicines in the public sector hospitals. The first NEML of Pakistan was prepared in 1994. A number of reputable organizations and experts in the pharmacy field participated to develop a list of most reliable and cost-effective medicines that could fulfil the medicinal needs of the community. An amendment to the national policy was made that required the NEML to be updated and revised each year, though not implemented [47].

It was mandatory for all the government and semigovernment health institutions in Pakistan to follow the NEML, when making bulk medicinal purchases. A plan was then developed to promote the concept of essential medicines and NEML in all public and private hospitals in the country. The use of generic drug names was also a basic component of NEML [76].

The NEML list has gone through various improvements since its formulation. It was revised and reviewed in 1995, 2000 and 2003. The current list is the fourth version, which was revised in 2007. It is comprised of 335 medicines [76], and the selection of medicines and the standard treatment guidelines is made in accordance to WHO guidelines [47]. A recent report estimates that approximately 80% of the public sector health facilities use this list [50]. The DRAP and WHO organized a meeting in December 2013 to revise the current NEML and make it in accordance with WHO's EDL. The inclusion and exclusion criteria were also redefined according to the prevalence of diseases in the country [45].

3.7.3 Prescribing Behaviour in General (Factors Affecting Prescribing Behaviour)

A prescriber is a sole decision-maker for the healthcare needs of a patient in Pakistan. The interests of patients as well as that of pharmaceutical companies revolve around the prescriber, who has become the focus of attention for both the stakeholders in the country. Ultimately, the prescriber has the authority to decide which specific drug, including the pharmacological class and brand of a drug, is to be used by the patient. An ideal prescriber should be unbiased and should focus on the drug itself, so that a cost-effective and good-quality medicine is chosen. However, in Pakistan, reality is different. With the increase in the number of pharmaceutical companies in Pakistan, competition to sway the prescriber to prescribe their medicines increased. Countless efforts are made by the pharmaceutical companies to make the medical practitioners prescribe their product and brand. Marketing strategies employed by drug companies include free drug samples, gifts, travel, both nationally and internationally, and promotional activities involving lavish dinners and sponsorships of conferences [77]. Moreover, the unavailability of the EDL and its medicines negatively influences the prescribers of public hospitals when prescribing [78].

Such factors contribute towards irrational and unnecessary prescribing practices. Patient's health beliefs also influence the prescriber's choice of medicines. In rural parts of the country, literacy rates are low, and a high number of the prescribers prescribe injectable medications and steroids to satisfy the patients who want an immediate cure. Likewise, unnecessary prescribing of antibiotics is a real cause of concern as it could contribute towards drug resistance. Prescribing antibiotics without antimicrobial testing is also a common practice, specifically in the private sector health facilities in Pakistan [79].

The medical practitioners in the public sector hospitals follow the EDL finalized by the Pharmacy and Therapeutic Committee (P&TC); however, pharmaceutical marketing also influence the prescribing behaviour of some of the physicians appointed there. In private sector hospitals, medicine brands are selected by the

hospital administration which is somewhat influenced by the pharmaceutical companies, and the prescription is almost always based on the promotional activities of the medical sales representatives [80].

3.7.4 Medicines' Promotional Practices

Promotional activities are largely centred in the big cities such as Karachi, Lahore, Islamabad, Multan, Peshawar and Quetta, etc. However, teams of trained and skillful medical sales representatives are spread throughout the country, promoting their medicines using multiple detailing aids such as brochures and product literature [65].

Despite the presence of legislation governing advertisement and promotion of pharmaceuticals (the Drugs Act, 1976), the pharmaceutical companies encourage prescribers to recommend their products. However, it is common knowledge that they use unethical marketing practices to promote medicines [80]. Most of the companies spend 20–30% of their revenue on marketing [80]. Vigilant inspection of promotional activities of pharmaceutical companies is needed by the DRAP to tackle this issue.

3.7.5 The Role of Pharmacist in Community and Hospital Environments

Traditional pharmacy education institutes and the number of professional pharmacists were very low, with the number of institutes offering pharmacy education (graduate degree programmes) <10 in 2000 [81], which has now increased to 34 (17 public sector and 17 private sector institutes) [82]. Pharmacy graduates are also increasing after the initiation of Pharm-D degree (a 5-year clinical oriented programme) in 2003. Since then, the pharmacist began to have a more prominent role in hospitals, industry, retail stores and pharmaceutical marketing. But, the profession and the professionals are still neglected in the healthcare system of Pakistan [83].

There are 8102 pharmacists and 31,000 pharmacy technicians in the country [69]. There are two types of licences: Category A and Category B. The qualified and registered pharmacists are 'Category A' licence-holders, and they can dispense all medicines, while pharmacy technicians having a 2-year diploma possess 'Category B' licence under which they can perform activities including compounding and dispensing under the supervision of a qualified pharmacist. These licences are provided by the Pharmacy Council under the Pharmacy Act, 1967 [84].

There are approximately 80,000 medical stores or private pharmacies in Pakistan [31]; however, these pharmacies are of varying quality. According to law, pharmacists have to be present in those pharmacies; however, that is not the case in all pharmacies. There is a shortage of pharmacists in the country (2587/year). Also, the

absence of reasonable drug storage, compounding and record-keeping as per the legislation stated in the Pharmacy Act 1967 also add to the problem [69].

Similar is the case of public sector hospitals where a small number of pharmacists are available [31]. About 10 pharmacists are appointed in each of the tertiary care hospitals, and one or two are appointed at secondary care hospitals. The pharmacists working in hospital environments account for <15% of the total pharmacists in the country [85]. There are no pharmacists appointed at the BHU level. Likewise, in most of the private sector hospitals, there are no pharmacists. According to an estimate, only 0.06 pharmacists are in reach of 10,000 people in Pakistan, compared to the international standards of availability of five pharmacists per 10,000 person population [31]. Those present in hospitals are restricted to the drug storage areas and have limited opportunities to perform patient-oriented services. In the area of drug regulation, only one pharmacist is present at *Tehsil* level, and two or three pharmacists are working at the district level as drug inspectors [85].

The pharmacist's role is not well established in Pakistan. They are being neglected in the healthcare system and are not remunerated appropriately [86, 87]. However, we hope that the recent attempts by the government to allocate pharmacists in public hospitals, forensic laboratories, DRAP, DTLs and customs department hopefully will improve the role of pharmacist in the country. Moreover, efforts of DRAP to ensure the presence of a pharmacist at all pharmacies and some chain pharmacies in urban areas (Fazal Din's Pharma Plus, Mahmood Pharmacy, Clinix Plus [88], Green Plus Pharmacie [89] and Servaid Pharmacy [90]) will also strengthen the role of pharmacist in Pakistan.

Pharmaceutical care involves patient-centred services of a pharmacist. It includes all actions performed by a pharmacist for the benefit of the patient to achieve the maximum therapeutic outcome and to improve overall the quality of life of a patient [91]. However, pharmaceutical care interventions are lacking in the country, except for a few private sector hospitals such as SKMCH&RC and AKUH which have well-established pharmacy systems and pharmacists performing patient-oriented services [74, 75].

3.7.6 Medicines Use Research (Including Drug Utilization Evaluation Research)

Drug utilization research is defined by WHO as a process that involves marketing, distribution, prescription, dispensing and safe administration of drugs by keeping medical and socioeconomic factors under consideration [91]. Pakistan lags behind the highly developed countries in the field of medicines use research. There is no specific organization solely working to investigate drug utilization in the country.

It is important to keep track of every step of drug, from manufacturing, import to dispensing and then perhaps medicine use by the patients. Medicine information system, electronic prescribing, documentation of patient registries and involvement of pharmacists in decision-making are also vital to improve healthcare.

3.8 Summary and Future Direction

Pakistan is a lower middle-income country, and estimates believe that it will be the fourth populous country in the world by 2050. The pharmaceutical industry is highly dynamic, and the local industry is able to cope with most of the pharmaceutical demands of the country.

There is shortage of pharmacists in the country, and pharmacies are of varying quality. Newly established pharmacies follow the modern international community pharmacies; however, they are restricted to the main cities. This leaves the population of small towns and villages with limited access to quality pharmacies and pharmacists.

As a summary, more funding is needed for healthcare. Health policies should be reviewed, and health sector must be given a priority while planning the annual budget. The upgrading and implementation of the NDP are also needed to safeguard patients by setting rules to ensure equitable and safe drug supply all over the country. The government is currently employing more inspectors to regulate the pharmaceutical sector, which is a positive move.

The Government of Pakistan should take firm initiatives for the establishment of the WHO-accredited drug investigation and testing laboratories, pharmacovigilance centres and bioequivalence laboratories. The national ADR-reporting database must be developed to monitor the occurrence of ADRs. Medicine supply and management system of the country must also comply with the international standards. Procurement and distribution of substandard drugs should be controlled. The supply system should be efficient and consistent to prevent lack of stock in the public sector health facilities. In addition, the government should monitor the prices of medicines and ensure that they are at a lowest possible cost while maintaining the quality of medicines. Generic prescribing should be mandatory for all the prescribers. Taxes and tariffs on medicines should also be minimized to cope with the unaffordability issues.

To ensure rational prescribing, prescribers should adopt evidence-based treatment guidelines. In addition, the NEML should be reviewed annually, and it should also be made available in every health facility, whether public or private. Furthermore, the DRAP should monitor marketing and promotional practices of pharmaceutical companies.

Despite being a lower middle-income developing country, Pakistan has a potential to upgrade and modernize its healthcare system. The country needs a strong political will to implement the concept of “health for all”.

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Chapter 4
Pharmaceutical Policy in the Philippines

Douglas Ball and Roderick Salenga

Abstract The Philippines has a large and well-developed pharmaceutical sector with a focus on production of generic medicines. Pharmaceutical regulation through the Philippines Food and Drug Administration is affected by resource constraints and substandard and counterfeit medicines remain a problem. Challenges to the supply of medicines include a decentralised public health system and chronic underfunding with the private sector playing an important role in access to medicines. The Department of Health maintains medicines access programs, and local government units provide services within their jurisdictions. National health insurance under PhilHealth covers about 82% of the population and is expanding out-patient pharmaceutical benefits. There is limited price regulation. The National Medicines Policy supports generic medicines and there has been a growth in generics-only pharmacies. However, appropriate use of medicines is a concern. Pharmaceutical care is underdeveloped and the professional role of the pharmacist is not well recognised. Despite these challenges, recent investments by the government in health and medicines seek to make quality medicines available and affordable to support Universal Health Coverage.

Abbreviations

ADR	Adverse drug reaction
AO	Administrative Order
ASEAN	Association of South East Asian Nations
BnB	*Botika ng Barangay* (village pharmacy)

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CHD	Center for Health Development
COBAC	Central Office for Bids and Awards Committee
DOH	Department of Health
DPRI	Drug Price Reference Index
EDPMS	Electronic Drug Price Monitoring System
EO	Executive Order
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GMAP	Government-Mediated Access Price
GOP	Government of the Philippines
HEMS	Health Emergency Management Staff
LGU	Local government unit
MAP	Medicines Access Programme
MDRP	Maximum Drug Retail Price
MeTA	Medicines Transparency Alliance
NCPAM	National Center for Pharmaceutical Management and Access
PDEA	Philippine Drug Enforcement Agency
PHAP	Pharmaceutical and Healthcare Association of the Philippines
PhilHealth	Philippines Health Insurance Company Inc.
PhilPSP	Philippine Practice Standards for Pharmacists
PIC/s	Pharmaceutical Inspection Co-operation Scheme
PNDF/PNF	Philippine National Drug Formulary/Philippine National Formulary
PPhA	Philippine Pharmacists Association
RA	Republic Act
SSFFC	substandard/spurious/falsely-labelled/falsified/counterfeit medicines
TB	Tuberculosis
UHC	Universal Health Coverage
WHO	World Health Organization

4.1 The Philippines Health System

The Philippines is an archipelago of 7107 islands in the Western Pacific with a total land area of 343,282 km. Its three major island groups are Luzon, Visayas and Mindanao, while Manila is its capital city. The total population is estimated at 101.4 million with an annual growth rate of 1.7%. The country is classified as a lower-middle income with a gross domestic product (GDP) of USD 284.6 billion and GDP per capita at USD 1649.35 in 2014.

4.1.1 Health System of Philippines

The 1987 Constitution established a republican government with a President, a bicameral legislature and an independent judiciary. The country has 18 administrative regions composed of provinces further subdivided into cities, municipalities

and barangays ('villages'). The barangays are the smallest local government unit (LGU). As of March 2014, there are 81 provinces, 144 cities, 1490 municipalities and 42,028 barangays [40].

A dysfunctional centrally planned healthcare system, using a vertical program approach, prompted decentralization of health services initially in the 1970s, but further in the 1990s [18]. The Local Government Code of 1991 was enacted to provide for a decentralised system of administration for health and other services. The central Department of Health (DOH) is the lead governing agency providing national policy direction through national health plans, technical standards and guidelines. The local government units (provinces and municipalities), together with the private sector, provide services to the population. The DOH provides technical assistance to local government units through regional Centers for Health Development (CHDs), but the local governments have administrative autonomy and responsibility for their own health services [18, 30]. Provincial and district hospitals are under the provincial government, while public health and primary care services are under the control of municipal government. The DOH has retained the management of a number of public tertiary care hospitals such as national specialty centres and regional hospitals (called DOH-retained hospitals) [49].

In 2010, the Aquino Health Agenda was launched to provide *Kalusugang Pangkalahatan*, or Universal Health Coverage (UHC) [49] directed towards goals of better health outcomes, sustained health financing and a responsive health system. The government aims to reach 100% population coverage for UHC in 2016.

4.1.2 Health Indicators

The country's total health expenditure was PhP 526.3 billion (around USD 11.1 billion) in 2013, which is 11.7% higher than in 2012. Private sources accounted for 68.2% followed by government (18.9%) and social insurance (11.5%). Per capita health expenditure at current prices was PhP 5360 (around USD 113) in 2013, which is a 9.8% increase from 2012 and the total health expenditure is estimated at 4.6% of GDP [45, 46].

The leading causes of morbidity in the country are infectious conditions (Table 4.1), which is partly explained by the country's propensity for natural disasters, being in the typhoon belt and also along the Pacific Ring of Fire (volcanoes) [11].

Annual mortality is around 5.2 per thousand with 498,486 registered deaths in 2011, nearly 58% male (death sex ratio 1.37). Cardiovascular diseases have been the leading cause of death for several years, comprising 21.5% of total deaths in 2011 (Table 4.2) [11].

The infant mortality rate was 12.8 deaths per thousand live births in 2011 with bacterial sepsis (16.5%), pneumonia (12.5%) and respiratory distress (10.8%) being the leading causes. The maternal mortality rate is 0.8 per thousand live births [11].

Table 4.1 Ten leading causes of morbidity in the Philippines, 2011 [11]

Cause	Morbidity rate per 100,000
1. Acute respiratory infection	1541.0
2. Acute lower respiratory tract infection and pneumonia	557.3
3. Hypertension	321.7
4. Bronchitis	239.3
5. Influenza	195.9
6. Urinary tract infection	185.8
7. Acute watery diarrhoea	159.3
8. TB, respiratory	50.8
9. Acute febrile illness	41.8
10. TB, other forms	41.4

Table 4.2 Ten leading causes of mortality in the Philippines, 2011 [11]

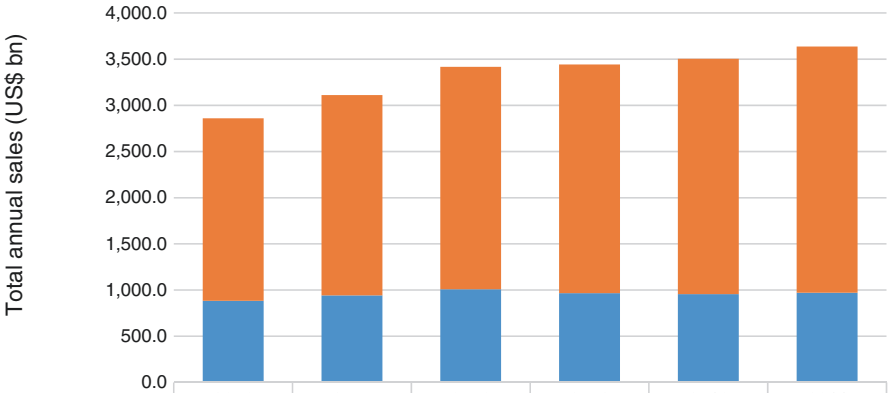
	Male	Female	Both sexes		
Cause of death	(*n*)	(*n*)	(*n*)	Rate per 100,000	%[a]
1. Heart disease	60,542	46,752	107,294	113.7	21.5
2. Vascular system disease	39,000	31,069	70,069	74.2	14.1
3. Malignant neoplasms	25,583	25,180	50,763	53.8	10.2
4. Pneumonia	24,280	24,152	48,432	51.3	9.7
5. Accidents	29,247	7037	36,284	38.4	7.3
6. Tuberculosis, all forms	16,812	7552	24,364	25.8	4.9
7. Chronic lung disease	16,042	7216	23,258	24.6	4.7
8. Diabetes mellitus	10,719	11,173	21,892	23.2	4.4
9. Kidney disease	8461	5592	14,053	14.9	2.8
10. Perinatal conditions	7110	4871	11,981	12.7	2.4

[a]Percent share from total deaths, all causes, Philippines

4.2 The Philippines Pharmaceutical Sector

The Philippines is said to have the third largest pharmaceutical market among the countries in the Association of South-East Asian Nations (ASEAN) community. It is considered a 'pharmerging' market due to its large population and recent increases in public spending on health. In 2013, pharmaceutical sales were valued at US$ 3.2 billion. Growth has mostly been seen among local manufacturers, following the passage of legislation promoting the use of generic medicines. Most major multinational firms have offices in the Philippines and while medicine imports are significant, a number use toll manufacturers in the Philippines to produce their products [47]. Of the total pharmaceutical market, public expenditure represents about 10% of sales, indicating the major role that the private sector plays in the provision of medicines in the country.

The Philippines has a relatively well-developed pharmaceutical sector with 316 licenced pharmaceutical manufacturers, 411 traders, 4770 wholesalers and



	2006	2007	2008	2009	2010	2011
Generics	1,975.2	2,169.4	2,407.8	2,476.6	2,548.0	2,667.1
Originator brands	884.3	942.3	1,009.0	965.8	956.5	970.4

Fig. 4.1 Relative market share of originator brand and generic medicines in the Philippines (2006–2011) (After PHAP [42])

distributors and 27,826 pharmaceutical retailers in 2013 [31]. In June 2014, a total of 20,901 products had market authorisation for human use (including multiple dosage forms of the same active ingredient), 739 for veterinary use, 408 vaccines and biologicals, 97 traditional medicines and 35 medical gases.

The majority of pharmaceutical manufacturers are domestic companies concentrating on generic medicine production. United Laboratories (Unilab) is the largest player in terms of both value and volume. Foreign firms constituted about 61.5% of the market by sales and 36.5% by volume in 2011. The sales of originator brand pharmaceuticals accounted for about 35.9% of the market by sales, down from 43.8% in 2006 (Fig. 4.1) [42]. Most of the local production of pharmaceuticals is for domestic consumption. In 2008, exports generated US$31.7 million [47] but have been increasing with US$14.8 million generated for the first quarter of 2015. Pharmaceutical exports comprise 0.08% of total export value [16].

The generics market is dominated by branded generics perceived to be of higher quality than products from lesser-known manufacturers. Prescription medicine sales contribute about 70% of annual turnover in the pharmaceutical market, with 53% attributed to branded generics, 41% to originator products and 6% to unbranded generics [31]. Since 2009, the share of branded generics in the market has increased from 50% to 56% by value and 60–67% by volume, mostly at the expense of originator products [31]. Branded generics account for 93% of sales of over-the-counter medicines.

Pharmaceutical manufacturing and distribution is centred on the capital city. However, some manufacturing and distribution sites are located in other cities to serve regional needs or to be close to import/export facilities. Key industry associations include the Pharmaceutical and Healthcare Association of the Philippines, the Philippine Pharmaceutical Manufacturers Association and the Philippine Chamber of the Pharmaceutical Industry.

The Philippines is part of the ASEAN economic bloc that has activities related to the harmonization of pharmaceutical regulation. It is envisaged that the ASEAN Economic Community established in 2015 will allow free movement of goods, services, skilled labour and investment. This should lead to increased trade in pharmaceuticals within ASEAN and could impact on the export potential of the Philippine pharmaceutical industry.

4.3 Pharmaceutical Regulation in the Philippines

The Food and Drug Administration (FDA) is responsible for the regulation of all health products, including medicines, medical devices as well as food and cosmetics. For pharmaceuticals this includes licensing and accreditation of pharmaceutical establishments; pre-marketing assessment and market authorization; and post-marketing surveillance including pharmacovigilance, inspections of pharmaceutical establishments, quality monitoring of marketed products and monitoring of pharmaceutical claims and promotion. Due to the geopolitical nature of the Philippines, the FDA also operates regional field offices.

Key laws (Republic Acts) are listed in Table 4.3. These are effected through Implementing Rules and Regulations and various Executive (EO) and Administrative Orders (AO). The FDA Act of 2009 created four centres under the FDA to deal with pharmaceuticals, food, cosmetics (including household hazardous substances) and medical and radiation devices. The Act also made provision for the FDA to retain income e.g. from licensing activities, for its operations and development.

Table 4.3 Key laws of the Philippines impacting on the regulation and supply of medicines

Code	Short title of legislation (date of enactment)
RA 2382	Medical Act (1959)
RA 3720	Food, Drug and Cosmetic Act (1963)
RA 5921	Pharmacy Law (1969)[a]
RA 6675	Generics Act (1988)
RA 7394	Consumers Act (1991)
RA 7581	The Price Act (1993)
RA 8203	Special Law on Counterfeit Drugs (1996)
RA 8293	Intellectual Property Code of the Philippines (1997)
RA 9165	Comprehensive Dangerous Drugs Act (2002)
RA 9184	Government Procurement Reform Act (2002)
RA 9502	Universally Accessible and Quality Medicines Act (2008)
RA 9711	Food and Drug Administration (FDA) Act (2009)

Key: RA Republic Act

[a]This act to be repealed and replaced with new Philippine Pharmacy Act that is pending debate and approval

Unfortunately, this has not been fully implemented and the FDA continues to suffer resource constraints in its operations [17].

The registration process should take 8–12 months, with applications for new drugs normally taking longer; however, that is not followed and there is a backlog. Product registrations are generally valid for 5 years. The ASEAN nations have adopted common standards and dossiers for registration, and a mutual recognition agreement for Good Manufacturing Practice inspections has been established. The FDA holds ISO 9001:2008 certification for its quality management system.

4.3.1 Quality Control

The FDA seeks to ensure the quality of pharmaceuticals on the market through the registration approval process; inspection of pharmaceutical establishments to assess compliance with the Good Manufacturing, Storage and Distribution Practice standards and through post-marketing surveillance activities. To support this, there is a central laboratory at the FDA with ISO/IEC 17025:2005 certification obtained in April 2010 (satellite laboratories are based in Cebu and Davao). The FDA is working towards membership of the Pharmaceutical Inspection Co-operation Scheme (PIC/s).

Since 2007, the Philippines FDA has received technical assistance from the United States Pharmacopeia to strengthen capacity in quality assurance and control of medicines. This focuses on anti-tuberculosis (TB) medicines. Main activities have included a post-marketing surveillance mechanism for TB medicines through sentinel sites, and the use of the GPHF-Minilab® for screening [57].

Every batch of a medicinal product that is imported is required to be analysed to confirm its conformity to specifications. Any procurement of pharmaceuticals by a public authority (DOH or local government unit) should also submit samples for confirmatory testing prior to the release of payment to the supplier. However, capacity constraints at the central FDA laboratory result in delays and there are anecdotal accounts of medicines being released for use before the certificate of analysis and compliance is received.

4.3.2 Pharmacovigilance

The Philippines established adverse drug reaction (ADR) reporting in August 1994 and joined the Uppsala WHO international drug monitoring program in February 1995 [32]. The FDA is the mandated National Pharmacovigilance Center with dedicated assigned staff. Pharmacovigilance activities include passive reporting complemented with active post-marketing surveillance and allow for reporting of product quality concerns, medication errors and treatment failures in addition to suspected ADRs. Adverse reactions related to herbal products and to traditional medicines are not commonly recognised or reported [32].

Pharmaceutical companies are required to submit ADR reports and periodic safety updates to the FDA. They are also required to conduct specific post-marketing clinical trials or collect safety data as part of their marketing authorisation for new products. A spontaneous voluntary reporting system operates for health professionals and consumer reporting has also been implemented.

In 2011, 3351 ADR reports were received by the FDA, which is a relatively low rate compared to the national population [56]. Resource constraints at the FDA, low awareness of the reporting system and concerns about legal challenges from the pharmaceutical industry for reporting suspected adverse reaction or product quality issues are possible reasons for the low reporting rate.

The FDA has adopted the ASEAN Post-Marketing Alert System to facilitate regulatory agencies to share information about actions taken related to poor quality or unsafe medical products and cosmetics.

4.3.3 Substandard and Counterfeit Medicines

The Philippine government has recognised the problem of substandard/spurious/falsely-labelled/falsified/counterfeit medicines (hereafter SSFFCs) and taken steps to address the issue. Capacity strengthening of the FDA has helped to improve the quality of medicines on the market, but SSFFCs remain a problem.

One publication suggested that the level of unregistered medicines on the market is less than 1% [56], but official sources have been quoted as saying that around 10% of the medicines on the market are counterfeit [37] and in 2003 the FDA reported that 30% of inspected drugstores carried SSFFCs [61]. Monitoring of tuberculosis medicines at sentinel sites has identified less than 1.5% non-compliant samples [57] with no cases of 'counterfeiting'. However, this is not likely to be representative of the market.

There are reports in the press announcing the seizure of SSFFCs, both small and large scale. Originator brand and domestic branded generic pharmaceutical companies have worked with the FDA and national enforcement agencies to seize SSFFCs infringing on their trademarks.

A Special Law on Counterfeit Drugs was enacted in 1996 that specified prohibited acts – the manufacture, supply, possession or false-labelling of counterfeit medicines – and allowed for administrative sanctions and penalties against those found guilty. Within the law [23], counterfeit medicines are defined broadly as:

"medicinal products with the correct ingredients but not in the [correct] amounts …, wrong ingredients, without active ingredients, with sufficient quantity of active ingredient, which results in the reduction of the drug's safety, efficacy, quality, strength or purity. It is a drug which is deliberately and fraudulently mislabeled with respect to identity and/or source or with fake packaging, and can apply to both branded and generic products."

However, the law also extends this to include trademark infringements, unauthorised repackaging, unregistered imported products and medicines containing less than 80% of the stated active ingredient.

Further to this, Presidential Proclamation (2082/2010) declared every third week of November as *National Consciousness Week against Counterfeit Medicines* when the DOH and the FDA organise events to raise public awareness on the issue of SSFFCs [29]. The Philippines has also participated in international and cross-border operations coordinated by Interpol through *Operation Storm*.

4.4 Medicines Supply System in the Philippines

The Department of Health is mandated to ensure access to basic public health services through provision of quality health care and regulation of health goods and services, including medicines. However, health service responsibilities are devolved to over 1600 local government units (LGUs), except for some centralised programs, and the private sector plays a significant role in the supply of medicines.

The DOH-Pharmaceutical Division (previously the National Center for Pharmaceutical Access and Management) was established in 2010 to implement the national medicines policy and the provisions of the Universally Accessible and Quality Medicines Act [12, 31]. Originally an *ad hoc* unit within the DOH called *Pharma 50* tasked to establish community-managed village drugstores, the DOH-Pharmaceutical Division now also acts as the secretariat for the Formulary Executive Council and for the Inter-Agency Committee on Antimicrobial Resistance and the DOH Advisory Council. It also manages the Generics Advocacy program and the medicines price monitoring.

Medicines management in the public sector happens at several levels due to decentralisation. However, if the medicine has to be purchased by any public entity, it must be listed in the *Philippine National Formulary* (PNF; formerly the *Philippine National Drug Formulary*, PNDF) [10, 13]. At the national level, DOH is responsible for the procurement and management of medicines for its vertical programs e.g. tuberculosis, family planning and rabies programs, medicines access programs and the medicines for emergencies and disasters. Local governments are responsible for providing medicines not covered by the DOH.

Procurement of medicines in the public sector is governed by the Government Procurement Reform Act. Competitive bidding is the main mode of procurement although alternative methods of procurement such as limited source bidding, direct contracting, repeat order, shopping or negotiated procurement can be used if justified and approved by the Central Office for Bids and Awards Committee (COBAC) [25].

4.4.1 The Medicines Supply System

The DOH supplies medicines for vertical programs, special medicines access program and medicines in emergency situations. The vertical programs are separately managed by different offices at the DOH. Estimated national requirements are procured through DOH Central Office for Bids and Awards Committee (COBAC) with

supplies delivered either to the DOH-Logistics Management Division or the DOH regional Centers for Health Development (CHDs). After FDA testing, the DOH distributes medicines through the Centers for Health Development to the Provincial Health Offices, which distribute to the Rural Health Units (RHUs). Medicines for pre-natal care and immunization programs are also dispensed at the level of Barangay Health Stations (low-level primary care centres run by local governments) through midwives and community health volunteers. The medicines in the DOH Package List for Emergencies and Disasters are managed by the Health Emergency Management Staff (HEMS) in a process similar to the vertical programs [36, 52]. The DOH has guidelines for donations of pharmaceuticals in times of emergency and disaster.

The DOH medicine access programs (MAPs) refer to government programs that guarantee access to certain medicines to a particular group or segment of the population. Examples include the Breast Cancer Medicine Access Program, Complete Treatment Pack Program and Medicine Access Program for Mental Health [12, 31] (see Sect. 4.5.4 for more details). Supply for medicine access programs is similar to that of the vertical programs except that after samples pass the FDA tests, suppliers deliver directly to the recipient health facility or identified distribution hubs. To illustrate, the Complete Treatment Packs for selected non-communicable diseases are delivered directly to RHUs and medicines for certain cancers are delivered to specialist hospitals.

At the local government unit (LGU) level, primary healthcare rural health units (RHUs) implement the DOH vertical and access programs through several barangay health stations. The local government unit is responsible for medicines purchase and supply outside these programs through their own local budgets. The Municipal Health Office submits procurement orders through the municipal mayor's office, in line with public procurement regulations. The medicines are supplied through municipal health centres and rural health units. Provincial, district and municipal hospitals also conduct procurement themselves or through their respective local government office.

The private sector plays an important role in the supply of medicines to patients due to the limited budgets of DOH and the local government units. Patients and their families commonly have to source medicines from private retail outlets due to shortages of medicines at public health facilities. In 2008, it was estimated that sales from drugstores (retail pharmacies) comprised about 80% of the market by value [41] with major distributors and retail chains dominating the market (Fig. 4.2).

4.5 Medicines Financing

In 2013, the total health expenditure was 4.4% of GDP, with general government expenditure on health at 31.6% of the total health expenditure [62]. Out-of-pocket expenditure on health was 82.9% of private expenditure on health showing the weak coverage and safety-net of health insurance benefit packages. National health account

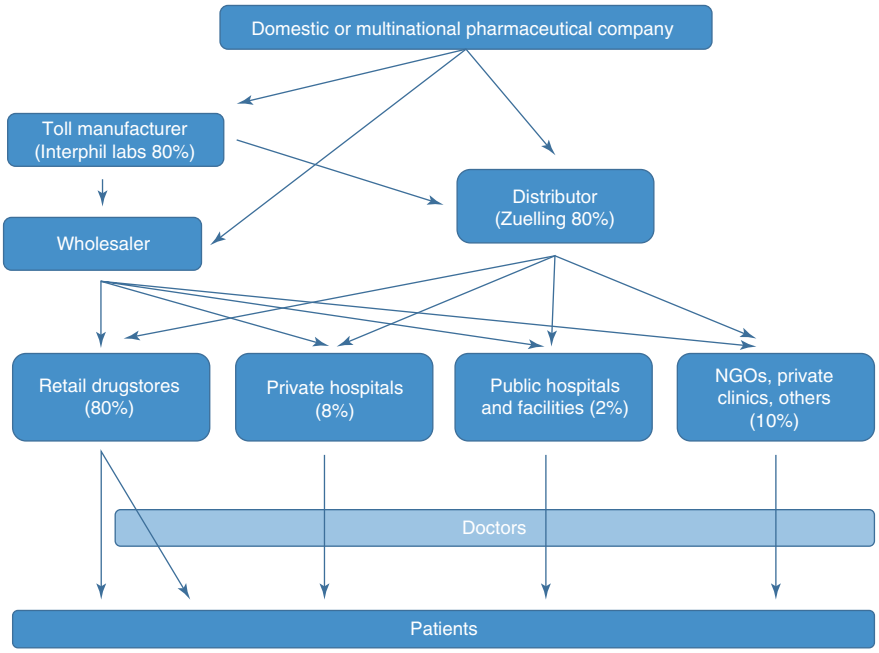


Fig. 4.2 Schematic representation of the Philippine pharmaceutical market (% by value; based on DOH [10] and PHAP [41])

indicators related to pharmaceuticals are not available due to the fragmented nature of funding for pharmaceuticals that is split between central government, local government units (provinces and municipalities), health insurance (national and private) and private out-of-pocket expenditure. However, data suggest that government expenditure on pharmaceuticals covers around 10% of the total sales, again underlining the importance of the private sector in medicines supply in the country.

The Philippines has a national health insurance scheme implemented under the Philippines Health Insurance Corporation (PhilHealth) with about 82% coverage of the population [31, 40, 43]. There are various programs to cater for the formally employed, the self-employed, senior citizens, sponsored members and the indigent (the poor whose membership is borne by the state). However, while in-patient medicines are covered under the basic package, there is no comprehensive coverage for out-patient medicines [31, 40, 43].

The basic package of PhilHealth covers the in-patient costs incurred when attending a public or private health facility accredited by PhilHealth. The provider is reimbursed based on a case-based rate i.e. a lump sum bundling medicine costs with other expenses. If the full cost of care is greater, the patient must cover the remaining balance. Under the 'No Balance Billing' policy, sponsored or indigent members should not be charged above the case-based rate if attending an accredited public health facility. However, it is not clear how widely this policy is being implemented by health facilities.

PhilHealth also offers certain disease or targeted packages for out-patient or ambulatory care [43]. Examples include packages to cover TB, malaria, HIV and animal bites. Out-patient medical and pharmaceutical expenses are otherwise not covered except under the primary care package (*Tamang Serbisyo sa Kalusugan ng Pamilya* or TSeKaP) introduced in 2012 [12, 31, 49]. Offered to indigent and sponsored members, this package allows for coverage of preventive and some diagnostic services in addition to medicines for ten common conditions: asthma, acute gastroenteritis, upper respiratory tract infection, pneumonia, urinary tract infection, diabetes mellitus, hypertension, dyslipidaemia, deworming and ischaemic heart disease. Eligible members receive 'vouchers' to be used at accredited hospitals or retail pharmacies, with the medicines provided as complete packs. Medicine reimbursement costs are based on the DOH *Drug Price Reference Index* with a 30% mark-up. Currently, other member categories have to pay for all chronic medication out-of-pocket [3, 12, 31, 49].

4.5.1 Medicine Pricing

In the public sector, at primary care facilities, certain groups are exempted from paying for medicines: indigent (poor) patients, children under 5 years of age, pregnant women and senior citizens, and in-patient costs should be borne by PhilHealth [3, 49]. However, poor availability of medicines means that patients often have to resort to out-of-pocket purchasing even for in-patient medicines.

Media reports have cited the Philippines as having some of the highest pharmaceutical prices in the region. Pricing surveys carried out using the World Health Organisation/Health Action International methodology have confirmed high prices with the most recent reporting prices of originator brands more than 30 times and generic medicines about 10 times the international reference price at both public and private sector retail facilities (Table 4.4) [2–4].

Table 4.4 Summary of median price ratios of a basket of medicines in public and private health facilities derived using the WHO/HAI medicine pricing survey methodology

	Median price ratio (local unit price/international reference price)			
	Originator Brand		Generic equivalent	
Year	Private sector	Public sector	Private sector	Public sector
2002[a]	16.0	18.2	8.4–17.8	–
2005[b]	17.3	15.3	5.6	6.4
2005[b]	–	14.2*	–	5.1*
2008[c]	–	15.7*	–	2.9*
2009[d]	37.1	30.2	10.8	9.8
2009[d]	–	26.3*	–	8.0*

*Public procurement prices only; other prices are retail prices

Note: The median price ratio shows how many times more the price is than an international reference price. Data from [a]Health Action International [63], [b]Batangan et al. [3], [c]Ball and Tisocki [2], and [d]Batangan and Juban [4]

The government has taken a number of measures to increase the affordability of medicines, although there remains no systematic price regulation in either public or private sector. The Price Act of 1993 mandated the DOH as the lead agency in identifying essential medicines and monitoring their prices [22].

While there were attempts to reduce medicine prices through parallel importation of generic medicines, sold through public-private pharmacy franchises (*Botika ng Bayan*) and village pharmacies (*Botika ng Barangay*) from 2003, it was the Universally Accessible and Quality Medicines Act (also known as the Cheaper Medicines Act) of 2008 [28] that further mandated price monitoring and made provision for the direct regulation of medicine prices. With this basis, an electronic price monitoring system was established and the DOH implemented the Maximum Drug Retail Price (MDRP) and Government-Mediated Access Price (GMAP) schemes.

The Maximum Drug Retail Price (MDRP) and Government-Mediated Access Price (GMAP) schemes are applicable at all retail pharmacies in both public and private sectors. Under the Maximum Drug Retail Price (MDRP) scheme, five drug molecules (amlodipine, atorvastatin, amlodipine/atorvastatin combinations, azithromycin, cytarabine, doxorubicin) on a named product basis have ceiling retail prices set by presidential proclamation (EO 821/2009). Under the Government-Mediated Access Price (GMAP) scheme, a wider range of drugs have had their prices voluntarily reduced by half by pharmaceutical companies. This was done after negotiation with the government (Table 4.5). However, competitor products have also reduced their prices, with prices falling to near the reference price [55].

The basis for the price reductions under these two schemes is unclear and the selection of drugs for inclusion under them has been questioned. No rationale was given for the 50% price reduction. Some products of questionable therapeutic value and not on the essential medicines list (*Philippine National Formulary*) have been included, and the mechanism has been criticised for not addressing real needs [6]. While the retail prices of some brand name products have been shown to now be comparable to other countries in the region (Table 4.6; [31]), an assessment of the effects of the price reductions have concluded that they did little to increase access to essential medicines for the poor, and many of the medicines under these schemes are not those prescribed for them [6].

In addition to the pricing regulations, the government has a legislation stating that the senior citizens and disabled persons are entitled to a 20% discount on retail medicine purchases. However, the discount is provided by the retailer out of their operating income and is not funded through taxation (although about one third can be offset through VAT returns). This may have resulted in increased prices of medicines in general to compensate for losses due to the discount. The DOH-Pharmaceutical Division has been working with stakeholders to facilitate the implementation and assess the impact of this regulation [31].

Since 2012, the DOH-Pharmaceutical Division has developed a *Drug Price Reference Index* (DPRI) that sets the ceiling price to be used in tenders for essential medicines in central and local government procurement. This DPRI is also used by PhilHealth as a basis for its calculations of pharmaceutical expenses in its care

Table 4.5 Generic names of medicines covered by the Maximum Drug Retail Price (MDRP) and Government Mediated Access Price (GMAP) schemes (as of September 2015)

CV disease	Cancer	Diabetes	Infection
Amlodipine + atorvastatin[a]	Bleomycin	Glibenclamide	Azithromycin[a]
Amlodipine[a]	Carboplatin	Gliclazide	Cefalexin
Atorvastatin[a]	Cisplatin		Ciprofloxacin
Clopidogrel	Cyclophosphamide	*Mental health*	Clarithromycin
Ezetimibe	Cytarabine[a]	Clozapine	Clevudine
Ezetimibe + simvastatin	Doxorubicin[a]	Paroxetine	Co-amoxiclav
Felodipine + metoprolol	Erlotinib		Levofloxacin
Irbesartan	Etoposide	*Pain*	Metronidazole
Irbesartan + HCT	Goserelin	Diclofenac	Oseltamivir
Losaratan + HCT	Ifosfamide	Fentanyl	Pipericillin + tazobactam
Losartan	Lapatinib	Meloxicam	
Nadroparin	L-Asparaginase		*Other*
Simvastatin	Megestrol	*Respiratory disease*	Betamethasone
Sotalol	Mercaptopurine	Salbutamol	Cetirizine
Telmisartan	Mesna	Salmeterol + fluticasone	Citicoline
Telmisartan + HCT	Methotrexate		Dutaseride
Trimetazidine	Metimazole	*Eye disease*	GGN
Warfarin	Mitomycin	Betaxolol	Miconazole
	Tamoxifen	Pilocarpine	Multivitamins
		SAP	Tolnaftate

[a]Covered by MDRP scheme. All others under GMAP

Key: *HCT* hydrochlorothiazide, *SAP* Sodium dihydroazapentacene polysulfonate, *GGN* Glucometamine + glucodiamine + nicotinamide

Note: Categories for guidance only. Price regulation is on a brand/company basis but various salts and dosage forms may be covered for each generic name. Five dialysis machines, dialysis fluids and some intravenous solutions are also covered under GMAP. Details available from: http://www.ncpam.doh.gov.ph/index.php/gmap-mdrp [Accessed 28 September 2015]

packages. This gives PhilHealth the potential to push for lower prices for essential medicines through accredited health providers.

4.5.2 Price Monitoring

The Price Act established the basis for price monitoring of essential medicines. The *Electronic Drug Price Monitoring System* (EDPMS) was implemented by the DOH (AO 9/2006) under which pharmaceutical manufacturers, wholesalers/distributors, importers and selected retail outlets report their prices and sales of selected essential

Table 4.6 Prices of selected medicines in the Philippines before and after price regulation compared to two regional countries

Medicine	Unit price (expressed as a ratio to an international reference price)			
	Philippines (before MRP)	Philippines (after MRP)	Malaysia	Thailand
Atorvastatin 10 mg tab (Lipitor®)	58.6	34.5	37.9	57.7
Azithromycin 500 mg tab (Zithromax®)	280.0	151.4	57.7	173.0
Gliclazide 80 mg tab (Diamicron®)	12.7	7.5	7.0	8.1

Key: *MRP* maximum retail price under MDRP or GMAP scheme
Data from Table 6 of Guerrero et al. [31]

Table 4.7 Extract from the Philippines Drug Price Reference Index 2013 showing past procurement unit prices and Drug Price Reference (DPR) to be used as a ceiling price for future public tenders

	Generic name	Dosage strength/form	Lowest–highest tender price (PhP)	DPR (PhP)
608	Ranitidine	25 mg/mL, 2 mL ampule	1.69 – 60.00	2.95
609	Ranitidine	150 mg tablet	0.49 – 6.00	1.09
610	Ranitidine	300 mg tablet	1.84 – 13.00	3.00
611	Regular, insulin (Recombinant DNA, human)	100 IU/mL, 10 mL vial	179.00 – 850.00	226.00
612	Retinol (vitamin A)	200,000 IU soft gel capsule with nipple	1.33	1.33
613	Retinol (vitamin A)	100,000 IU soft gel capsule	1.36	1.36

medicines. Originally coordinated through the FDA, this has since migrated to electronic submissions to DOH-Pharmaceutical Division. While compliance with reporting is an issue (less than 20% of registered establishments report; [31]), retail prices are collated from a selection of DOH-retained hospitals, private hospitals and at major chain drugstores. Price comparisons of selected medicines between these establishments are made available on the *Drug Price Watch* website [15].

In addition, the *Drug Price Reference Index* is updated annually and gives the lowest and highest prices for essential medicines from competitive tenders at DOH-retained hospitals (i.e. those owned and operated by DOH rather than under local government units) and regional health offices (Table 4.7). Ratios (highest/lowest price) of up to 130 have been observed and analysis has shown that procurement prices were unrelated to volume, distance of distribution or hospital capacity with prices from the same supplier varying between hospitals for the same item [31]. A median 'index' price forms the basis of ceiling prices in public tenders and for

reimbursement calculations by PhilHealth. The *Drug Price Reference Index* is a potentially useful management and transparency tool for public procurement.

4.5.3 Medicines Access

Despite the actions taken by the government to increase access to essential medicines in the Philippines, it is still estimated that around 30% of the population lack regular access to essential medicines [12]. Rational selection, sustainable financing, affordable prices and reliable health and supply systems are identified as key components to promote access to essential medicine [60]. Each of these remains challenging in the Philippines. A WHO pharmaceutical sector study found that the average availability of 15 key medicines was 53% at public pharmacies and 100% at private pharmacies [4]. However, when examining a larger number of products (44 medicines), availability was only 28% and 20% in public and private facilities respectively and only two-thirds of public facilities were able to dispense at least 75% of prescribed medicines showing that wider availability is poor. Both public and private hospitals are often surrounded by retail drugstores due to the need for patients and their carers to seek medicines from outside.

4.5.4 Medicines Access Programs of the DOH

To facilitate access to essential medicines for special groups or priority diseases such as tuberculosis, hypertension and cancer, the DOH has established medicines access programs (MAPs) (Table 4.8). The goals of these are to increase access, availability and appropriate use of essential medicines for these groups through innovative strategies such as pooled procurement, price negotiation and parallel importation [31]. Medicines access programs were found to increase availability of essential medicines in local government rural health units (primary care centres) from around 25% to 54% between 2010 and 2012, with a similar but smaller effect in municipal and regional hospitals [31].

The medicines access programs of the DOH need to be seen in the context of the Philippines health system where provision of medical services, including the procurement of essential medicines, is largely the role of local government units (provincial and municipal governments). These local governments have limited resources to fulfil this mandate. DOH, by utilising centralised procurement, parallel importation and other measures, has supported access to quality-assured low-cost medicines. However, while all medicines in the access programs are from the essential medicines list (*Philippine National Formulary*), the rationale for the selection of some medicines is open to question. For example, a wide range of specialised antipsychotics including clozapine, olanzapine, quetiapine, risperidone

Table 4.8 Medicines access programmes of the Department of Health

Medicines access programme	Notes
DOH Complete Treatment Pack (ComPack)	Provides packages of complete treatments for ARI, pneumonia, UTI, other common infections, bronchitis, hypertension, diabetes, hypercholesterolemia and asthma) for free to rural health units for poor patients. Formerly the P100 program.
Acute Lymphocytic Leukemia Medicines Access Program (ALLMAP)	Free anticancer medicines for indigent patients with acute lymphocytic leukaemia at designated access sites.
Breast Cancer Medicines Access Program (BCMAP)	Free breast cancer screening and medicines for indigent patients through designated hospitals.
Rare Disease Medicines Access Program (RDMAP)	Free access to enzyme replacement therapy for paediatric patients affected by rare genetic disorders (Gaucher's disease, Pompe's disease) in partnership with the University of the Philippines Institute of Health Genetics and the Philippine Society of Orphan Disorders.
DOH Insulin Access Program	Insulin manufacturers offer their products to patients through DOH-retained hospitals at reduced prices using a consignment system. Free insulin provided to poor patients by the DOH.
Geriatric Health Medicines Access Program (GHMAP)	Centralised procurement of chronic care medication for senior citizens at Eva Macaraeg-Macapagal National Center for Geriatric Health in Manila and geriatric wards at other hospitals.
Mental Health Medicines Access Program (MHMAP)	Free medicines for mental illness provided through designated access sites.
Micronutrient Supplementation Program (MSP)	Vitamin A, iron, iodine and zinc supplementation for children twice a year.
Expanded Program for Immunization (EPI)	Covers vaccine-preventable diseases in childhood namely tuberculosis, poliomyelitis, diphtheria, tetanus, pertussis, measles with rotavirus and pneumoccocal vaccines for priority cases.
Food and Waterborne Diseases Prevention and Control Program (FWDPCP)	Outbreak response for food and water-borne diseases such as cholera, typhoid and hepatitis A. Intravenous fluid and giving sets along with priority medicines are stockpiled at selected regional and central stores.
Health and Well-Being of Older Person Program (HWOPP) (Vaccine for Indigent Seniors)	Free vaccination against influenza virus and pneumococcal pneumonia for senior citizens.
National Filariasis Elimination Program (NFEP)	Supports free mass treatment of endemic areas.
National HIV/STI Prevention Program (NHPP)	Central procurement of medicines that are then provided free to HIV-positive patients at designated centres.
National Leprosy Control Program (NLCP)	Free provision of anti-leprosy treatment at designated treatment sites.
National Malaria Program (NMP)	Rapid diagnostic testing and medicines provided free through the national programme.

(continued)

Table 4.8 (continued)

Medicines access programme	Notes
National Tuberculosis Control Program (NTCP)	Medicines procured centrally and distributed through designated TB treatment sites by the national programme.
National Rabies Prevention and Control Program (NRPCP)	Free post-exposure prophylaxis and vaccination through national Animal Bite Treatment Centers.
Schistosomiasis Control Program (SCP)	Supports free mass treatment nationwide campaigns.
Soil Transmitted Helminthiasis Control Program (STHCP)	Supports free mass treatment nationwide campaigns.

and escitalopram are available under the Mental Health medicines access program. This appears to be contrary to the essential medicines concept and recent evidence [33]. The multiplicity of access programmes, each of which has separate procurement and logistics management, also leads to a fragmented approach in medicines supply although DOH-Pharmaceutical Division is moving to unify these activities.

In addition, to increase access to low-cost essential medicines for rural populations, since 2003 over 12,000 *Botika ng Barangays* (BnBs; village pharmacies) have been established [31]. These are run by trained operators from the local population and offer a small selection of 21 essential medicines (including eight prescription medicines for acute and chronic diseases) at low prices. Similar franchised operations have been set up by non-governmental organizations.

4.5.5 Industry Patient Assistance Programmes

A number of pharmaceutical companies have programmes to expand access to their medicines. Examples include pharmaceutical donations to DOH or non-governmental agencies, assistance programs for financially constrained patients and various discount cards [42]. These latter ‘payment assistance cards’ are usually brand specific and offered to patients through their doctors. Subscribers receive a substantial discount (of the order of 50%) upon purchase of the brand product from participating retail pharmacies, which helps the company maintain brand loyalty and market share.

4.5.6 Generic Medicines

The promotion of generic medicines has been one of the tools used since the original National Drugs Policy of 1987 (Box 4.1) [10, 12]. The Generics Act of 1988 [21] mandates the use of generic names in public health institutions and public procurement. It further requires the use of prominent generic names on

pharmaceutical packaging, promotes local production of generic medicines and endorses public and health professional education about generic medicines. This initial law and accompanying regulations was strengthened through provisions of the recent Universally Accessible and Quality Medicines Act [28]. Education and awareness campaigns have culminated in the establishment of an annual 'Generics Summit' since 2008. The recent *Philippine Medicines Policy* [12] also advocates the use of generic medicines to increase access (Box 4.1).

One of the most obvious signs of the effects of government policy and legislation has been the growth of retail pharmacy chains specifically providing generic medicines e.g. *The Generics Pharmacy*, *Generika*. Analysis of sales has also shown an increase in market share of generic medicines (Fig. 4.1) and a broad awareness of generics among professionals and the public [55]. However, perceptions remain that the generics may be of lower quality and are not safe.

Box 4.1: Criteria for pharmaceutical donations in times of emergency and disaster

- Shelf life of at least 12 months on arrival in the Philippines
- Labelling with English translation (or easily understood language)
- Packaging appropriate to international shipping standards
- Weight per carton does not exceed 50 kg
- Not mixed with other supplies
- Proof of compliance to applicable quality standards
- Proof that the items were derived from reliable source

(AO 17/2007)

The Philippine National Medicines Policies of 1987 and 2011

The original Philippine National Drug Policy (PNDP) of 1987 was described as 'the government's response to the problem of inadequate provision of good quality essential drugs to the people'. The PNDP was established on five mutually reinforcing pillars 'designed to eventually bring about the availability and affordability of safe, effective, and good quality drugs for all sectors of the country, especially for the poor who need them most, but who can least afford them'.

I: Assurance of the 'safety, efficacy and usefulness of pharmaceutical products through quality control'.
II: 'Promotion of the rational use of drugs'. This included the establishment of the PNDF and regulation of pharmaceutical advertising.
III: 'Development of self-reliance in the local pharmaceutical industry'.
IV: 'Tailored or targeted procurement of drugs by government … making available … the best drugs at the lowest possible cost'.
V: People empowerment... to assist people in exercising an informed choice in the purchase of cost-effective medicines.

The most recent *Philippine Medicines Policy (2011–2016)* encapsulates these original pillars in the SARAH Medicines Access Framework:

S – *Safety, Efficacy and Quality*: by assuring safety, efficacy and quality of medicines throughout the supply chain through the FDA
A – *Affordability and Availability*: through promoting generics, rational pricing, price monitoring and regulation
R – *Rational Use of Medicines*: using the PNF as basis of selection, provision of patient information, promotion of clinical guidelines
A – *Accountability, Transparency and Good Governance*: through promoting good practices by all stakeholders, reducing bureaucracy
H – *Health Systems Support*: by providing an enabling environment with human, technical, technological and financial resources and instruments

DOH [10, 12]

4.6 Medicines Use

4.6.1 Medicines Use in General

In the Philippines, medicines are classified as any one of the four categories [7, 24, 25]:

(a) Dangerous drugs – listed in the Comprehensive Dangerous Drugs Act, supplied only on Special DOH Prescription Form (Yellow Prescription) by a physician licensed by the Philippine Drug Enforcement Agency (PDEA)
(b) Exempt dangerous drugs – containing any amount of prohibited or regulated drugs, supplied on ordinary prescription forms with license number by a physician licensed by PDEA
(c) Prescription medicines – supplied on prescription only
(d) Non-prescription medicines – supplied without prescription

Only physicians, veterinarians and dentists are authorised to prescribe medicines [19, 26, 27], while only registered pharmacists can dispense and sell medicines under the Pharmacy Law [20]. The latter requires that every drugstore (pharmacy) be supervised by a pharmacist who should be physically present at all times. However, smaller drugstores may be found without a pharmacist and prescription medicines are widely available without a prescription at community drugstores.

Under the Generics Act [21], physicians are required to prescribe using generic names only; however, they can still prescribe their preferred brand name as long as the generic name is indicated. Pharmacists are required to inform the patients of all available generic equivalent products and their prices. Generic medicine packaging is required to carry a statement that the medicine ‘has the same therapeutic efficacy’ as other generics or the innovator product.

4.6.2 Essential Medicines and Standard Treatment Guidelines

A revised Philippine National Formulary System (PNFS) was established in 2012 under which essential medicines are selected based on evidence of their efficacy, safety and cost-effectiveness. *Core medicines* are considered the most efficacious, safe and cost-effective for priority diseases and health care needs to be available at all times in appropriate dosage forms and lowest possible cost. Conversely, *complementary medicines* are those used as alternatives, in specialised care, for life-threatening non-prevalent diseases, for diseases in populations of special need and for epidemics [8].

The Philippine National Formulary System is operationalised through the Formulary Executive Council with the assistance from independent evidence review groups. To include a medicine in the formulary, the evidence review group has to prepare an evidence summary, which includes a benefit-risk assessment, cost-effectiveness and health system and budgetary impact. The Council follows an algorithm for listing/delisting of medicines that comprises assessment of quality, benefit-risk assessment and pharmacoeconomic assessment, including both therapeutic benefits and adverse effects. New medicines should only be listed if they are shown to be more cost-effective than and as safe as another medicine already listed for the same indication.

In 2014, the *PNF Manual for Primary Healthcare* [13] was released. Compared to previous permutations, this version of the essential medicines list includes individual drug monographs with a cross-reference index and also contains the most recently published clinical practice guidelines regarding community-acquired pneumonia, hypertension and diabetes mellitus developed by relevant specialty medical societies.

Under its mandate of promoting rational use of medicines, the DOH-Pharmaceutical Division plans to develop further evidence-based national clinical practice guidelines [13]. The guidelines will form the basis for inclusion of medicines in the formulary. In 2015, the DOH created the National Antibiotic Guidelines Committee comprised of infectious disease specialists, DOH program managers and pharmacists [14].

4.6.3 Pharmacoeconomics

While the *Philippine National Formulary* is reviewed through a process that nominally involves cost-effectiveness analysis, pharmacoeconomic capacity is weak within the Philippines and health technology assessment is still at an early stage [31, 49]. Currently, in cases where more robust pharmacoeconomic evaluation is required, expert assistance is sought from international agencies such as the WHO.

4.6.4 Prescribing Behaviour

Self-medication by patients is very common as a result of various factors such as strong pharmaceutical promotion in media, prescription recycling and sharing by patients, ready over-the-counter availability of prescription medicines. Surveys on doctors' prescribing habits show that pharmaceutical products are sometimes prescribed inappropriately. Commonly encountered practices include irrational prescribing of broad spectrum antibiotics, prolonged duration of prophylaxis and polypharmacy [54]. Medical representatives and the commercial medicine lists, e.g. *Philippine Index of Medical Specialties*, are often the most accessible information resources, apart from the internet.

Generic prescribing is more practiced by physicians in the public sector than in the private sector. Barriers cited are perceptions regarding quality of generics, lack of regulation, dispensing behaviour of pharmacies, marketing of branded products, patient's choice and doctor's previous experience. Sources of influence of physician prescribing include the consultants under whom they are trained, perceived quality of generics, marketing practices of medical representatives and the financial status of the patient. [58].

4.6.5 Medicines Promotional Practices

Pharmaceutical promotion regulations prohibit direct-to-consumer advertising of prescription medicines and require FDA authorization of promotional materials to promote the use of generic names [48]. In 2013, the FDA adopted the *Mexico City Principles*, a code of business ethics governing the marketing, distribution and promotion of products in the biopharmaceutical sector. The DOH recently issued guidelines for ethical interaction between the industry and healthcare professionals in relation to promotion and marketing of prescription pharmaceutical products [9].

The two major pharmaceutical associations have their own codes of conduct [35] but many companies are not members and self-regulation has limited effectiveness due to the presence of conflicts of interest. While there is no specific formal code of practice governing the relationship between pharmacists and the pharmaceutical industry, the Philippine Medical Association has a code of ethics that includes articles on the relationship with the health products industry, but it is neither particularly detailed nor restrictive [44]. The FDA is under-resourced to effectively monitor pharmaceutical promotion.

4.6.6 Role of Pharmacist

Drugstores – then known as *boticas* and managed by Spanish, German and American pharmacists – started to operate in the country during the 1800s, even before the formal offering of the first pharmacy course in 1871. Since 1984, the Bachelor of

Science in Pharmacy program has a minimum 4-year national curriculum with internship components (community, hospital and manufacturing) set and updated by the Commission on Higher Education. Several universities also offer other undergraduate programs (5-year BSc in Industrial Pharmacy at the University of the Philippines, 5-year BSc in Pharmacy majoring in Clinical Pharmacy at private universities), post-baccalaureate programs (PharmD at Centro Escolar University) and postgraduate degree programs. In 2013, there were 80 schools of pharmacy, with only 31 members of the Philippine Association of Colleges of Pharmacy.

In spite of the Filipino pharmacists' education, expertise and accessibility, they remain underutilised in the healthcare system. According to the Pharmacy Law [20], a person needs to be at least 21 years of age and Board of Pharmacy-certified in order to practice as a pharmacist.

The Philippine Pharmacists Association (PPhA), the government-accredited national organization of pharmacists representing over 16,000 practitioners from 82 local chapters and 10 affiliate organizations, has adopted the *Seven-star Pharmacist* to outline the expected roles of the pharmacists these include pharmaceutical care provider, decision maker, researcher, leader, manager, teacher and communicator [59]. The Association has added three equally important roles: entrepreneur, lifelong learner and agent of positive change [53].

In 2015, the *Philippine Practice Standards for Pharmacists* (PhilPSP) were released. The publication outlined the minimum professional standards for pharmacists in academia, manufacturing, regulatory, community, hospital and institutional and public health pharmacy settings. The PhilPSP contains general statements aimed to guide, advise and provide reference to pharmacists on how they can best fulfil their duties and responsibilities in collaboration with other health professionals. The 29 competency standards include a set of core competencies across practice settings. The creation of the standards was an effort to mainstream Good Pharmacy Practice in the country. This was in response to recognition of the growing need and demand for pharmaceutical care services [53].

4.6.7 Pharmaceutical Care Interventions and Assessment of Community Pharmacy Practice

Most pharmacists in the Philippines (about 70%) are employed in the community setting [34]. Although the profession continues to evolve towards clinical pharmacy, there is a rather slow progress in the implementation of pharmaceutical care practice and the majority of clients still perceive community pharmacists as mere drug sellers.

Studies on the barriers to implementing pharmaceutical care in the country identified that lack of support by physicians and other health professionals is the main obstacle. While health professionals readily accept the traditional roles of pharmacists in supply and distribution of medicines, many do not agree with their clinical roles in medication therapy management. Other barriers include lack of information technology support for data collection and documentation, lack of economic

incentives and proper remuneration for providing pharmaceutical care services, absence of standards and guidelines, lack of time and lack of patient demand for these services [1]. Many of these can be partially addressed if pharmacists in the healthcare system start documenting and disseminating evidences of the benefits of providing these services. In recent years, more pharmacies are providing patient care services in the form of medication counselling, blood pressure and glucose monitoring, provision of daily dose packs and patient adherence monitoring.

Many of the pharmacists in practice today were educated and trained according to the old product focus paradigm. To fully implement pharmaceutical care, they need to be given the opportunity to acquire new knowledge and skills required for patient-oriented roles [38]. Recent studies revealed that while pharmacy personnel have high level of knowledge about drugs, they achieved lower scores for their dispensing, counselling and referral skills [54] and that most are conservative in rating their pharmacology and disease states management knowledge [50, 51]. Many expressed need for continuing education in areas such as new drug products, medication adherence, disease management, medication counselling and good pharmacy practice. Universities have started to mainstream pharmaceutical care in the undergraduate pharmacy program guided by the national curriculum, and students now perceive that they are better prepared to fulfil pharmaceutical care roles [5].

4.6.8 Medicines Use Research

There is no institutionalised national system to measure or monitor drug utilization research in the country, and research is lacking. Small studies are conducted, usually initiated by academic institutions, either with small funding or as student projects, and the fragmented nature of the medicines supply chain in the country makes such studies difficult. The DOH needs to invest in effective data systems and capacity building of health care professionals to conduct such studies.

A study in 2012 found evidence of irrational use of medicines including rationing (locally termed as *dibydiby*), buying medicines (specifically antimicrobials) piecemeal without physician prescription, dispensing whatever alternative medicines are available, often leading to incorrect medicine substitution and prescribing maximum doses of antibiotics for longer periods of time when the first-line antimicrobials are unavailable. Other problems include irrational combination of medicines and over-prescription [13].

Cultural preferences and beliefs also contribute to irrational use of medicines. There is a popular local practice of recycling (reusing) prescriptions for recurrence of symptoms initially assessed by a doctor, reinforced by belief that a particular drug suits a specific patient. Prescription sharing between friends and neighbours also occurs. Self-medication is a prevalent practice mainly because of the cost of consultation and the confidence in the prescribing doctor [54]. Non-implementation of prescription controls in community drugstores support the practice.

In terms of the use of anti-infectives, common misconceptions include that there is a specific remedy for every symptom; antibiotics are wonder drugs and the more expensive a medicine, the more effective it is. Furthermore, injections are considered more 'powerful' forms of medicine and patients believe medicine use should be stopped when symptoms subside [54].

Patients and caregivers generally consider antibiotics to be relatively risk-free and are often not troubled by considerations of under-treatment or development of resistant organisms [54]. In 2015, the WHO supported the DOH-Pharmaceutical Division to produce the first ever *Country Report on Antimicrobial Drug Consumption* for the period from 2011 to 2013. Correlations between antimicrobial consumption and resistance rates of bacterial organisms were found statistically significant at the drugstore, hospital and combined settings across regions in the country [14].

4.7 Conclusions and Way Forward

Given the historical and geopolitical context of the country, the Philippines has a complex medicines supply system. The epidemiologic transition, evidenced by increasing population, change in health trends and steady but non-inclusive economic growth, brings a new set of challenges. While the government has increased investments in health recently, much remains to be done to ensure equitable access to safe, effective and quality-assured essential medicines. Access to essential medicines is constrained by concerns of availability, quality, costs, irrational use, unethical pharmaceutical promotion and lack of confidence in existing governance structures. The health sector appears fragmented and uncoordinated largely due to the effects of decentralization and clearly defined policies at the national level are not always effectively implemented especially at local government level.

Various initiatives have been taken to achieve the objectives of the *Philippine Medicines Policy* –these include the promotion of generic medicines and rational drug use, regulatory systems strengthening, drug price referencing and creation of medicines access programs among others. However, some appear more as stop-gap measures than part of a coordinated approach, and adequate resourcing and implementation is often lacking. Coordination of pharmaceutical services within the DOH needs to be strengthened along with improved logistics information management. The FDA needs to be strengthened and adequately resourced as envisaged in the FDA Act to ensure the efficacy, quality and safety of medicines on the market. PhilHealth benefit packages need to guide rational, cost-effective care and cover medicines costs adequately for both in-patients and out-patients. A coordinated approach to research on prescribing and medicines use in both public and private sectors would help to guide and evaluate policy interventions. Addressing these issues in an integrated manner while improving information management, building human resources and investing in physical

infrastructure would help to make the health system resilient and achieve the goals of Universal Health Coverage and the Philippine Medicines Policy that eventually no Filipino will be denied access to essential medicines because of availability or cost.

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Chapter 5
Pharmaceutical Policy in Vietnam

Tuan Anh Nguyen, Agnes Vitry, and Elizabeth E. Roughead

Abstract Health sector reforms since 1989 have transformed Vietnam's healthcare system from a publicly funded and provided healthcare system to public–private mix. With the shift toward a market economy, Vietnam has introduced several market-oriented measures including the introduction of user fees, legalization of private pharmacy and medical practices, and liberalization of the production and sale of pharmaceuticals. Private pharmacies have become the dominant medicines supplier in the market. At the same time, the provision of free medicines dispensed through the public health system was discontinued. Spending on medicines, user fees, and increased autonomy for health facilities and healthcare providers led to substantial increases in out-of-pocket health expenditure. Because of high medicine prices, poor quality of medicines, irrational selection and use of medicines, unsustainable pharmaceutical production and distribution systems, and a lack of a financial support system for drug procurement, access to the right medicines at the time people need them remains a major challenge for the majority of the population.

A number of legislative and regulatory reforms have been introduced to address the side effects of the market economy on access to essential medicines. The initiatives, however, have not been able to keep up with the rapid changes in the health and pharmaceutical sectors. Furthermore, the provisions were not routinely monitored or effectively enforced.

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5.1 Introduction

From the perspective of key indicators of health outcomes such as child and maternal mortality, Vietnam has achieved standards similar to those found in much wealthier countries [57]. However, Vietnam's healthcare system is deemed to be weak in the distribution of health attainment across regions, income groups and medical conditions [50, 57]. The gap in health outcomes between the rich and the poor has widened, especially with respect to child survival [57]. A large proportion of health spending is financed by out-of-pocket patient expenses [53], although the Vietnam government has initiated reforms aimed at redressing this imbalance, including subsidization of the poor and expansion of public health insurance [57].

Medicine expenditure accounts for a large component of total healthcare costs. In 2005, Vietnam spent USD 3.18 billion on health (USD 1 = VND[1] 15,907.00), of which 53.3% was for medicines, an almost threefold increase in absolute terms from 2000 [52]. Rising prices for medicines have been reported to account for most of this increase [57]. From 2003 to 2004, prices of some medicines soared fourfold [4], and the medicine and health component of the consumer price index (CPI) increased by 13.8%, almost double the CPI [22]. Medicines play a crucial role to improve health outcomes. However, they have become unaffordable for the lowest paid unskilled government worker, thus being unaffordable for the large percentage of the population who earn less than this benchmark [38]. Pharmaceutical policy reform is therefore central to current efforts to improve Vietnam's healthcare system.

This chapter aims to analyze the pharmaceutical policy in Vietnam to identify scope for improvement. It begins with an overview of Vietnam's health system and pharmaceutical situation. A section follows on regulatory environment, highlighting the function of Vietnam's medicines regulatory authority, the drug quality control system, the pharmacovigilance and situation of substandard, and counterfeit medicines in the country. This chapter continues with sections on the supply system, financing and use of medicines, analyzing the causes of the dysfunction within the pharmaceutical sector, as well as the issues impacting on rationale medicines use in the country. This chapter ends with conclusions and recommendations to move forward.

5.2 Vietnam Health System

Vietnam's healthcare system has evolved from health systems established separately in North and South Vietnam. During the war period (1945–1975), North Vietnam established an extensive network of primary healthcare facilities with the aim of achieving universal healthcare coverage. In urban areas, nearly 100% of the

[1] Vietnam Dong: Vietnamese currency.

population were covered, as were 75% of the population in rural areas [54]. In South Vietnam, a strong private health sector dominated until, upon unification with the North in 1975, private enterprises were banned [25].

Post 1975, Vietnam suffered severe financial pressures, including costly postwar reconstruction, an economic blockade by the United States, withdrawal of aid from the former Soviet Union and a rising inflation rate [6, 54, 55]. This had significant impacts on the healthcare system. The expansion of the network of free public health services that had been set up in North Vietnam to include the South added further economic strain, resulting in poor maintenance of healthcare facilities and lack of basic equipment and medicines in many health stations and hospitals [54]. At this time, the domestic pharmaceutical industry was only able to meet 30% of the population's demand for medicines, and most essential medicines had to be imported, as there was no capacity to manufacture in country [55].

The economic reform process known as "DoiMoi", initiated in 1986, led to important policy shifts in the healthcare system in the late 1980s and early 1990s. A number of market-oriented measures were implemented, including the introduction of user fees at public health facilities, legalization of private pharmacy and medical practices, and liberalization of the production and sale of pharmaceuticals [51]. Free access to healthcare was gradually replaced by a system of direct payment by patients [25]. The provision of free medicines dispensed through the public health system was also discontinued [25]. As a result, Vietnam's near-universal, publicly funded and provided health services were converted into an unregulated public–private mix [44].

One result of the country increasing its reliance on market mechanisms was substantial increases in consumer's out-of-pocket (OOP) health expenditure [57]. Between1995 and 2008, OOP expenditure ranged from 55 to 66% of total health expenditure [53]. The rising household OOP spending on health was partly because of increasing user fees in public hospitals [37]. Increases in medicine prices also contributed to the growing magnitude of absolute household OOP expenditure on health.

To address the growth in OOP payments that placed financial barriers to healthcare access, the government issued a national Health Insurance Decree in 1992, introducing compulsory health insurance for people in salaried employment. Since then, health financing from social health insurance as a percentage of public health expenditure has risen, from 7% in 1995 to 32% in 2008 [53]. In 2008, the Health Insurance Law was passed and came into effect in July 2009. The law stipulated that the government was responsible for fully subsidizing health insurance for children <6 years of age, the elderly, and the poor, and for partially subsidizing health insurance for the near-poor and students. The law also provided a road map for universal health coverage. By 2011, healthcare coverage in Vietnam exceeded 64% of the population [46]. Medicines eligible for public health insurance reimbursement are limited to medicines listed on the basic schedule issued by the Ministry of Health (MOH). The current schedule comprises 900 Western medicines and 57 radioactive substances and marking compounds [35]. The public health insurance scheme does not cover medicines that are purchased at private retail pharmacies.

5.3 The Pharmaceutical Situation

The health sector reforms, introduced since 1989, have also impacted on Vietnam's pharmaceutical supply chain, shifting it from a centrally controlled system to a market-oriented system [25]. The opening of the country to foreign trade and the liberalization of rules governing pharmaceutical manufacture, sale, and distribution led to a 300% increase in medicine production and a tenfold increase in importation of medicines between1988 and1992 [54]. To improve coordination of pharmaceutical policies, the National Drug Policy was promulgated in 1996, with two basic goals: ensuring regular and adequate supply of good-quality medicines at affordable prices, and ensuring rational use of medicines [21].

To facilitate the implementation of the National Drug Policy, the Drug Administration of Vietnam was established in 1996 with responsibility for state management of pharmaceuticals [20]. The Drug Administration of Vietnam adopted a road map of good practices to ensure the quality of medicines across all aspects of the supply chain. In Vietnam, manufacturers have to comply with the code of Good Manufacturing Practice (GMP), importers with Good Storage Practice (GSP), distributors with GSP and Good Distribution Practice (GDP), and retailers with Good Pharmacy Practice (GPP).

Vietnam's pharmaceutical market is, however, heavily dependent on imports. Imported medicines account for more than 50% of the market share, focusing on specialized products. By the end of 2011, there were 15,552 imported medicines covering 971 active substances, averaging 16 brands per active substance [36]. The range of imported products is wider than those locally produced, and there is trading duplication of some active substances. For example, one substance, cefixim, had 458 imported brands with a valid registration number in Vietnam by 2011 [36].

Domestic medicine production accounts for an increasingly growing market share, rising from 36% in 2001 to approximately 50% in 2011, reaching USD 1.14 billion [36]. However, the domestic pharmaceutical industry is characterized by limited R&D facilities, insufficient financial capacity, and poor management [2]. Most local pharmaceutical manufacturers comprise small-scale operations with outdated manufacturing technology and duplicated production processes. About 90% of the raw materials used in domestic production are imported [5], thus making domestic medicine prices subject to price fluctuations in international prices, as well as fluctuations in the exchange rates. Nearly 95% of imported active pharmaceutical ingredients are antibiotics, vitamins, antipyretics, analgesics, and antispasmodic drugs [31], reflecting a concentration of domestic pharmaceutical production on only some therapeutic classes. By the end of 2011, there were 13,268 locally produced medicines, representing 524 active substances registered for sale in Vietnam, averaging 25 locally produced brands per active substance. Thus, local manufacturers compete for a very limited, and often uneconomic, market share, an example being 1044 registered products for one medicine, paracetamol, by 2011 [36].

5.4 Regulatory Environment

5.4.1 Medicines Regulatory Authority

The Drug Administration of Vietnam (DAV) on behalf of the Ministry of Health is the medicine regulatory authority in Vietnam. The DAV is responsible for state management of pharmaceuticals. It includes developing pharmaceutical legislation and regulations; registering medicines; issuing, suspending, or withdrawing drug import–export licences and certificates of GMP, GSP, good laboratory practice (GLP), and good agricultural and collection practice (GACP) for medicinal plants; controlling pharmaceutical manufacture, importation, pricing, promotion and advertising, and pharmacy practice. The DAV also carries out postmarketing surveillance and pharmaceutical inspection in collaboration with the National Institute of Drug Quality Control and the MOH Pharmaceutical Inspection at central level. At provincial level, there is often a unit of pharmaceutical management within the provincial health department assisting provincial health department executives in implementation of state management of pharmaceuticals in the provinces.

Most medicines must have product registration, as indicated by a valid registration number, prior to marketing in Vietnam. The MOH can allow medicines without a registration number to be marketed on a case-by-case basis, to avoid shortage of medicines. By law, within 6 months from the date of receiving complete and legitimate registration applications, the MOH shall issue medicine marketing authorization for the medicine. To ensure the quality, efficacy, and safety of medicines marketed, the pharmaceutical manufacturer must meet the GMP standards and the products must pass laboratory quality testing and clinical trials either in Vietnam or in exporting countries. Where applications fail to meet relevant requirements, the MOH will release written reasons for refusing registration [34]. By the end of 2011, there were 28,820 medicines registered in Vietnam [36].

5.4.2 Quality Control

A system of drug quality assurance/quality control (QA/QC) has started since 1957 with the establishment of the Drug Quality Control Department under the MOH, which later became the National Institute of Drug Quality Control of Vietnam (NIDQC). After the unification of the North and the South, in 1977, a Sub-Institute of Quality Control in Ho Chi Minh City was established under the administration of the NIDQC for drug quality control in southern provinces. Currently, the drug QA/QC system includes NIDQC, Ho Chi Minh City Sub-Institute of Quality Control, and 61 drug quality control laboratories of the provincial health departments [36].

Drug quality control is regulated by the Circular 09/2010/TT-BYT of the Ministry of Health of Vietnam. It stipulates quality control areas including development, issuance, and implementation of drug quality standards; management of drug

quality testing in pharmaceutical production, import–export, distribution, and use; and processes for suspending medicines from circulation, withdrawing, and destroying medicines not meeting the quality standards. *Vietnam Pharmacopoeia*, currently in the 5th edition, stipulates the national standard of medicines and methodologies for testing drug quality.

Vietnam aims to ensure the quality of medicines throughout the supply chain, first through a series of good practices including GMP, GSP, GDP, GPP, GACP, and GLP. However, the inadequate number of pharmaceutical inspectors leads to weak, irregular inspections of manufacturers and ineffective inspections of distributors' premises. It was reported that some private pharmacies had been tampering with labels, selling, and dispensing medicines with unknown origin and even counterfeit medicines [56].

Second, the postmarketing surveillance is in place with random quality testing of about 30,000 samples, bioequivalent testing of about 20 medicines, and solubility testing of 50 substances being conducted by the QA/QC system, annually. The QA/QC system has capacity to provide analytical services and quality testing for most essential medicines in Vietnam. However, the system faces difficulties in testing new active pharmaceutical substances, new pharmaceutical formulations, biological products, or high-tech medicinal products. This is because of the limited investment to the system from state budget. While the NIDQC and the Sub-Institute are well equipped, provincial laboratories have basic equipment only, and some still lack essential equipment of high-performance liquid chromatography and drug solubility testing machine [36].

5.4.3 Pharmacovigilance

In 1996, Vietnam established two adverse drug reaction (ADR) centers in Hanoi and Ho Chi Minh City to gather ADR reports throughout the country. The circular 08/BYT-TT of 04/07/1997 on regulating the organization, responsibility, and function of hospital Drug Therapeutic Committees then stipulated the establishment of drug information unit in each hospital, as well as requirement for ADR reporting. In 1999, Vietnam became the 55th member of the global ADR network, and ADR reporting has become an official indicator for annual assessment of hospitals since 2009. In 2009, a National Drug Information and ADR Centre was also established in Hanoi University of Pharmacy, Hanoi, and 2 years later, a South Vietnam Drug Information and ADR Centre was established in Ho Chi Minh City. The number of ADR reports continue to increase, from 519 reports in 2001 to 2407 in 2011, nationally [36].

The pharmacovigilance activity, however, is challenging because of an incomplete drug information network from central to local level that lacks coordination throughout the system. The most challenging hurdle is a lack of human resource with many district hospitals not having advanced pharmacists (i.e., those with a university level), who are competent and have sufficient knowledge in drug

information and ADR. Drug information units in hospitals are often not properly invested, and hospital executives often underestimate the importance of drug information and ADR work [36]. Hospital pharmacists mainly fulfill their logistic task of procuring and dispensing medicines rather than clinical function.

5.4.4 Counterfeit Medicines

Law on Pharmacy No. 34/2005/QH11 defines counterfeit medicines as products manufactured in any form of a medicine with a deceitful intention, and falling into one of the following cases:

(a) Counterfeit medicines have no pharmaceutical ingredients.
(b) Counterfeit medicines have pharmaceutical ingredients, which are, however, not at registered contents.
(c) Counterfeit medicines have pharmaceutical ingredients different from those listed in their labels.
(d) Counterfeit medicines imitate names and industrial designs of medicines which have been registered for industrial property protection of other manufacturing establishments.

The law prohibits trading counterfeit medicines. Those committing this prohibited act shall be imposed a fine in accordance with the Government Decree No. 185/2013/ND-CP on providing the penalties on administrative violations in commercial activities, production of or trading in counterfeit or banned goods, and protection of consumer rights. They might even be sentenced to a term of imprisonment according to Vietnam Penal Code.

There are limited data on the extent to which counterfeit or substandard medicines circulate in Vietnam. The postmarketing surveillance of medicines in circulation by the QA/QC system has discovered a number of substandard or counterfeit medicines. Table 5.1 shows the rate of substandard, counterfeit medicines in random sample quality testing from 2006 to 2011.

Table 5.1 Rate of substandard and counterfeit medicines during the period 2006–2011

	2006	2007	2008	2009	2010	2011
Substandard Western medicine overall (%)	3.18	3.30	2.90	3.33	3.10	2.81
Domestically produced medicines (%)	3.52	3.04	2.94	3.21	2.94	2.74
Imported medicines (%)	1.59	5.75	2.30	4.47	4.32	3.22
Substandard traditional medicines (%)	11.55	10.80	8.00	9.13	9.82	6.09
Counterfeit medicines (%)	0.13	0.17	0.10	0.12	0.08	0.09
Number of samples (n)	29,819	25,460	29,490	31,542	28,816	35,508

Source: MOH of Vietnam [36]

5.5 Medicines Supply System

Pharmaceutical supply chain in Vietnam is a complex system, which involves a number of intermediaries between manufacturers and consumers, including:

- 180 domestic pharmaceutical manufacturers (including 22 Foreign Direct Investment (FDI) producers), 90 importers, and 800 domestic wholesalers/distributors [14]
- Three FDI enterprises investing in drug logistics [14]
- 438 foreign pharmaceutical companies [14]
- 39,172 retail medicine outlets, including 9066 private pharmacies [14]
- 13,460 public healthcare facilities, including 974 hospitals, 781 regional polyclinics, and 10,917 commune health stations [23]
- 74 private hospitals and more than 30,000 private health clinics [37]

Figure 5.1 shows a schematic representation of the current pharmaceutical supply chain in Vietnam. Locally produced medicines from Vietnam's pharmaceutical manufacturers can be distributed directly to retailers and healthcare facilities or indirectly through wholesalers or distributors. Vietnamese manufacturers holding a retail license are able to supply medicines directly to end-users. Classified as domestic pharmaceutical producers, Foreign Direct Investment producers can directly distribute the products that they manufacture in Vietnam.

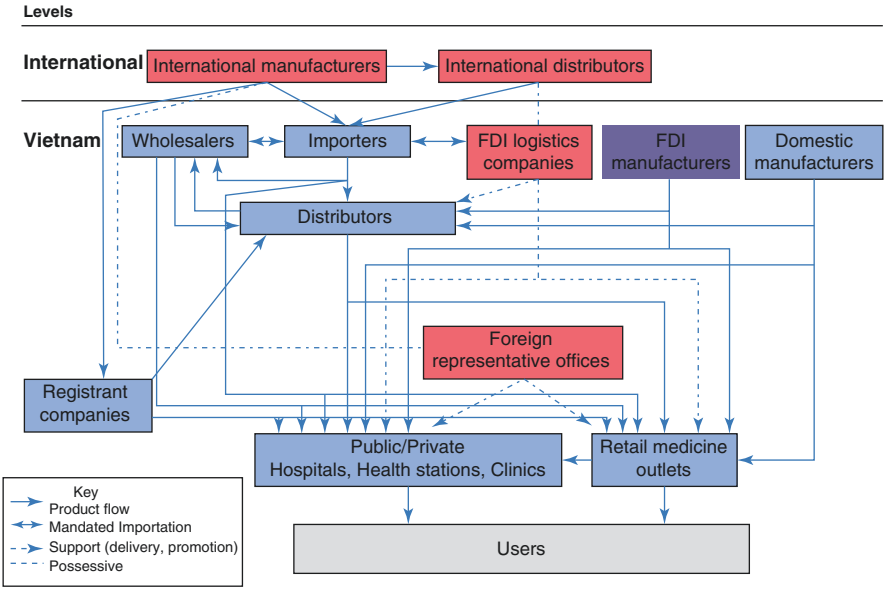

Fig. 5.1 The pharmaceutical supply chain in Vietnam. *FDI* Foreign Direct Investment (*Source: authors' analysis*)

Foreign Direct Investment logistic companies and foreign pharmaceutical companies are not permitted to distribute pharmaceutical products directly in Vietnam. Their products have to be sold to domestic pharmaceutical distributors for distribution. Foreign distributors are only permitted to supply their medicines to a local importer. Foreign pharmaceutical manufacturers with a trading license in Vietnam who are not established in Vietnam as a Foreign Direct Investment producer can supply their medicines via their local registrant company or a local importer [33] (see Fig. 5.1).

The medicine procurement system has been decentralized to provincial level and individual health facility level. Joint Circular No. 01/2012/TTLT-BYT-BTC of January 19, 2012 required public hospitals to purchase medicines using a tendering system. The tender may be conducted by the provincial government for all hospitals in the province, or at the individual hospital level. Tender boards are responsible for drawing up the tender schedule of medicines and then deciding on successful tenders. Membership of provincial tender boards comprises provincial government officials and nominees of selected hospitals in the province. Membership of hospital tender boards often comprises the director of the hospital as chairperson, the chief pharmacist as deputy chairperson, together with senior clinical department heads and the hospital finance officer.

Tender medicines are drawn from the basic schedule, also known as the public health insurance reimbursement list, issued by the Ministry of Health. The local hospitals customize their tender in accord with the Ministry of Health basic schedule and the needs of the medical specialties offered by their clinical departments. A notional tender fee is required on the submission of both provincial and hospital tenders. Tender intervals may vary from 6 months to 1 year, and in some circumstances may be extended up to 2 years. Unlike hospital tenders, provincial tenders are let by name only, with no guarantee as to the volume of medicines that may be used. Provincial tenders have been established since 2006 with the objective being to achieve economies of scale in the tender process and also to simplify administrative processes and their attendant costs. Inpatients will be charged at hospital procurement price with no mark-up.

Outpatients can buy medicines from retail medicine outlets or hospital pharmacies. Accounting for 60–70% of retail pharmaceutical market share was more than 1000 public hospital pharmacies, and the rest 30–40% belongs to private pharmacies and other retail medicine outlets [48]. Pharmacists with a university degree and 5 years of experience can be licensed to operate private pharmacies. In remote areas, assistant pharmacists are able to apply for licenses. By law, licensed pharmacists must always be physically present when the pharmacies are open for business. In practice, licensed pharmacists are not always on duty [9].

The current pharmaceutical supply chain needs reorganization. The many layers within the distribution network, each contributing a compounding mark-up along the supply chain, serve to inflate the final price of medicines to patients. Unnecessary duplication in manufacturing, importing, and trading medicines leads to fierce counterproductive competition for an uneconomic share of an increasingly shrinking market [40].

5.6 Medicines Financing

5.6.1 Medicines Expenditures in General

Multiple policy reforms directed at mobilizing different resources for healthcare since 1989 have resulted in a fundamental transformation of Vietnam's health financing system. Vietnam's public funded health services have shifted to a mixed health financing system [44]. The structure of health financing has recently improved with a higher proportion of public health expenditure (i.e., General Government Expenditure on Health) and reduced private expenditure [37]. In 2008, the proportions of public and private health expenditure were 38.5 and 61.5% of total health spending, respectively [53].

Different existing data sources confirm that medicines account for an important share of the total health expenditure in Vietnam. Data from the National Health Account of Vietnam show that from 2005 to 2007, medicines expenditure ranges from 40 to 50% of all expenditure on health, much higher than the average of 30.4% in the low-income countries in 2006 [28]. Commercial data show a lower share for the period from 2013 to 2014 in Vietnam, yet still ranging from 32.5 to 34.4% of the total health expenditure and forecast an increasing trend for the period 2015–2019, ranging from 35.7 to 39.7% [3]. In absolute term, the total medicines expenditure increases at an average of 18% annually, growing from USD 472.3 million in 2001 to USD 2.4 billion in 2011. It makes the per capita spending on medicines increase from USD 6.0 to USD 27.7 during this period [36]. While increase in medicine consumption plays a role, rising medicine prices have been reported to contribute substantially to this increase [57].

Financing for medicines mainly comes from households' out-of-pocket payment, accounting for 72% of the total medicines expenditure, of which 58% was for self-treatment medications and 14% was for prescribed medications [36]. Increasingly important was public health insurance, accounting for 17%, whereas state budget financing and other sources account for the rest of 6% and 5%, respectively. Public health insurance pays for medicines in the MOH's main medicines schedule prescribed by hospital physicians. State budget pays for medicines in national priority programs, including free medicines for tuberculosis, HIV/AIDS, schizophrenia, and epilepsy [36].

5.6.2 Pharmacoeconomics, Medicines Pricing, and Access

Given that medicines are one of the single, largest cost components of Vietnam's healthcare system, sound medicine pricing policies are critical to keep the cost of medicine within sensible limit and improve access to essential medicines. Our previous studies have provided comprehensive analyses of the medicine pricing policy reforms and the impact of the reforms on pharmaceutical prices and accessibility

[38–40, 42]. In brief, following the shift toward a market economy, Vietnam has allowed pharmaceutical companies to set prices of their products based on market forces, subject to stabilization by the state. A number of legislative and regulatory reforms have been introduced to regulate medicine prices in Vietnam, which were intended to ensure transparency of prices along the supply chain, through price declaration and publication of price information. The initiatives, however, have been less successful than expected because they did not address the need for reasonable prices or the need to differentiate between declared, published, and selling prices. Further, the provisions were not routinely monitored or effectively enforced. The medicine pricing policies are still in the start-up phase, and there is currently no requirement for Health Technology Assessment to support medicine pricing [42].

The suboptimum medicine pricing regime means that medicine prices were high in Vietnam. Adjusted for purchasing power parity, the prices to patients in the public sector were 11and 47 times the international reference price for the lowest priced generics and originator brand medicines, respectively [38]. Measuring affordability as the number of days' wages needed by the lowest paid unskilled government worker to purchase a course of treatment for an acute disease or a month's treatment for a chronic disease, a worker would have had to work 0.7 days to treat an acute respiratory infection with the lowest priced generic amoxicillin (250 mg three times daily in 7 days), but would pay 15.9 days' wages with lowest priced generic ceftriaxone (1 vial, 1 g daily in 7 days) in the public sector. Medicines, therefore, were unaffordable for the lowest paid unskilled government worker, and even less so for the population who earned below this benchmark. Compared to countries in the Western Pacific Region, medicines in Vietnam were much less affordable, causing difficulty in access [38, 40].

5.6.3 Generic Medicines

Generic medicines with proven safety and efficacy represent a key strategy used by governments and third party payers to contain the cost of healthcare and improve access to existing medicines [41]. Vietnam adopted a National Drug Policy in 1996, but there were no generic medicines policies embedded. Some components of a generic medicines policy, however, have been provided in the Law on Pharmacy No. 34/2005/QH11, allowing for medicine substitution (Article 27.c) and encouraging the purchase of domestically produced medicines with cheaper prices for public procurement purposes (Article 49.2.a). The Minister of Health decision No. 04/2008/QĐ-BYT of February 1, 2008 regarding regulation on prescribing and prescription-only medicines stipulates the requirement of prescribing doctors to include the generic name on the prescription.

In 2009, an Aide Memoire on Strategic Collaboration in Pharmaceuticals was signed by WHO and the MOH of Vietnam, which mentioned a strategy to develop and promulgate a national generic medicines policy to ensure affordability of safe and quality medicines [49]. The Prime Minister Decision No. 68/QD-TT of January

10, 2014, approving the strategy for the development of Vietnam pharmaceutical sector in the period up to 2020 and a vision to 2030, also emphasizes the focus on investment to develop generic medicines production in Vietnam. However, a comprehensive generic medicines policy with strong regulatory requirements in combination with incentives for the development of the generic markets, acceptance, and rational generic medicine use has not been implemented, although it is proposed in the MOH proposal of a new National Medicines Policy for the period up to 2020 and a vision to 2030 [36].

Barriers to increasing generic medicine use include mistrust in generic medicines in terms of quality, efficacy, and safety among physicians, pharmacists, and patients. While Circular No. 44/2014//TT-BYT on regulation of medicines registration has alluded to the requirement of bioavailability and bioequivalence data regulated by Circular 08/2010/TT-BYT, there have been only 12 active substances out of about 1500 required bioequivalence data submission. Limited assessment of bioequivalence as a regulatory requirement in generic medicines registration and lack of appropriately skilled inspectors and monitoring to ensure the quality of generic medicine products contribute to the mistrust [41]. Lack of knowledge of generic medicines and misconceptions that a cheaper price equates to poorer quality also contributed to low acceptance of generics. Vietnam did not have any financial incentives to promote prescribing of generic medicines [41], whereas promotional incentives from pharmaceutical industries for prescribers to recommend more expensive branded products are prevalent. In addition, the suboptimal pharmaceutical pricing regimes led to some generic medicines being more expensive than their corresponding originator brands [40].

5.7 Medicines Use

5.7.1 Medicines Use in General

Post 1989, expenditure on medicines markedly increased. Per capita medicine consumption increased from USD 0.5 in 1986 [16] to USD 16.45 in 2008 [14]. Nevertheless, medicine consumption represents only 1.4% of Vietnam's GDP [2]. Moreover, the increase in per capita medicine consumption has not been accompanied by a rational use of medicines. Self-treatment, lack of regulation of the pharmaceutical market, and a lack of information infrastructure needed for optimal use of available resources have all resulted in the irrational use of medicines and wasteful expenditure by customers who are unable to assess their quality [9, 54].

Self-medication continues to be the most common response to illness in Vietnam. It is estimated that two-thirds of people rely on self-medication when they get sick [17, 18, 26], with private pharmacies becoming the first, and often only, contact with health services. Dramatic increases in self-medication have arisen because of laxity in pharmaceutical law enforcement. "Prescription-Only" medications are freely available for direct purchase, contrary to the law with little accompanying

information relevant to their use. Antibiotics are the "Prescription-Only" medicines, which are most frequently purchased from private pharmacies without prescription or adequate user instruction [11–13]. Use of pharmaceuticals through self-medication is therefore often inappropriate.

The Ministry of Health has issued a number of regulations relating to private pharmacy practice designed to link pharmacies into the health system. However, a lack of, or inadequate, enforcement of regulation of the pharmaceutical market, especially in the private sector, has led to medicines frequently being dispensed by unqualified staff [51]. Consequently, the quality of pharmacy services is often substandard [7].

The use of medicines prescribed by a health worker in clinics or hospitals can be problematic. The income of health workers is directly linked to prescribing patterns, both in the private sector [24] and in the public sector [51]. This has encouraged overprescribing with little concern for clinical need. Falkenberg et al. [16] found that on average, there were as many as 3.8 medicines per prescription with a high rate of injections being common. Overprescribing is also related to the lack of an information system to document medicine-related morbidity and mortality, so that health workers are not held accountable for accidents or errors in the prescribing and administration of medicines [51].

5.7.2 Essential Medicine List, Selection of Essential Medicines, and Standard Treatment Guidelines

The schedule of essential medicines and promotion of rational use of medicines was the first element of the 1996 National Drug Policy to be implemented, with the current essential medicine list (EML, established in 2013) consisting of 466 medicines. However, EMLs were not fully utilized as the basis for pharmaceutical procurement, reimbursement, or prescribing. Instead, the MOH simultaneously developed alternative expanded lists of main medicines used in public health facilities for this purpose. The current list of main Western medicines (established in 2011) contains 957 medicines/active substances, double the number of current essential medicines. Adoption of too wide a schedule of medicines, including some that are less cost-effective, counters the basic principles of an essential medicines schedule.

Hospital Drug and Therapeutic Committees (DTC) have been established, and standard treatment guidelines and national pharmacopoeia developed. Nevertheless, the dissemination of these measures, in the absence of ongoing monitoring and supervision of prescribing practices and adherence to the pharmacopoeia, has impeded achievement of the National Drug Policy goals in promoting rational use of medicines. National standard treatment guidelines need to be updated and strengthened based on the best available evidence regarding efficacy, safety, quality, and cost-effectiveness. In alignment, the current essential medicine list should be reviewed, evaluated, and revised systematically, based on the standard treatment guidelines, taking into account the current WHO model list of essential medicines and using a collaborative approach that involves all relevant stakeholders at differ-

ent levels of the healthcare system. The EML needs to be used as the basis to develop formularies for hospitals and for procurement, and reimbursement decisions made by public health insurance authorities.

5.7.3 Prescribing Behavior in General

In alignment with literature, several groups of factors were found to have been influencing the prescribing behavior of physicians in Vietnam. The first group includes factors related to the prescriber, such as physicians' knowledge, skills, attitudes, and predisposition [27, 47]. In the past, the lack of up-to-date medical knowledge led to the situation that physicians often prescribed medicines that were no longer used, or had even been withdrawn by the manufacturer as in the case of Mexaform (clioquinol) for the treatment of simple diarrhea [55]. More recent studies show that due to lack of knowledge and to protect themselves from legal issues of treatment failure, many doctors *"choose broad spectrum antibiotics"* for any infection *"to cover everything"* [40].

The second group is related to patients. There was evidence that patients sometimes demand medicines, which they believe to have better efficacy than those that are prescribed. Preference for, and/or aversion to, injections or oral dosage forms of medicine is quite common in Vietnam [16].

The third group, system factors, include pharmaceutical policies, reimbursement, formularies, practice organization, and pharmaceutical company promotion [27, 47]. Because physicians work in a regulated system, their medical practice is influenced by government policies and rules and/or regulations of the institutions and associations to which they belong. For example, in inpatient treatment blocks, prescribed medicines were limited to the hospital formulary list and the availability of medicines in hospital pharmaceutical departments. Having to seek prior approval for prescribing expensive medicines with an asterisk mark on the reimbursement medicines schedule has been also reported to deter Vietnamese physicians from prescribing those medicines [40].

5.7.4 Medicines Promotional Practices

The pharmaceutical industry with its direct marketing activities is alleged to be an influential factor in inappropriate prescribing [1, 19]. This is also true in Vietnam where the income of health workers was linked to prescribing practice [24, 51]. A comprehensive study examining the relationship between medicines promotion practices and prescribing behavior in Vietnam shows that economic survival pressures in an imperfectly competitive market forced both pharmaceutical companies and prescribers to be inextricably linked financially [40]. In many cases, this led to unethical practices in the prescribing of medicines, based on supply-driven demand for private gain, rather than on evidence-based clinical need. Individual factors such as professional ethics and personal value influenced prescribers' behaviors and their

response to inappropriate offers of informal payments. However, entrenched or intractable systemic issues including lack of transparency and accountability and poor legislative enforcement emerged as important factors perpetuating unethical practices. The magnitude of reported inappropriate behavior varied across geographical regions, sectors, and prescribers' specialties [40].

5.7.5 *Role of Pharmacist*

A large proportion of Vietnamese patients self-medicating or consulting directly with pharmacies makes pharmacies and other medicine outlets be the most frequently used healthcare facilities, accounting for about two-thirds of all health service contacts [58]. Meanwhile, the number of medicine outlets increasingly grows. In 2009, there were 39,172 medicine outlets (including 9066 private pharmacies) [14], and the number increased to more than 40,000 in 2011 (including nearly 12,000 private pharmacies) [15]. In addition to pharmacists working in private pharmacies, there are pharmacists (university or postgraduate level), intermediate pharmacists, and assistant pharmacist (secondary school level) working in pharmaceutical departments/outlets of public healthcare facilities, including 974 hospitals, 781 regional polyclinics, and 10,917 commune health stations. The GPP has been implemented following the Decision No. 11/2007/QD-BYT of January 24, 2007 to improve the quality of pharmacy services, with the role of pharmacists being not only a quality medicines supplier but also a communicator, a supervisor, and a health promoter involving ineffective medication therapy management.

In practice, although private pharmacies have grown and taken over a large proportion of primary healthcare as first-line medical care providers, the regulatory system has not been able to keep up with this rapid change [25]. Lack of human resource for monitoring and regulation enforcement means that licensed pharmacists are not always physically present when their pharmacies are open for business. Many private pharmacies, whose owners are public servants and licensed for after-working time only, still operate their pharmacies during working hours [9]. Dispensing of prescription-only medicines without a prescription is a common practice in private pharmacies [2]. Meanwhile, clinical pharmacy is fledgling, and the role of hospital pharmacists is mainly for logistics, rather than to engage in pharmaceutical care and quality use of medicines [40].

5.7.6 *Pharmaceutical Care Interventions and Assessment of Community Pharmacy Practice*

From government perspective, implementation of GPP is the only intervention to enhance the role of pharmacists in pharmaceutical care and to improve the quality of pharmacy services. However, the GPP implementation is slow. Two years after the launch of GPP, by March 2009, only 5% of private pharmacies (444 pharmacies)

met GPP standards [14]. More recent data from provincial health bureau reports show that by December 31, 2010, there were 3455 private pharmacies having been granted a GPP certificate, accounting for about 30% of the total private pharmacies in the country. One of the reasons for slow implementation of GPP in private pharmacies is that the pharmaceutical sector regulations have not been sufficiently enforced. There have been no financial benefits for private pharmacies in return for accreditation and compliance with GPP. In fact, GPP private pharmacies that are required to adhere to GPP requirements such as the convention of prescription-only medicines are disadvantaged in competing with non-GPP private pharmacies, which commonly follow no such conventions [40]. To date, there has been no study assessing the impact of GPP implementation on the pharmacy services in Vietnam.

While the government focuses on the implementation of GPP, some nongovernment organizations and researchers have examined different interventions including educational and training methods, peer influence and regulatory enforcement, or the combination of these interventions [8, 10, 32]. The authors found that providing training, especially training in combination with multicomponent interventions, improves community pharmacy practice. These intervention studies together with a number of other studies assessing community pharmacy practice in Vietnam have indicated the shortcomings in pharmacy practice in terms of questions asked, advice given, and appropriate medicines dispensed, as well as limited involvement in preventive services and a high degree of discrepancy between pharmacy staff stated intentions and practice [7, 9, 11–13, 43, 45]. One of the reasons for low quality of pharmacy service in community pharmacies is the absence of the pharmacist in charge. A study shows that in up to 76% of community pharmacies in Vietnam, the pharmacist in charge was not present during working hours [29].

5.7.7 Medicines Use Research

A few studies on medicines use in Vietnam have been undertaken. A recent systematic review on irrational use of medicines in China and Vietnam identifies 29 studies and shows that overall the medicines use research in Vietnam was of high quality (scoring 7.86 out of 10 on average), with the majority (66.5%) being cross-sectional/case–control studies [30]. Twenty-seven studies (93.2%) were peer-reviewed publications, and 62.1% were published during the period from 2009 to 2013. Much of this work studied pharmacy practice with a focus on diarrhea management, pneumonia susceptibility, and antibiotic overuse. Eighteen studies (62.1%) looked at patients and general population, while clinicians (prescribing) and pharmacy staff (dispensing) were examined at 44.8% and 31.0%, respectively. Medicines use research in Vietnam mainly used rural setting as study sites (51.7% using rural areas and 20.7% examining both rural and urban areas compared to only 27.6% investigating urban areas). Different data collection methods have been used with qualitative interviews accounting for 34.5%, population-based survey (29.4%), pharmacy survey (24.1%), healthcare facility survey (17.2%), prescription survey (13.8%),

and medical record review (3.4%) [30]. However, other existing data sources including commercial medicine utilization data (e.g., IMS Health), sale data from pharmaceutical importers, manufacturers, wholesalers, and especially reimbursement data have not been used in medicines utilization research in Vietnam.

5.8 Summary and Way Forward

Vietnam's transition from a socialist economy to a market-based economy has presented a number of challenges for its healthcare system. Free access to healthcare, including medicines, has been gradually replaced by a system of direct payment by patients. Increased reliance on market mechanisms has led to relative neglect of social mandates and a surge in healthcare costs. The government has introduced a number of pharmaceutical policies, aiming to address these challenges and increase access to affordable healthcare. Nevertheless, the regulatory system has not been able to keep up with the rapid changes in the healthcare system. In addition, the existing regulations have not been sufficiently enforced.

A range of policy measures and changes are required to improve access to medicines in Vietnam. Short-term recommendations include amendments to pharmaceutical policies, with better enforcement of current regulations. Medium-term measures include the public health insurance system taking an active role in price setting, pooling procurement through a national tendering procurement system, and reform of the domestic market through rationalization with appropriate capital and technological investment to achieve improved efficiencies and economies of scale. Long-term goals include health system improvements to address poor governance, low remuneration of prescribers, with additional measures to limit the scope for corrupt practices.

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Part II
Upper Middle Income Countries

Chapter 6
Pharmaceutical Policy in Argentina

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Abstract The Argentinian health system consists of three subsectors: 46.4% of the people have health coverage in the social insurance subsector; 36.1% in the public subsector; and 5.1% have voluntary private insurance. The country is the fourth largest pharmaceutical market in Latin America and has a considerable production capacity. Argentina's pharmaceutical policies regulate all issues related to access, quality, and rational use of medicines, except pricing. Argentina has taken measures to harmonize national regulations with international standards including regulations on clinical trials, good manufacturing practices, and bioequivalence and bioavailability

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standards. Recently, the National Medicines Traceability System was implemented aiming to control counterfeit medicines. Regarding access to medicines, the *Remediar* Plan, implemented in the health system's public subsector, has had positive redistributive impacts. However, Argentina still faces challenges to provide equitable access to medicines because of the huge fragmentation of the health system and the existence of different lists of essential medicines for each health system subsector. Argentina has also taken measures to encourage rational use of medicines, such as the promotion of prescription and dispensation of generic medicines; the definition of the essential medicines list for the public subsector; and the development of treatment guidelines for the diseases covered by the social insurance subsector. Moreover, a law is currently under discussion for the creation of a National Health Technology Agency. The research on medicines use needs to be strengthened in the country. Although some initiatives been undertaken by the academics and professional organizations and there are few studies available in the scientific literature.

6.1 The Health System of the Country (Health System and Health Indicators)

Argentina is a federal republic located in South America. The country is subdivided into 23 provinces and one autonomous city, Buenos Aires, which is the country's federal capital. The provinces and the capital have their own constitutions, but all existing under a federal system [6]. Argentina ranks third in South America in total population, and is also one of the oldest-population countries in the region where 10.2% of the population are 65 years old or over, 25.5% are 0– 14 years old, and 64.3% between 15 and 64 years old [35]. Other demographics and health indicators can be found in Table 6.1.

In 2012, the main causes of death in Argentina were ischemic heart disease (15.9%), stroke (9%), lower respiratory infections (6.8%), chronic obstructive pulmonary disease (3.5%), trachea, bronchus, lung cancers (3.4%), diabetes mellitus (3%), hypertensive heart disease (2.8%), colon and rectum cancers (2.5%), kidney diseases (2.4%), and cirrhosis of the liver (2.2%) [73]. Additionally, the heaviest burden of disease, in Years of Life Lost, was related to noncommunicable diseases (71%) followed by communicable diseases (16%) and injuries (13%) [74].

The Argentinian health system currently consists of three subsectors. The public subsector corresponds to the public health system and the Federal Program *Incluir Salud*. The social insurance subsector comprises the *Obras Sociales,* and the National Institute of Social Services for Retirees and Pensioners (INSSJyP). The private subsector corresponds to voluntary health insurance by direct payment or through the *Obras Sociales* [2, 59].

According to the 2010 census, 46.4% of the population had health coverage by affiliation to the *Obras Sociales* (including INSSJyP), 10.6% had coverage by a private insurance company through the *Obras Sociales* (*desregulados – unregulated*

Table 6.1 Demographics and health indicators

Indicators	
Population (inhabitants) (2013)[a]	41,446,246
GDP per capita (current USD) (2013)[a]	14,715.2
GDP per capita PPP (2013)[a]	Not Available
Gini index (2011)[a]	43.6
HDI Rank (2013)[b]	0.808
Life expectancy at birth (2012)[c]	76
Healthy Life expectancy (2012)[c]	67
Under-5 mortality per 1000 live births (2013)[c]	13
THE as % of GDP (2013)[d]	7
Government expenditure on Health as % of THE (2013)[d]	68
Private expenditure on Health as % of THE (2013)[d]	32
Government Expenditure on Health as % of general government expenditure (2013)[d]	32
Government expenditure on health per capita PPP (2013)[d]	1725

Sources:
[a]World Bank [107]
[b]United Nations Development Programme [102]
[c]World Health Organization [108]
[d]World Health Organization [109]
Abbreviations: *GDP* Gross Domestic Product, *HDI* Human Development Index, *THE* Total Health Expenditure, *PPP* purchasing power parity value

affiliation), 5.1% had voluntary private insurance (prepaid medicine), and 1.8% had coverage by state health programs or plans. The other 36.1% did not have health coverage in any other way and are dependent on the public subsector for medical attention [35].

In the public subsector, each of the 23 provinces and the Autonomous City of Buenos Aires is responsible for providing healthcare services in their own territories. Healthcare services are provided by public hospitals and healthcare units, which are financed through national, provincial, and municipal resources. National regulations related to the health system are not binding in the provinces. This is the reason why the National Ministry of Health, within the Federal Health Council (COFESA), negotiates the implementation of national regulatory measures with the provincial ministries or secretaries of health. In addition, the Federal Program *Incluir Salud* as a public health insurance system guarantees access to health services for mothers with seven or more children, disabled people, and adults over 70 years old, and Noncontributory Pensions (PNC) holders [48]. Although being organized at the national level and operating under the aegis of the National Ministry of Health, these health services are provided by the provinces [100].

The social insurance subsector consists of about 280 national *Obras Sociales* (regulated by Law 23.660 and Law 23.661), armed forces, universities' *Obras Sociales*, and the INSSJyP. All of them are regulated by the National Ministry of Health and the Superintendence of Healthcare Services.

On the other hand, the provincial *Obras Sociales* depend on and are regulated by the Ministry of Health of each province [63, 93]. From their creation in 1940 until 1993, the national *Obras Sociales* were associated with different industrial sectors that had a monopolistic right over the formal labor force of each sector. In 1993, the deregulation of the *Obras Sociales* [52] broke the monopoly allowing workers to choose an insurance fund of their preference, including the option for private insurance companies. The deregulation also allowed the *Obras Sociales* to hire private insurance companies to manage their resources and healthcare services [2, 87].

The national social health insurance is funded by compulsory payroll deductions from employees (3%) and employers (6%) [63]. In Argentina, there are almost 300 *Obras Sociales*. The number of beneficiaries per entity varies between 3000 and more than one million. Almost 70% of the affiliates concentrate in only 30 *Obras Sociales*, and the distribution according to age and gender of the population among these *Obras Sociales* is heterogeneous [93].

The INSSJyP is funded by a portion of the compulsory payroll deductions from employees, income-dependent retirement holders (3–6%), and national resources [59]. The provincial social health insurance is funded by compulsory payroll deductions from the civil servants (3–5%) and contributions of the provincial governments in their capacity as employers (4–6%).

The private subsector consists of private insurance companies of diverse nature (commercial societies, civil associations, for-profit or not-for-profit organizations) called *empresas de medicina prepaga* (prepaid medicine companies). These companies concentrate in bigger cities and focus on the high-income population, and the healthcare services are provided by private facilities [93]. Affiliation to a private insurance company can be in two ways: (a) by the *deregulation* mechanisms, that is, the person is affiliated to an *Obra Social* that has an agreement with a private insurance company or (b) by a voluntary private insurance that can be hired by an individual or a company. In the case of the *deregulation*, the *Obras Sociales* transfers part of the compulsory payroll deductions to the insurance company and the user must pay an additional premium and copayments to get access to the healthcare services.[1] In the case of voluntary private insurance, the person or company hires the service directly from the insurance company.

6.2 Pharmaceutical Situation of the Country (Key Statistics, Pharmaceutical Industry, Import–Export Trade)

Argentina is the fourth pharmaceutical market in Latin America behind Brazil, Mexico, and Venezuela [57]. The country has a solid industrial base consisting of 160 pharmaceutical industrial facilities of national capital and 30 of them are foreign capital. Some of them are certified by health authorities in developed countries, for

[1] In Argentina, the people that choose this type of affiliation are called *deregulated affiliates.*

instance, the US Food and Drug Administration – FDA (USA), the European Agency for the Evaluation of Medicinal Products – EMEA (EU), and the Therapeutic Goods Administration – TGA (Australia). About 230 laboratories supply the pharmaceutical market in Argentina. These laboratories are engaged in the production of a wide range of products to meet the demand of the domestic and foreign markets [62].

In 2014, national capital firms sold 66% of the medicine units, which corresponds to 60% of the sector's turnover, while foreign capital firms sold 34% of the units, representing 40.0% of the turnovers. Most capital firms are subsidiaries of multinationals from the United States, Germany, and Switzerland. Although the locally manufactured medicines (70,5%) represent most part of the total sales in domestic consumption of medicines, the participation of imported medicines in the market has increased in the last years, from 6.9% in 1994 to 19.3% in 2000 and 29.5% in 2014. This growth is a consequence of the increase in importation of innovative biotechnological medicines for the treatment of complex and expensive diseases such as multiple sclerosis, rheumatoid arthritis, and cancer [62].

Exports also increased by 217.5% in the period 2003–2014, which is equivalent to a cumulative annual growth rate of 11.1%. However, in 2014 exports dropped 7.3% compared with the rate recorded in 2013, reaching a value of US $ 845.9 million. Measured in medicine units, exports fell 1.5%, while imports rose 1.1% in 2014 in comparison with 2013. It is worth noting that the volume traded in units showed positive balances from 2003 due to a better placement of the national products abroad [62].

On the other hand, the supply of pharmaceuticals in Argentina is divided into three segments: innovative products, licensed products, and multisource products (similar branded, similar unbranded, and generic). Branded medicines (innovator medicines and branded generics) represent 90% of the market in terms of values; prescription medicines represent 89.7% in terms of values, and 74.9% in terms of units [62].

Argentina is one of the few countries in Latin America that has state-owned pharmaceutical manufacturers of medicines. The country has 39 public labs conducting pharmaceutical research in 13 of its 24 provinces [64]. However, the production capacity is highly variable among these companies. In order to strengthen the public medicine production and make public pharmaceutical industries an alternative for supplying the national health programs, the National Network of Public Pharmaceutical Industries was created in 2007 [89].

Lately, additional measures to consolidate the public production were taken. Among them, Law 26.688 recognized "the research and public production of medicines, pharmaceutical ingredients, vaccines and medical devices" as of national interest [33]. Law 27.113 [34] recognized "the activity of public production of pharmaceuticals" as of national and strategic interest. These public pharmaceutical companies belong to national, provincial and municipal governments, the Autonomous City of Buenos Aires, the armed forces, and the public universities. In addition, Resolution 2011/2015 transferred the National Programme for Public Production of Medicines, Vaccines and Medical Products under the National Agency of Public Laboratories (ANLAP) – a decentralized body in the orbit of the Ministry of Health.

6.3 Regulatory Environment of the Country

The right to health is currently recognized by the National Constitution because of the adherence of Argentina to international treaties of human rights such as the Universal Declaration of Human Rights (UDHR) and the International Convention on Economic, Social and Cultural Rights (ICESCR), which are considered of constitutional status. Since Article 25 of the UDHR and Article 12 of the ICESCR recognize the access to essential medicines as part of the right to health, the National Constitution also protects the right to essential medicines. Article 42 of the National Constitution also provides that "consumers of goods have the right to the protection of their health and safety, and to adequate and accurate information". In this way, the National Constitution provides that these rights must be recognized as rights of consumers and beneficiaries of the Argentinian Health System.

In Argentina, there is not an official National Medicines Policy but a group of pharmaceutical policies. The Federal Health Plan has some guidelines and also standards and laws related to pharmaceutical policies and medicine provision programs to improve the access to medicines (Table 6.2). Moreover, the Ministry of Health has a Medicines Committee that develops and discusses policies, which needs to be implemented.

6.3.1 Medicines Regulatory Authority

The Argentina's Drug Regulatory Authority was created by Law No. 16.463/1964 under the name of National Institution of Regulation of Drugs and Medicines. It was later called the National Institute of Pharmacology and Food Sciences (INFyB) and then National Institute of Medicines (INAME). In 1992, the creation of the National Administration of Drugs, Food and Medical Technology (ANMAT) as a decentralized entity was a milestone in the licensing and monitoring of medicines in

Table 6.2 Pharmaceutical policy aspects covered in Argentina

Aspects of policy	Covered	Aspects of policy	Covered
Essential medicines selection	Yes	Pharmacovigilance	Yes
Medicines financing	Yes	Rational use of medicines	Yes
Medicines pricing	No	Human resource development	Yes
Procurement	Yes	Research	Yes
Distribution	Yes	Monitoring and evaluation	Yes
Regulation	Yes	Traditional Medicine	No

Source: PAHO Pharmaceutical Profile 2010 (Argentina, Ministry of Health [50])

Argentina. Currently, the ANMAT is in charge of the protection of the human health by ensuring efficacy, safety, and quality of the medicines, food, and medical devices in the whole country. In this sense, the ANMAT is responsible for licensing, monitoring, and overseeing these products and also controlling and overseeing medicine producers and importers. In 2011, the ANMAT was recognized as the National Regulatory Authority of Regional Reference of Medicines by the Pan American Health Organization (PAHO) [27].

6.3.2 Marketing Authorization

In 2010, 55,664 pharmaceutical products were licensed in Argentina [50]. In order to obtain marketing authorization for a new medicine, the producer or importer must submit to the ANMAT a set of documentation of toxicological and pharmacological studies in animals and clinical trials data to support the evidence of safety and efficacy of the drug.

In case of a multisource medicine with an active pharmaceutical ingredient previously licensed, there is a simplified procedure that does not require all the abovementioned tests (Art. 3rd – final part, Decree No. 177/93) [5]. The medicine producer and/or importer must be authorized, in the first instance by the Jurisdictional Health Authority. In 2012, Provision No. 4622/2012 regulated the licensing of medicines for rare diseases, allowing a fast-track process considering only the evidence of clinical studies phase I or II, and requires case-by-case assessments [20]. A summary of the marketing authorization regulations can be found in Table 6.3.

6.3.3 Intellectual Property

Argentina is a member of the World Trade Organization. Although the country has a patent law, the National Legislation has been modified to implement the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Based on the TRIPS, the national law includes flexibilities and safeguards. These flexibilities are compulsory licensing provisions that can be applied for reasons of public health, Bolar exceptions, as well as provisions related to parallel importing.

The country has been engaged in initiatives to strengthen its capacity to manage and apply intellectual property rights so as to contribute to innovation and to promote public health. Additionally, there are legal provisions on data protection for pharmaceuticals (Art. 39.3 of the TRIPS Agreement). Until now there are no legal provisions on patent extension, or linkage between patent status and marketing authorization [50].

Table 6.3 Marketing authorization/registration laws and regulations

Legal basis	Scope	Reference
Law No. 16.463	Provisions on the import and export of all pharmaceutical preparations. This law established scientific and sanitary criteria for approval and marketing authorization of medicines, including the identity of the active pharmaceutical ingredient, the evidence of the pharmacological effect, the meeting of the quality specification of the Argentinian National Pharmacopeia or other internationally recognized bodies. In addition, this law provides the criteria of proven efficacy, security, therapeutic, scientific, economic, or technical advantages, or maintenance of useful therapeutic purposes in line with scientific advances.	[29], p. 463
Decree No. 150/1992	Regulations for the marketing authorization, preparation, distribution, prescription, and marketing of pharmaceutical products (imported and exported). This decree aimed to ensure greater competition in the market and the entry of new active ingredients to the country. In this way, it created a fast-track registration of medicinal products imported from countries with a high level of health surveillance. The decree also kept this fast track registration for products similar to those already licensed in Argentina and in countries with a high level of health surveillance. Amendments: Dec. No. 968/1992, Decree No. 1890/1992, Decree No. 177/1993, Decree No. 1528/2004; Resolution No. 452/2014-MEFP & 1227/2014-MS.	[9], p. 92
Decree No. 177/93	This decree establishes requirements for obtaining marketing authorization. Some of these requirements include the product description with its defined and verifiable formula, active ingredient identity, methods of analysis, manufacturing processes, bioavailability information and evidence of its efficacy and safety (relative innocuousness). Amendments: ANMAT Resolution No. 5755/1996; ANMAT Resolution No. 6897/2000; ANMAT Resolution No. 3595/2004	[51]
ANMAT Resolution No. 4622/2012	This resolution provides for pharmaceutical licensing for rare, severe, low-prevalence diseases that poses a high burden for the family environment and the health system (orphan medicines).	[19]

MS Ministry of Health, *MEFP* Ministry of Finance

6.3.4 Manufacturing and Quality Control

According to the ANMAT, medicine is "any preparation or pharmaceutical product used for the prevention, diagnosis and/or treatment of a disease or condition, or to modify physiological systems for the benefit of the person to whom it is given" [9].

As stipulated in Provision No. 2819/04 [12] and Provision No. 2372/08 [15] of the ANMAT, the pharmaceutical industry must comply with the Good Manufacturing Practices and Control guidelines adopted by the World Health Assembly in 2003. More recently, in 2013, Provision No. 5569/2013 [23] provided inspectors with a

Table 6.4 Manufacturing and quality control regulation

Legal Basis	Scope	Reference
National Pharmacopoeia of Argentina	Provides for an official code describing specifications relative to origin, preparation, identity, purity, valuation, and other conditions that ensure consistency and quality of the medicines in Argentina.	[24]
ANMAT, Disposition No. 2819/04	Approves Good Manufacturing Practice guide for producers and importers/exporters of medicines.	[12]
ANMAT, Disposition No. 2372/08	Approves the Good Manufacturing Practice guide for inspectors for medicinal products and classification of noncompliance with Good Manufacturing Practices	[15]
ANMAT, Disposition No. 4394/2013	Approves the rules of good practice applicable to the Bioanalytical Laboratory Centres for Bioavailability/ Bioequivalence.	[25]
MERCOSUR/GMC XLVII/RES. No. 50/02	Provides for procurement outsourcing services for pharmaceuticals in MERCOSUR with the objective of guaranteeing control and sanitary inspection of pharmaceutical products produced under the system of outsourcing in MERCOSUR.	[91]

Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. Such legal provisions establish that importers, wholesalers, and distributors have to be licensed and they have to comply with the Good Distributing Practices.

The ANMAT also regulates the bioequivalence of multisource medicines. The regulation, in 1999, also included high-risk medicines (e.g., anticonvulsants with a narrow therapeutic range), antiretroviral drugs, immunosuppressants, and some antipsychotics. Provision No. 4326/2012 of the ANMAT [18] is the most recent bioequivalence regulation that adopts the World Health Organization criteria for the requirement of in vivo bioequivalence studies [1]. A summary of manufacturing and quality control regulations can be found in Table 6.4.

6.3.5 Clinical Trials

Clinical research involving humans is regulated by Provision No. 5330/1997 [10]. It establishes Good Clinical Practice guidelines in line with international standards such as the International Declaration on Human Rights, the Nuremberg Code, and the Declaration of Helsinki. These guidelines are later updated by Resolution No. 1490/2007, which incorporated the standards for clinical research of the World Health Organization (WHO) Operational Guidelines for Ethics Committees that Review Biomedical Research; the Ethical Guidelines for Clinical Trials – Council for International Organizations and Medical Sciences (CIOMS); and the Ethical Rules for Research Related to Healthcare in Developing Countries – Nuffield Council on Bioethics. This change aimed to include the recommendations of the Pan American Network for Drug Regulatory Harmonization approved by the Pan American Health

Organization in 2005 [38]. Subsequently, the Ministry of Health created the Clinical Trials Registry through the passage of Resolution No. 102/2009 [40].

The ANMAT is responsible for approving the clinical studies (phases I, II, III, and IV) and conducts inspections of the study sites and reviews the periodical and final reports sent by principal investigators to sponsors [76]. Between January 1994 and August 1997, the ANMAT approved 1892 clinical trials, 157 studies proving the bioequivalence of high-risk drugs or ARVs, and rejected approximately 100 protocols. Most of the conducted clinical trials are phase III studies (59%), followed by phase II (19%) and phase IV (18%). Phase I clinical trials are less frequent (4%). The main clinical research sponsors in Argentina are multinational pharmaceutical companies that carry out almost 60% of the studies, followed by contract research organizations (23%), domestic laboratories (11%), and independent researchers (6%) [66].

6.3.6 Pharmacovigilance and Postmarketing Surveillance

Pharmacovigilance is a "sine qua non" condition for the control and supervision of medicines, allowing early detection of adverse and/or unexpected effects in the stage of their widespread use as well as therapeutic failures as a consequence of quality deficiencies. The National Pharmacovigilance System (SNFVG) – the formal mechanism for spontaneous, voluntary and confidential reporting of suspected adverse reactions – was created in 1993 [21]. In 1994, Argentina was accepted as a member of the WHO Program for International Drug Monitoring, and it sends periodical reports on adverse events to the WHO's Uppsala Monitoring Centre (UMC) [103].

Within the structure of the ANMAT, the Pharmacovigilance Department depends on the Direction of Medicinal Products (DEM). This Department is responsible for the Central National Pharmacovigilance System that aims to detect, assess, understand, and prevent adverse effects and other problems related to medicines, including intensive monitoring of certain medicines defined by the ANMAT (e.g., intensive monitoring of clozapine) [11]. The Pharmacovigilance Department is also in charge of the inspection of all pharmacies in the country to verify appropriate implementation of the Argentinian pharmacist act [26].

Additionally, the ANMAT is in charge of the medicine control and postmarketing inspection by means of a sampling program for quality control of the medicines in the market. This program is a responsibility of the National Medicine Institute (INAME), a department of the ANMAT. Besides, since 2008, the INAME has been a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S).

6.3.7 Counterfeit Medicines

In Argentina, counterfeit medicines mean medicines with adulterated batch code or expiration date, stolen products, smuggled medicines, unregistered products, free drug samples, and expired products. With the aim to combat counterfeit

medicines, in 1997, the national health authority – the industrial pharmaceutical sector and professional associations – signed a mutual agreement to cover all aspects related to this issue. This resulted in the creation of the National Research Program of Unlawful Medicines. With the same purpose, the Public Prosecutor's Office through the Attorney General's Office, under Resolution No. 54/97, established a commission of prosecutors in order to conduct and take part in the judicial inquiry [98].

In 2008, it was estimated that 10% of the medicines on the market were fake [81] and that the counterfeit medicine market in Argentina, according to official data, were around USD$ 120 million dollars [65]. On top of that, most counterfeit and adulterated medicines are expensive and indicated for the treatment of serious illnesses such as cancer, HIV [101], and hemophilia [86].

In 2011, in order to combat these crimes, Provision 2124/2011 [16] restructured the ANMAT's organization and created the National Program for Market Control of Medicines and Medical Devices, extending the scope of the former National Research Program of Unlawful Medicines to include legitimacy control of the various medicinal products in the market. Subsequently, Resolution 435/2011 [41] established the National Drug Traceability System that ensures control and monitoring of medicines throughout the distribution chain (laboratories, distributors, logistics operators, drugstores, pharmacies, healthcare facilities, and patients) by assigning each medicine a unique barcode identification.

Later, Provision No. 3683/2011 established requirements for natural or legal persons involved in the marketing, distribution, and dispensing chain of licensed medicines to comply with the implementation of the traceability system. Furthermore, this provision instituted a database for monitoring the traceability system, which supersedes the former bar coding system. The traceability system has been implemented gradually and is based on medicine categories. The medicines included in the system are normally expensive medicines and/or mainly derived from biotechnology [17]; also narcotic medicines were incorporated in 2013 [22]. Also, the traceability system is used by the Unified Reimbursement System (SUR) within the social insurance subsector to prevent fraud involving those high-cost medicines.

6.4 Medicines Supply System and Financing

In 2015, the total pharmaceutical sales in Argentina were 6.910 billion dollars, which is equivalent to 1.13% of its GDP and 26.2% of its expenditure on health [60]. The country has no legal or regulatory provisions for medicine pricing. Although there is a free market economy in which the prices are set by the free play of supply and demand in the market, there are some voluntary pricing agreements between the government and the pharmaceutical industry [56, 78].

The government runs an active price monitoring system for retail medicines. The Ministry of Health calculates the Average Drug Price Index (IPPM) and an index of weighted prices based on the REMEDIAR Program's essential medicines list. Both

indices are monthly updated to monitor drug prices [50]. Furthermore, the Superintendence of Healthcare Services established maximum reimbursement rates for the high-priced medicines covered by the Unified System of Reimbursement (Sistema Único de Reintegro – SUR).

The results from the 2010 survey on the use of health services and expenditure on health indicated that 44% of the population's expenditures were on medicines. In comparison with 2005 survey, the population's average expenditure on medicines rose 72.79% by 2010 [80].

In the public sector, the National Ministry of Health and the provincial ministries of health normally undertake mainly public procurement for medicines. In the case of the *Plan Remediar*, which is funded by the National Government, the procurement is centralized, and the medicines are distributed directly to the pharmacies in the Primary Care Centres (CAPS) [68], where vulnerable population has free access to healthcare services and essential medicines. The *Remediar Plan* also aims to consolidate a federal supply system [8].

According to analyses of the National Ministry of health, the supply of medicines free of charge in the public sector by means of the *Remediar Plan* has had positive redistributive impact. This is shown by 22% decrease in medicines expenditure in 2010 [47]. Furthermore, it was shown that the centralized procurement system of the *Remediar Plan* can achieve prices up to 70% lower than the market, which favors savings in the pharmaceutical expenditure and encourages the local pharmaceutical production [46].

The National Ministry of Health has specific programs for funding and supplying high-priced medicines. These programs distribute medicines to the provincial health ministries or provincial referral services for the treatment of *catastrophic diseases*. The provincial ministries of health undertake public procurement to complement the national programs. Among these programs are the Medicines Bank (*Banco de Medicamentos)*, which delivers cancer medicines; the HIV-AIDS Program, which provides antiretroviral and immunosuppressants; and the High Cost Services and Low Incidence Diseases Program (PACBI). These programs offer free access to medicines for patients with no formal health coverage [100].

The PACBI is funded by part of the per capita monthly resources that the National Medical Benefit Directorate (*Dirección Nacional de Prestaciones Médicas)* transfers to the provinces. The Directorate retains the PACBI's resources and reimburses the provinces only if they present the documentation proving that the patients with the catastrophic diseases were given treatment [100].

In the social insurance sector, each national and provincial *Obra Social,* and the INSSJyP, organizes the healthcare services network within their own clinics or hospitals, and/or by hiring private (profit and nonprofit) or public institutions. For the supply of medicines, the *Obras Sociales* and the INSSJyP make agreements with pharmacies, drug stores, or companies specialized in pharmaceutical

services. The contract modalities include payments on a per capita basis and negotiation of prices by products. The beneficiaries of the social insurance sector are required copayments to have access to ambulatory care medicines. For most of the medicines the copayment is 60%, but in the case of medicines for chronic diseases the copayment is 30%, and high-priced medicines covered do not require copayments [72].

The national *Obras Sociales* and the INSSJyP must provide their beneficiaries with the basic package of healthcare services and medicines, which is called Mandatory Medical Program (*Programa Médico Obligatorio – PMO*). In order to remedy the inequality among the national *Obras Sociales* and guarantee compliance with the PMO, the Solidarity Redistribution Fund (FSR) was created. The FSR is funded by the *Obras Sociales* through mandatory contributions that vary between 10 and 20% according to the beneficiaries' salary range [63]. The INSSJyP and the provincial *Obras Sociales* do not contribute to the FSR.

High-priced medicines are financed with resources from the FSR, which are managed by the SUR and works as a sort of reinsurance against catastrophic diseases for the national *Obras Sociales* [100]. The application process for reimbursement requires the national *Obras Sociales* to submit online all the documents related to the patient's medical data, the prescription, and information from the medicine traceability system. This is to improve the transparency of the process [110]. However, according to some stakeholders, these measures have made the reimbursement process more complicated.

In the private sector, since 1996 [30], all private insurance companies must guarantee the mandatory Medical Program (PMO) to their affiliates. In contrast to the Obras Sociales, private insurance companies do not contribute to the Solidarity Redistribution Fund (FSR) and cannot request reimbursement from the Unified Reimbursement System (SUR) when they supply high-cost medicines to their affiliates. However, in the case of deregulated affiliates, the private insurance company can receive the reimbursement through the national Obra Social. If a voluntary private insurance affiliate requires a high-cost medicine, one that is not explicitly excluded from the policy, the company must buy it with its own resources without the possibility of reimbursement. Since 2013, a proposal about strategies for the reimbursement of high-cost medicines and low-incidence disease treatments has been under discussion [44].

In the last years, lawsuits have become an alternative pathway to access to high-cost medicines, especially in both social insurance and private subsectors. A patient can require a medicine that is not included in the *Obras Sociales*'s list or in the insurance policy by resorting to the judiciary system. If the court decision favors the patient, the *Obras Sociales* or the private insurance company must supply the medicine and buy it with their own resources [61]. A general overview about the financing of medicines in Argentina is shown in Fig. 6.1.

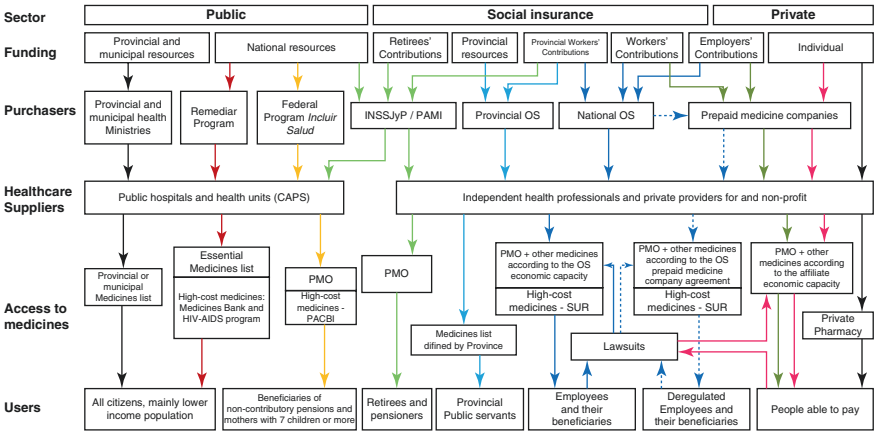

Fig. 6.1 Health system and access to medicines in Argentina (Source: Vargas-Peláez [105])

6.5 Medicines Use (Issues Impacting the Rational Use of Medicines in the Country)

6.5.1 Promotion of Generic Medicines Use

Law 25.649/2002 [31] defines the concept of *generic drugs* according to their composition. This law also regulates generic prescription and dispensing of medicines by pharmacists, and entitles these health professionals to dispense a cheaper medicine with the same active pharmaceutical ingredient, strength, dosage form, and quantity of units based on the *National Vademecum of Medicines*. The *Vademecum* is an official source of information that comprises data about all the medicines marketed in Argentina, including retail price, use restrictions, and whether the product is under the National Drug Traceability System [28].

By Decree 987/03 [54] prescribers have to prescribe according to the International Nonproprietary Name (INN); they can, however, include the trade name of the medicine in the prescription. The pharmacist is responsible for verifying the prescription validity and should advise the patient about different medicine options with the same active ingredient, and their prices. However, the pharmacist is not authorized to change the product in two situations: (a) when the physician justifies the prescription of a specific branded product or (b) if the medicine prescribed is defined by the ANMAT as not interchangeable because of its bioavailability characteristics and narrow therapeutic range. If the pharmacist does not provide information about other medicine options, he/she can be subject to sanctions in accordance with the Consumer Protection Act or Law 24.240 [4].

The ANMAT is the authority responsible for licensing the medicines and defining the list of medicines, which cannot be generically substituted by the pharmacists.

6.5.2 Selection of Essential Medicines

Argentina does not have a unique list of essential medicines as a result of the fragmentation of the health system. Likewise, the country does not have a National Health Technology Assessment (HTA) agency or health economic guidelines [58]. Consequently, the HTA activities are completely decentralized, and the definition of the medicines covered in each health system's subsector depends on different actors: the Ministry of Health, the Provincial Health Secretary, the Superintendence of Healthcare Services, the *Obras Sociales*, and private insurers (*Prepagas*). Currently, a law project aiming to create a national HTA agency (AGNET) is being discussed in the Senate. AGNET will be part of the Ministry of Health and will operate in a decentralized way. AGNET will be responsible for the assessment of health technologies and the development and implementation of clinical guidelines [49]. The initiative is supported by stakeholders such as the *Obras Sociales* and the *Prepagas*, as it will contribute to control the amount of medicines requested by lawsuits [90].

In the public sector, the *Remediar Plan* has a list of essential medicines that comprise 76 active pharmaceutical ingredients and 101 dosage forms required for primary care [42]. Although this plan is implemented by the national government, the coverage of medicines varies greatly among the provinces, depending on their development level and management capacity [93].

In the social insurance sector, the PMO package that must be provided by the national *Obras Sociales* and the INSSJyP is defined by the National Ministry of Health [53]. Although some benefits have been incorporated into the PMO in the last years (emergency hormonal contraception, assisted fertilization, and obesity treatment) [61], the medicines list has not been systemically updated since 2004 [37]. Currently, the PMO comprises more than 170 active pharmaceutical ingredients and more than 500 dosage forms. Furthermore, as the PMO is the minimal coverage package, each *Obra Social* can include other medicines according to its economic capacity. The *Obras Sociales* are free to update or not their list of coverage.

In contrast, for the provincial *Obras Sociales* the PMO coverage is not mandatory. As the provinces are autonomous, each province defines the coverage of healthcare services and medicines for their beneficiaries [93].

In the private sector, similarly to the social insurance subsector, the medicines coverage is somewhat variable. For the *deregulated* affiliates, the list of covered medicines

varies according to the agreement made between the *Obras Sociales* and the insurance company. In turn, for the voluntary private insurance the medicines coverage depends on the beneficiaries' ability to pay, but it cannot be below the PMO's coverage.

6.5.3 Measures to Promote Rational Use of Medicines

In the public sector, the *Remediar Plan* aims to strengthen the responsiveness of the primary care level through the promotion of the Primary Health Care Strategy and the rational use of medicines [8] by defining the list of essential medicines and publishing the National Formulary [42].

In the social insurance sector, particularly for the National *Obras Sociales,* the Superintendence of Healthcare Services is in charge of developing treatment guidelines for the diseases included in the SUR coverage. Furthermore, in 2013, a follow-up system for safety and efficacy of the medicines covered by the Supervisory System for Emerging Sanitation Technologies was created. In this system, the national *Obras Sociales* are responsible for collecting data related to the effectiveness and safety of the medicines financed by the SUR [45].

6.5.4 Medicines Advertising and Promotion

Only over-the-counter (OTC) medicines are allowed to be advertised in the media and after the broadcast the ANMAT carries out an inspection process [13]. Additionally, the advertising of prescription medicines can be targeted only to health professionals [14]; despite the nonexistence of a legal provision that requires preapproval for medicines advertisements, there is a national code of conduct concerning medicines advertising and promotion. The code applies to both domestic and multinational manufacturers and includes a formal process for complaints and sanctions. Adherence to it is not voluntary [50].

The regulation for medicine advertising in Argentina follows the criteria established by the WHO; however there is little regulatory compliance in practice. In an assessment of the promotional material displayed in health facilities and pharmacies, it was found that most of the material omitted important data on the rational use of medicines, such as adverse reactions, contraindications, warnings, posology, and in turn included information about off-label indications [104].

6.5.5 Pharmacist's Role

Law No. 17.565 amended by Law No. 26.567 [7] governs the exercise of the pharmacists as health professionals. This law requires pharmacists to be registered and stipulates that OTC medicines must be dispensed by pharmacists or by authorized

personnel. It also states that only the licensed pharmacies can manufacture, manage, and dispense the medicines. Public pharmacies do not sell medicines; they only dispense the medicines supplied by the public subsector of the health system [50].

In Argentina, pharmacies must be licensed and need to meet quality standards. However, the regulations are different if the pharmacy is private, public, or located in a hospital [39, 43, 55]. Furthermore, the 23 provinces and the Autonomous City of Buenos Aires are free to regulate Good Pharmacy Practice guidelines [50].

6.5.6 Research on Medicine Use

Two national surveys have been carried out and gathered information about medicine use. The 2010 survey collected data from the general population on the use of health services and expenditure on health [80] and the 2012 survey focused on the quality of life of older adults [36].

According to the 2010 survey, 69% of the population used medicines for 30 days prior to the survey. The use of medicines was more prevalent in women (75%) than in men (64%). In addition, the use of medicines increased with the age – while the percentage of people between 0 and 14 years old who used medicines during the month prior to the survey is 50.7%, this percentage rises to 86.9% with people older than 60 years. The medicines most frequently used by the respondents were those indicated for the control of pain (25.3%), cardiovascular diseases (14.1%), and the control of the flu symptoms including fever and cough (11.9%). Antibiotics corresponded to 7.9% of the medicines used, while 3.6% of the medicines were used for the treatment of asthma or allergies, 3.1% for the control of diabetes, and 2.7% for the control of cholesterol levels [80].

The 2012 National Survey on Quality of Life of Older Adults showed that 52% of the people of 60 years or older used medicines for 30 days previous to the survey; most of them were women (57%). The medicine use was higher in people of 75 years or older (57%) in comparison with people between 60 and 74 years old (50%). The results of this survey also indicated that 30% of the older adults used tranquilizers, anxiolytics, or sedatives and 8% of this use was by self-medication [36].

Initiatives by professional and academic associations encourage the development and publication of the local research. The Hospital Pharmacist Association of Argentina promotes pharmacovigilance through the Argentine Network for Safety Monitoring of Medicines and develops annual meetings for disclosure of the local research related to medicines. Meanwhile, the Pharmacology Centre at the University of La Plata (CUFAR) has recently published a new edition of the National Drug Formulary (2016). As a collaborating center of the Pan American Health Organization (PAHO), this group periodically reviews methodologies and criteria for the selection of biomedical information and medicines, and so on develops and updates the National Drug Formulary.

In a search on the Pubmed and Lilacs databases with the keywords “drug utilization study” and “Argentina”, 20 studies published from 2000 to date were identified. Seven studies investigated the use of psychotropic medicines [69, 82–85, 95, 99];

five studies analyzed the use of antibiotics in hospitals [75, 77, 96, 97, 106]; three studies explored results of public policies for improving the access to medicines [3, 67, 92]. The other studies analyzed the use of medicines at the Division of Neonatology at University Hospital [70]; the use of influenza vaccines in children under 2 years old [71] and the exposure to nonsteroidal anti-inflammatory drugs among older adult patients hospitalized for peptic ulcer disease [79]. Other studies include the use of medicines in noninstitutionalized elderly people [94]; and the design of a system of drug–drug interaction alerts [88].

6.6 Conclusion

Despite the fact that Argentina does not have an official National Medicines Policy, most of the issues related to access, quality control, and rational use of medicines have been considered in different public policies harmonized with international standards. Argentina is at the forefront in the region with its two most recent policies: the implementation of the National Medicines Traceability System to follow the medicine's route from the producer to the patient; and public policies to strengthen the state-owned pharmaceutical manufacturers. Another important advance in the country is the expected creation of a National Health Technology Agency.

The implementation of the *Remediar* Plan in the health system's public subsector is one of the most important strategies for improving the access to medicines in the country, since it has improved the redistribution of the pharmaceutical expenditure and has strengthened the bargain capability of the government. In the case of the social insurance subsector, the measures focused on high-cost medicines have also been positive towards the control of the pharmaceutical expenditures. However, the country still faces challenges to provide the population with equitable access to medicines. Some of these challenges are the fragmentation of the health system and the lack of a pricing regulation.

Rational use of medicines is also a challenge in the country. Some of the required measures include a more robust control of pharmaceutical advertising; health awareness campaigns targeted to the general public for rational use of medicines, and the strengthening of the research in this area.

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Chapter 7
Pharmaceutical Policy in Brazil

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Abstract Brazil's pharmaceutical policies have undergone significant changes in recent decades resulting in improved access, surveillance, and support for national industry. This chapter highlights the numerous challenges in upholding the right to health embedded in the Brazil's 1988 Constitution and implementing a universal health system. Difficulties include geographic diversity, epidemiological variation, and entrenched social inequalities in a continental-sized country; changing patterns of morbidity and mortality, associated with communicable and noncommunicable diseases that require low-, medium-, and high-complex medical care; and continued dependency on imported pharmaceutical products. The structure of the national health system is also discussed in detail along with the country's pharmaceutical situation focusing on past and recent regulations and results. An overview of the pharmaceutical market, including local production and manufacturing of active pharmaceutical ingredients and finished dosage forms, is provided. The "Health Industrial Complex" as a political commitment linking health system needs with industrial policies is briefly described. The chapter also highlights regulations, financing and supply systems, as well as efforts to promote the rational use of medicines and data collection systems of adverse drug reactions. Finally, we end the chapter discussing Brazil's alignment with international trends, such as the United

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Nation's 2030 Development Agenda, and the way forward for future programs and efforts. Despite ongoing challenges, medicine policies have played a central role in the Brazilian government's efforts to improve social conditions and push more than 26 million people out of extreme poverty.

7.1 Brazil's Health System

Brazil is the largest and most populous country in South America, with an area of 8.5 million square kilometers and an estimated population of 202.8 million as of 2015. More than 80% of its inhabitants are in urban areas. The Presidential Federative Republic of Brazil includes one Federal District, the seat of the Federal Government, 26 states, and 5,570 municipalities. Brazil is distributed into five culturally and socioeconomically diverse geopolitical regions: the North, the Northeast, the Southeast, the South, and the Midwest [1].

Inequalities in health, education, standards of living, and income distribution, among others, have shaped Brazil's development model over the last 40 years. This model has promoted Brazil's socioeconomic development, but has also marginalized large portions of the Brazilian population that lives in low-income communities, usually located in the large metropolitan areas. Lack of basic public services and inadequate and congested housing characterize these communities, and these are referred to as slums, shantytowns, or *favelas.*

In terms of economic inequality, the top 20% richest have an average income 17 times greater than the poorest 20% of the population [2]. The distribution of household income measured by the GINI index reached 0.54 in 2013. Despite some progress in reducing income inequality made in the last decade, a high degree of inequality still persists. The North and the Northeast regions are the least socioeconomically developed regions. In contrast, the Southeast, where 44% the Brazilian population live and 50% of the country's gross national product (GDP) come from, is the most populated and most economically advanced region. Estimated by purchasing parity power, Brazil's GDP totaled US$3.276 trillion in 2014 [3], placing the country in seventh place in the World Bank's GDP ranking, and its GDP per capita stood at US$11,614 [4].

According to the World Bank [5], from 2003 to 2013, Brazil experienced a decade of economic, social, and environmental progress, including macroeconomic stability and significant reductions in poverty and income inequality. The growth in income of the 40% poorest was higher (6.5%) than the growth in income of the total population (3.5%). During these years, more than 26 million people were lifted out of poverty, and inequality fell significantly. However, since 2013, progress in reducing inequalities stagnated due to a slowdown in the country's economic growth [5].

Among noncommunicable diseases (NCDs), diabetes and hypertension are the most prevalent in Brazil; other infectious diseases include tuberculosis, leprosy, congenital syphilis, malaria, Chagas disease, and HIV/AIDS. NCDs were

responsible for around 70% of the overall mortality in 2011 [6]. The main causes of mortality were cardiovascular diseases (including stroke), followed by cancer, external causes (car accidents and violence), and diabetes [7].

Regarding achievements in the public health system since 1990, Brazil has been implementing extensive reforms to its national health system, and this was in order to comply with the Federal Constitution, enacted in September 1988. The Constitution marked the end of the transition period to democracy that started in 1985 following 21 years of military dictatorship. The Constitution recognizes health as a citizen's right and also a state duty.

Law 8080/90 implemented constitutional health-related provisions [8], including rules for the reorganization of the national health system. This system, currently in effect, comprises three subsectors: the public subsector, known as SUS (*Sistema Único de Saúde* or Unified Health System), whose services are funded by taxpayers; the private (for-profit and nonprofit) subsector, whose services are contracted by SUS (and also known as SUS complementary) or by private funds; and the subsector of private health insurance. The vast majority of the Brazilian population, around 75%, depends exclusively on the SUS [9].

SUS is organized according to the following constitutional principles and guidelines (Art. 196 and 198):

1. *Universality* and *equality* meaning that all Brazilian citizens and residents are entitled to free access to healthcare and services necessary for promotion, prevention, and care.
2. *Integrality*, which means that SUS is composed of a large and interconnected network of public, private, and nonprofit contracted services that includes primary healthcare (PHC) and medium to complex healthcare services, including high-cost treatments.
3. *Societal participation* in the processes of formulation, control, and monitoring of health policy implementation in the three levels of government (i.e., federal, state, municipal).
4. *Decentralization of health actions and services* in order to ensure better management and greater geographical accessibility across the country and societal participation in the processes of formulation, control, and monitoring of health policy implementation in the three levels of government (i.e., federal, state, municipal).

SUS's institutional framework aims to promote and strengthen negotiations and agreement across all stakeholders, including civil society representatives. These stakeholders are involved in decision-making process and the management of the system at all three levels of government. SUS's decision-making bodies include the following:

1. The National Health Conference - a kind of national health assembly, composed of delegates of whom 50% are civil society representatives and 50% are representatives of health system workers and managers. It is organized every 4 years and adopts a bottom-up process of discussion, negotiations, and decision-making

(from municipalities to the federal level) and the election of all delegates. Its main objectives are to define health needs and priorities and to provide guidance to SUS administrators.

2. Participatory bodies (50% civil society and 50% of health workers and managers) include the federal level National Board of Health (*Conselho Nacional da Saúde*), state (*Conselho Estadual de Saúde*), regional (*Conselho Regional de Saúde*), and municipal (*Conselho Municipal de Saúde*) boards of health. Their main objective is to monitor the implementation of health policies.
3. Inter-managers commissions are the Ministry of Health (MoH, federal manager) along with the state secretaries of health and the municipal secretaries of health. Inter-managerial commissions are comprised of the following: (1) the MoH plus the Board of States Secretaries plus the Board of Municipal Secretaries (tripartite managerial commission – *Comissão Intergestores Tripartite*) and (2) Board of States Secretaries of health plus the Board of Municipal Secretaries of health (*Comissão Intergestores Bipartite* or bipartite commission). These decision-making bodies carry out negotiations, establish agreements, and define priorities and commitments.

This framework ensures that policies are defined in a unified way and their implementation is decentralized (Fig. 7.1).

It has been challenging to implement healthcare reforms in Brazil's healthcare system in the 1990s, and this is mainly due to the country's regional diversity, its sheer big size, and its vast social inequality and a growing HIV epidemic [11]. Despite these obstacles, Brazilian authorities and society adopted a rights-based system and learned important lessons that have been shared with the other countries in the region. It is important to mention that the implementation of SUS was possible, inter alia, because of the strong support the MoH received from a widespread pro-reform social mobilization, known as the sanitary health movement [12].

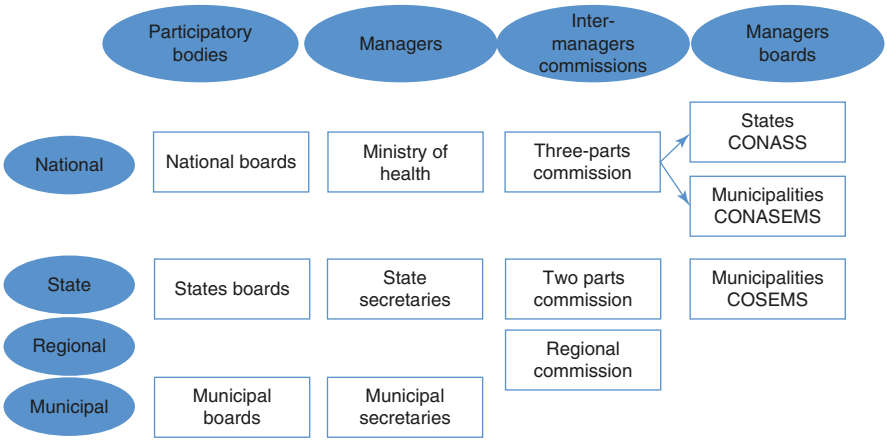

Fig. 7.1 Unified Health System (SUS) institutional decision-making framework (Source: Noronha et al. [10])

Since the early 2000s, SUS implementation and organization has prioritized PHC. The main effort in this area has been the Family Health Strategy (*Estratégia de Saúde da Familia* (ESF)), involving mobile teams of healthcare workers who attend vulnerable people from lower socioeconomic backgrounds [13], and also the latest National Health Plan reinforced this effort [14].

After 15 years of implementation, SUS has achieved significant progress, even though the path to universal coverage has faced structural challenges that must be overcome. These include socioeconomic, cultural, and interregional inequalities. Also, there is a need to strengthen inter-sectorial policies so that broader development policies could be implemented.

7.2 Health Workforce and Public Health Services Infrastructure in Brazil

There are about 933,000 employee positions in health facilities (only the ones with three or more workers were surveyed in the study) consisting of 636,000 physicians, 94,000 dentists, 163,000, nurses and 40,000 pharmacists [15]. Physicians and nurses occupy the majority of the total professional health positions. The Federal Council of Medicine reported that there are 432,000 doctors in the country as of 2015 (2.1 per 1,000 inhabitants), meaning that many physicians occupy more than one work post [16]. In general, the majority of health professionals, especially physicians, live in the big cities. There were 143,000 pharmacists in Brazil in 2010, but only 36% work in state capitals.

There are about 94,000 healthcare facilities throughout the country, and 55.3% of them are public. Most private healthcare facilities (95.6%) work on a for-profit basis, and 27.1% of them are contracted by SUS. Some specialized services, such as hemodialysis, diagnostic tests, and other outpatient services, may be provided by both the public and private sector. There are 34,000 hospital beds, 35.4% are public and 65% private [15].

7.3 Brazil's Pharmaceutical System

Medicine policies have been a concern of the Brazilian government since the 1930s [17]. In the last five decades, the state has implemented a series of policies and initiatives aimed at expanding access to medicines. In 1971, the Federal Government created the *Central de Medicamentos* (*CEME*) as a public institution to regulate the production and distribution of medicines to the Brazilian population. This was an important step forward toward the construction of the National Medicines Policy (NMP). In 1997, during the implementation of SUS and in the context of its decentralization, CEME was decommissioned.

In 1998, after almost 2 years of negotiations and discussions among main stakeholders, Brazil enacted its NMP [18]. In 2004, the first National Conference of Pharmaceutical Services assessed progress made and defined future steps to improve access and the organization of the supply of medicines across country. This resulted in formulating a National Policy on Pharmaceutical Services [19].

Currently, the Department of Pharmaceuticals and Health Products (DAF),[1] linked to the Science, Technology, and Health Products Secretariat (SCTIE/MoH), is in charge of NMP implementation through a broad range of activities, including production, procurement, distribution, use, and pharmaceutical services management.

7.3.1 Industrial Policy for Medicines

During the last 13 years, Brazil has adopted an industrial policy for medical and health products. The purpose is to integrate public policies from the MoH and the Ministry of Science, Technology, and Innovation and thus coordinate action across several ministries to stimulate technological development and strengthening Brazilian internal capacity to produce active pharmaceutical ingredients (APIs). The main objective of all these efforts is to help reduce prices of medicines within the health system. These include medicines for HIV/AIDS as well as NCDs such as cancer medicines.

This strategy includes public-private partnerships and has recently evolved into biotechnology products, with a strong role played by state-owned manufacturers. The Federal Government has devised various public policies to align industrial support for social objectives, including "Industrial, Technological and Foreign Trade Policy (PITCE)" in 2003 [20], Policy for Productive Development in 2008 [21], and plan "Brazil Greater" in 2011 [22]. All these sequential policies have enabled the constitution of public-private partnerships within the Health Industrial Complex in Brazil. This is in order to encourage the local production of APIs and final products for an agreed list of prioritized medicines. This is established and updated annually by the Ministry of Health. By the end of 2015, this policy has resulted in 98 partnerships, and it has been forecasted to produce 6 vaccines, 60 medicines, and 27 health products, involving 69 partners (19 public and 50 private manufacturers) in the near future [23]. This also represents projected cost savings of up to R$ 5.3 billion (or US$1.5 billion).

More recently, this initiative has expanded to biotechnology products and diagnostics. Considering the high costs of these products, the Health Industrial Complex in Brazil aims to increase national capacity, decreasing external dependency on imports and therefore positively impacting on Brazil's trade balance. Several papers have discussed the sustainability of these efforts [17, 24, 25], demonstrating the

[1] http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/sctie/daf

links between national development and the social and economic base centered on health, creating jobs and contributing to investment in research and development.

7.3.2 *Brazil's Pharmaceutical Market*

The Brazilian pharmaceutical market has been expanding in terms of sales and units (volume) since 2003, with turnover reaching US$ 28.1 billion in 2014.[2] The market share in generic medicines has also grown from 6.4% of the total sales in 2003 to 24.6% in 2014 [26]. This was the result of the Generics Law which came into effect in 1999 [27] (Table 7.1).

Brazil is among the countries with the largest pharmaceutical market, moving from tenth to sixth place from 2008 to 2013 [28]. As such, Brazil is among the 21 countries[3] which are defined as "pharmerging" markets by the IMS health. It is estimated that between 2012 and 2017, these countries will account for US$187

Table 7.1 Brazilian pharmaceutical market in sales (US$) and in units and generic sales, 2003–2015

Year	Total sales in billion US$[a]	Unit sales in billion (Volume)	Sales of generics in billion US$[a]	Generic sales in relation to total sales (%)
2003	4,853	1,219	312	6.4
2004	5,903	1,333	449	7.6
2005	7,954	1,374	716	9.0
2006	9,868	1,437	1,059	10.7
2007	12,180	1,518	1,523	12.5
2008	14,649	1,632	2,026	13.8
2009	15,407	1,767	2,319	15.1
2010	20,632	2,070	3,552	17.2
2011	25,717	2,341	5,258	20.5
2012	25,395	2,588	5,703	22.5
2013	26,910	2,893	6,355	23.6
2014	28,123	3,160	6,925	24.6
2015[b]	23,873	3,354	6,172	25.9

Source: IMS Health
Authors: Sindusfarma/Gerência de Regulação de Mercados
[a]Ex-factory prices (without discounts and with taxes included)
[b]12-month period ending October 2015

[2] IMS Health adopts the methodology for *pharmacy purchase price* (PPP). Data collected is provided by wholesalers and/or distributors on sales from pharmaceutical companies and covers both OTC and prescription only medicines [26].

[3] IMS Health [29] classifies the 21 countries into three tiers as "pharmerging" markets: (a) tier 1 China; (b) tier 2 Brazil, India, and Russia; (c) tier 3 Poland, Argentina, Turkey, and Mexico, Venezuela, Romania, Saudi Arabia, Colombia, Vietnam, South Africa, Algeria, Thailand, Indonesia, Egypt, Pakistan, Nigeria, and Ukraine.

billion of global annual sales, representing two-thirds of the growth of the world pharmaceutical market. During this period, it is expected that the "pharmerging" countries share would increase by ten percentage points (from 23% to 33%) [29].

Medicines marketed in Brazil are imported or produced locally. Local production includes multinational companies with subsidiaries in Brazil (mainly pharmaceutical products), national private companies (pharmaceutical products and/or active pharmaceutical ingredients (APIs)) [30], and a network of public sector (or state-owned) manufacturers (pharmaceutical products) that mainly supply medicines to government public health system [31, 32]. However, Brazil remains highly dependent on pharmaceutical imports (both finished products and APIs), as shown in its trade deficit for the sector (Fig. 7.2) [30].

From the demand side, the consumption of medicines involves both private and public sectors in Brazil. Drug expenditures include out-of-pocket spending by families or government purchases and the public system supplying medicines free of charge [33].

According to the National Health Accounts 2010–2013 [34], in 2013 the consumption of goods and services on health (including medicines) accounted for 8% of GDP, of which 3.6% came from government and 4.4% from families and nonprofit institutions (NGO, faith-based facilities, etc.).

Spending on medicines as a share of total health expenditures varied from 22.3% in 2010 to 20.6% in 2013. In absolute terms, the total health expenditures reached R$ 424 billion (US$121 billion) in 2013 and medicines accounted for R$ 84.8 billion (US$ 24.2 billion) of the total [34].

As a percentage GDP, household out-of-pocket health purchases reached 1.6% of GDP in 2010 and remained at 1.5% from 2011 to 2013. Government demand represented 0.2% of GDP from 2010 to 2013. This resulted in the fact that the

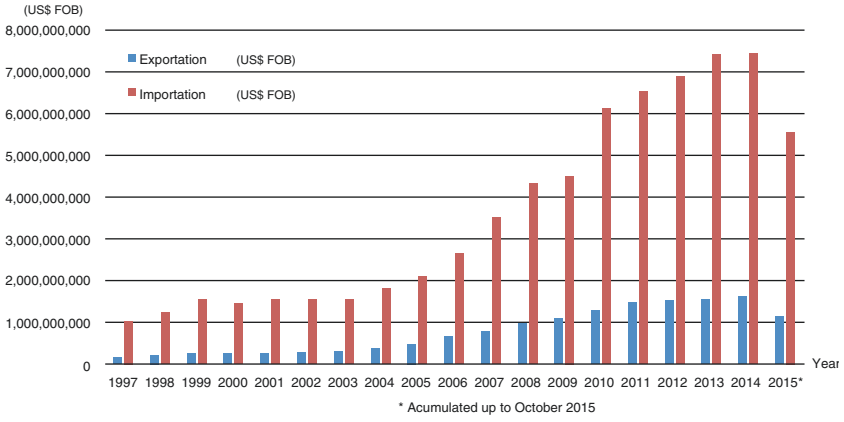

Fig. 7.2 Trade Balance for pharmaceutical products in Brazil (Chapter 30 (pharmaceutical products) of the Mercosur Common Nomenclature (NCM)), 1997–2015* (US$ FOB) (Source: MDIC/SECEX – Sistema Alice. Elaborated by Sindusfarma/Gerencia de Regulacao de Mercados)

household expenditures are around eight times higher than the government as a percentage of GDP during this period [34].

7.3.3 Brazil's Regulatory Environment

The National System of Health Surveillance (SNVS) was established in 1999 [35]. It involves a set of actions implemented at the three federal levels. Lawmakers also created the National Agency on Health Surveillance (Anvisa) (similar to the US Food and Drug Agency), a regulatory agency linked to the Ministry of Health but with administrative independence [36].

Anvisa's mission is to protect population health by overseeing the production and marketing of health- and medical-related products, services, and related technologies, including impact on environment and border control [35].

The scope of this section presents an overview of the role of Anvisa for the following activities related to medicines. These are quality control, pharmacovigilance, and issues related to falsified/counterfeit medicines.

Current legislation for the quality control of medicines and APIs was enacted in 1976 [37]. "Quality control" is defined as a "set of measures to ensure that the production of batches of medicines and other products covered by this Act that meet the standards of activity, purity, efficacy and safety". The Act [37] requires every manufacturer to have an independent department responsible for quality inspection of raw materials and to implement tests needed to follow up the production processes. Manufacturers are given the option to hire institutes or official laboratories to develop these quality control measures.

The National Institute for Quality Control in Health (INCQS), linked to the Oswaldo Cruz Foundation (Fiocruz), initially became the National Health Surveillance System (SNVS) as a national reference lab on quality control of products and services. In 2012, Anvisa created the Brazilian Network of Analytical Laboratories in Health (Reblas) [38] which has accredited laboratories throughout several states. In January 2016, Reblas had 105 laboratories in ten states [39].

The Brazilian Pharmacopoeia, whose first edition was published in 1929, stipulates quality control standards. In 2010, Anvisa published the fifth edition, which is available online.[4] In 2010, Anvisa also updated regulations for Good Manufacturing Practices (GMP) [40], incorporating the recent guidelines from the World Health Organization (WHO) [41]. These efforts also reflect the intention to align with the international standards.[5]

[4] http://www.anvisa.gov.br/hotsite/farmacopeiabrasileira/index.htm

[5] The Common Market of the South (Mercosur) was initially composed by Argentina, Brazil, Paraguay, and Uruguay and lately included Venezuela and Bolivia. It is considered a process of regional integration in which health is regularly discussed and negotiated.

7.3.4 Medicine Pricing in Brazil

In 2003, Anvisa established the Medicines Market Regulatory Chamber (*Câmara de Regulação do Mercado de Medicamentos* (CMED)) to regulate medicine prices in the following three market segments: factory prices (*Preço Fábrica ou Preço Fabricante* (PF)), maximum consumer prices (*Preço Máximo ao Consumidor* (PMC)), and public sector prices (*Preço Máximo de Venda ao Governo* (PMVG)) [42]. CMED has six different categories to establish factory prices. These are applied to transactions made by drug manufacturers, importers, and distributors to pharmacies and government bodies when a medicine is introduced in the market [43]. The first category is for those medicines that provide a significant therapeutic advance over existing medicines in terms of efficacy, price, and adverse reactions. The factory price may not be higher than in producers' home country or any of the following nine countries including Australia, Canada, Spain, the United States, France, Greece, Italy, and New Zealand. The second category applies to new products that do not fall into the first category. These medicines cannot have a higher price than comparable treatments already available in the market. Medicines classified in the third category are new dosage forms. The prices of these medicines also cannot be higher than the reference medicines. Category four includes new dosage forms or new formulations, which are not already produced by a company. In this case, the factory price cannot be higher than the average price of the similar dosage forms with the same API, which is already available in the market. Novel combinations of APIs and new pharmaceutical forms not already on the domestic market fall into the fifth category. In case of new API combinations, the price cannot be higher than the nine aforementioned countries or exporter's market. Lastly, the sixth category of medicines includes generics, for which the price may not exceed 65% of the reference drug. The formula for annual price adjustments is adjusted to the inflation for that period.

In retail market involving retail pharmacies, CMED sets the consumer price ceiling (*preço máximo ao consumidor* (PMC)). For purchases of certain medicines made by the public sector (i.e., procurement from local, state, or federal entities), CMED also mandates an additional minimum discount, called the Price Adequacy Coefficient (*Coeficiente de Adequação de Preços* (CAP)), which is 24.38% since 2011. Medicines that must include the CAP discount include those that are sold in the exceptional or high-cost medicines categories. These include blood-derived products, cancer drugs, and treatments for HIV/AIDS and for sexually transmitted diseases, as well as for medicines involving court-ordered price reductions. Anvisa regularly updates prices on its website using a formula that also takes into account inflation, market concentration, and productivity gains.

The pharmaceutical industry in Brazil was claiming that the medicines' prices in Brazil are low, and hence they asked to increase the drug prices. However, CMED intervened, and an Anvisa study reported that CMED's policies resulted in on average a 35% lower than what was requested by the industry [44]. Nevertheless, consumer activists argue that Brazil is still paying too much for several medicines. For example, SUS spent US$1,239 for the cancer drug rituximab (500 mg) and

US$82 for tuberculosis drug linezolid (600 mg) versus US$0.65 and US$2.50 for generic versions of the same drugs in the international market [45]. In addition, a study in Brazil's South noted that mean drug prices for originator and generic brands were 65% and 74% higher, respectively, than the international prices [46].

To evaluate SUS funding for new technologies, in 2011, the MoH created the National Committee for Technology Incorporation (*Comissão Nacional de Incorporação de Tecnologias no SUS* (CONITEC)). Similar to the United Kingdom's National Institute for Health and Care Excellence (NICE), the body undertakes pharmacoeconomic evaluations of new health technologies and makes decisions to include medicines for reimbursement or otherwise. Until 2014 medicines were responsible for 63% of demands for evaluation, from which 40% were accepted [47].

7.3.5 Pharmaceutical Patents in Brazil

It is also noteworthy that Anvisa regulates the examination of patent applications for pharmaceutical products and process. In order to incorporate the World Trade Organization Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement into the national level, Brazil changed its Industrial Property Law 9279 in 1996 [48, 49]. This law was amended in 2001 (Act 10, 196), incorporating article 229-c which establishes that the "granting of patents for pharmaceutical products and processes depend on the prior consent of the National Health Surveillance Agency – ANVISA."

To comply with this legislation, Anvisa created the Coordination of Intellectual Property (COOPI) to implement examinations of pharmaceutical patent applications, assessing the patentability requirements (novelty, inventiveness, and industrial application), and worked in coordination with the Patent Office (*Instituto Nacional de Propriedade Industrial* (INPI)).

From a public health perspective, Anvisa's role is to ensure a narrow examination of patent criteria to avoid granting secondary patents and improper monopolies that affect medicines prices [49]. Since its creation, this mechanism has led to tensions among different stakeholders [50].

7.3.6 Falsified or Substandard Medicines

Cases of falsified[6] medicines in Brazil have been documented since 1877, and 172 cases were reported to the Ministry of Health between 1997 and 1998. In response to these cases, Brazil amended the Criminal Code in 1998 (Acts 9677 and 9695) in order

[6]There is a difference between "falsified medicines" and "counterfeit medicines." The former refers to criminal attempts to sell fraudulent products that are harmful to public health, and the latter refers to trade and intellectual property related to trademarks (counterfeit). "A falsified

to classify "falsification" as a serious crime. This is subject to a penalty of 10 to 15 years and fines. Since then, the MoH has issued several ordinances to regulate different stages of the pharmaceutical chain (manufacturers, distributers, transporters, importers, retail pharmacies) and to avoid the negative effects of falsified medicines [52].

In 2009, Brazil passed legislation establishing the National System for the Control of Medicines [53, 54]. Under this system, any product in the country (produced, dispensed, or sold) must have identification numbers using "technology for capture, electronic storage and data transmission" (p.121). This is in order to ensure traceability across the entire chain, including dispensing [53]. A bidimensional code with a "Medicine Unique Identifier" (*Identificador Unico de Medicamento*) must be printed using a security label as the mechanism for ensuring authenticity and traceability.

A study conducted between 2005 and 2009 on the profile of batches of medicines seized by Anvisa based on "false medicines" criteria found that 77% were for erectile dysfunction (citrate de sildenafila (Viagra®) and tadalafila (Cialis®)) and 18% were products for anabolic function (Deca Durabolin®, Durateston®, Hemogenin®); the remaining products included medicines for cancer and infections [52]. Data provided by the Federal Police from January 2007 to September 2010 confirmed these findings [55]. Anvisa keeps an annually updated list of products[7] classified as "falsified" and provides specific characteristics regarding identification, destruction, and seizure. The sale of medicines through the Internet is not allowed for prescription drugs in Brazil [56].

7.3.7 Pharmacovigilance

Although there is legislation enforcing pharmacovigilance that dates back to 1976 [37], Anvisa implemented these strategies at the national level in 2001. At the state level, São Paulo [57] and Ceará [58] were pioneers in creating pharmacovigilance programs. In 1998, São Paulo, home to the largest number of pharmaceutical industries in Brazil, created the "State Program for Iatrogenic Reduction" and, in 2000, approved an ordinance making it mandatory for companies in the state to report adverse drug reactions [57].

In terms of organizational structure, Anvisa established a "pharmacovigilance management" unit (GFARM) and the National Center for Monitoring Medicines (CNMM). The pharmacovigilance program also relies on a Hospital Sentinel Network involving over 100 hospitals distributed in all states across the country [59].

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medical product gives a false representation of its identity and/or source and/or record keeping for traceability; pretends to have been assessed and approved by the competent regulatory authority, pretending to be a genuine quality product; has an intention to deceive by a fraudulent activity; is falsified for profit motives, disregarding public health and safety; and that disputes concerning patents or trademarks must not be confused with falsification of medical products" [51].

[7] http://portal.anvisa.gov.br/wps/content/Anvisa+Portal/Anvisa/Pos+-+Comercializacao+-+Pos+-+Uso/Fiscalizacao/Produtos+e+Empresas+Irregulares/Produtos+Falsificados

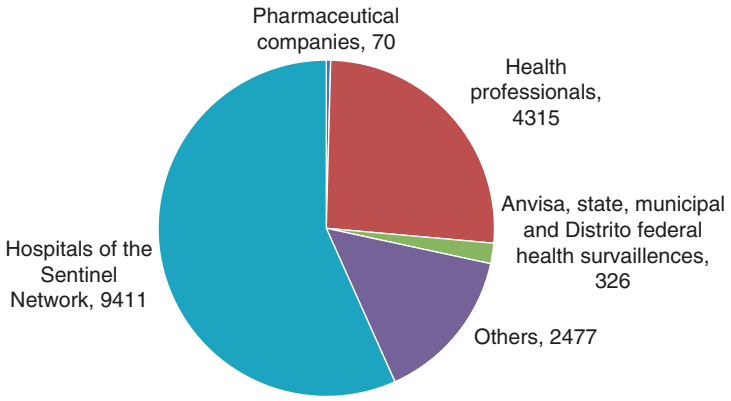

Fig. 7.3 Distribution of adverse drug reactions, by type of informant, 2008–2011 (n = 16,511) (Source: Anvisa, 2012 [60])

Between 2008 and 2011, this network was responsible for reporting 57% of all prescription drug-related adverse reactions (Fig. 7.3) [57].

In 2009, Anvisa published guidelines concerning pharmacovigilance for Medicines Registration Holders (*Detentores de Registro de Medicamentos* (DRMs)) [61].

According to these guidelines, DRMs must set up an organizational structure for implementing pharmacovigilance strategies. This includes adapting to current legislation, codifying and assessing suspected adverse reactions reports, and contacting informants for further information. DRMs must also implement a risk management plan, to produce periodic reports on pharmacovigilance, conduct self-inspections, and to establish mechanisms through which third parties can send reports.

From 2008 to 2011, the number of medicines-related adverse events registered in the National Notification System for Adverse Events and Technical Complaints (Notivisa) has increased every year, from 2,563 reports in 2008 to 5,729 reports in 2011. A few examples of medicines withdrawn from the market with the support of GFARM/Anvisa between 2000 and 2011 include phenylpropanolamine, phenolphthalein, tiratricol, rofecoxib®, lumiracoxib, efalizumab, rosiglitazone, anfepramone, phemproporex, and mazindol [60].

From 2010 to 2012, DRMs sent 936 documents to Anvisa, of which 59% were periodic reports on pharmacovigilance and 17% were pharmacovigilance risk management plans. Anvisa has also taken measures addressing drug labels and medicines inserts [57]. Table 7.2 provides an overview of pharmacovigilance legislation and related laws and steps implemented in Brazil.

Pharmacovigilance comprises a set of actions addressing patient safety.[8] Other actions regarding patient safety related to medicines include a strict package insert regulation (content and format) and regulation of advertising.

[8] http://www20.anvisa.gov.br/segurancadopaciente/

Table 7.2 Overview of pharmacovigilance legislation[a] and related measures implemented in Brazil

Legislation	Measures implemented
Act 6360/76	Mandated manufacturers to report any accident or harmful reactions caused by medicines to health authorities
Ordinance 577/78	Established a communication channel with WHO for any restrictions or prohibitions adopted in Brazil
Ordinance 3916/98	National Medicines Policy: recognizes pharmacovigilance as a means to deal with adverse reactions and to guarantee the rational use of medicines
Act 9782/99	Creation of National Health Regulatory Agency (Anvisa) with one of its purpose to control and monitor products harmful to health
Ordinance 696/01	Creation of Anvisa's National Center for Monitoring Medicines (CNMM). In this same year, Brazil became a member state of WHO's International Program for Monitoring Medicines
2006[b]	Creation of the National Notification System for Adverse Events and Technical Complaints (Notivisa) as a web platform for reporting confirmed or suspected adverse drug reactions and cases of technical complaints.
Ordinance 1660/09	Establishment of the Health Surveillance Registration and Investigation System (VIGIPOS) to strengthen post-marketing and post-use product surveillance
RDC[c] 04/2009	Considered the landmark legislation on pharmacovigilance in Brazil. Establishes a set of activities to be implemented by Medicines Registration Holders (DRMs) and includes guidance for inspecting companies' pharmacovigilance activities
Anvisa's Instruction No 14/2009	Guidelines on pharmacovigilance: (1) good inspection practices regarding pharmacovigilance for DRMs, (2) preparation of periodic reports on pharmacovigilance, (3) preparation of pharmacovigilance plans and risk management plans, (4) glossary

Source: Summary based on Anvisa [57, 60], 2012a e b

[a]This is a summary of the main legislation related to pharmacovigilance in Brazil. It is not an exhaustive overview of the legislation

[b]Anvisa's Board Resolution

[c]Although Notivisa (http://www.anvisa.gov.br/hotsite/notivisa/apresenta.htm) was implemented in 2006, the legislation supporting it includes the following: Ordinance n° 1660/2009; Ordinance n° 529/2013 (Ministry of Health); RDC n° 36/2013 (Anvisa)

7.4 Medicines Financing and Supply System

Since 2004, there have been three key mechanisms for distributing medicines in Brazil: (1) free of charge provision through the public healthcare services of SUS, (2) the Popular Pharmacy Program (*Programa Farmácia Popular* (PFP)), and the (3) out-of-pocket purchases in private retail pharmacies (Fig. 7.4).

Medicines provided through SUS are completely free of charge. These medicines are financed at the federal, state, and municipal levels and categorized into medicines for primary healthcare, medicines for strategic programs, and medicines for specialized healthcare programs. Medicines are covered for both ambulatory and hospitalized care. Besides a budget to cover medicines, there is also a budget for pharmaceutical-related infrastructure as well [62].

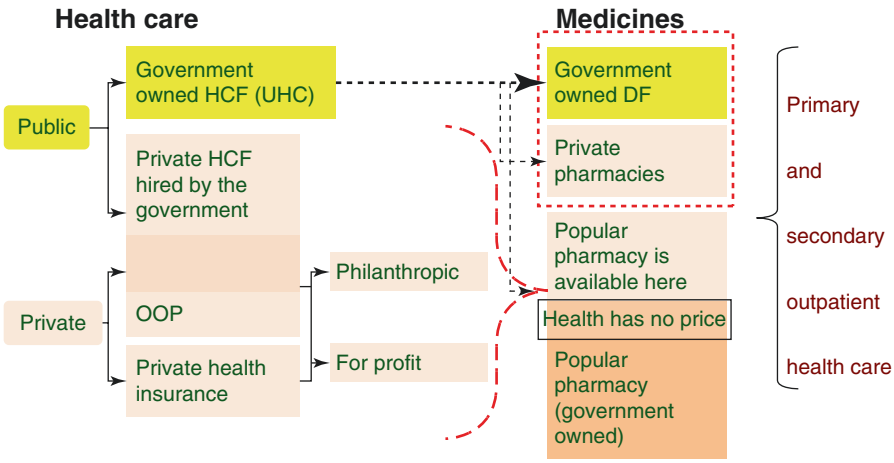

Fig. 7.4 Healthcare and medicines provision in Brazil. *HCF* healthcare facilities, *UHC* universal healthcare, *DF* dispensing facilities, *OOP* out-of-pocket payment (Source: Author's elaboration)

Funds are raised through general taxation with specific budgeting procedures at each federal level. A specific bank account for medicines exists at each federal level. This is in order to prevent diversions and to facilitate accountability.

Federal, state, and municipal levels share responsibility for financing medicines for primary healthcare. Since 2013, the minimum amount contributed by each federal level per year for the purchase of medicines is R$5.10 from the MoH and R$ 2.36 from both states and municipalities (respectively, US$ 2.27 and US$ 1.05 considering July/2013 rate) [63]. Up to 15% of this amount may be used for infrastructure improvements. Procurement is carried out mostly at the municipal level. In addition, the MoH also finances, procures, and distributes insulin (regular and NPH) and birth control products to municipalities. The medicines' package for PHC includes items on the national essential medicines list (RENAME) [64], as well as allopathic, phytotherapeutic medicines, homeopathic matrices, mother tinctures, and health products.

Mendes et al. reported that 58.5% of phytotherapies were available at the PHC level [65]. A study also showed that 66.6% of PHC users stated that the availability of medicines should be improved [66].

The strategic medicines budget component comprises medicines used in strategic health programs such as to treat endemic diseases and also other health conditions with a high socioeconomic impact such as tuberculosis, *hanseniase* (leprosy), STDs/AIDS, blood and blood products, food and nutrition products, tobacco control products, and influenza medicines.

The MoH is responsible for treatment guidelines, funding, procurement, and distribution of these medicines. States are in charge of stocking and distribution to municipalities, which are responsible for dispensing. The MoH forecasts demand in a bottom-up manner, starting at the municipal level, which is then integrated at the

state level and then consolidated by the MoH. Most of these medicines are dispensed at the PHC level.

The third budget component, relating to specialized medicines, comprises mostly high-cost treatments and seeks to provide comprehensive care to patients with organ transplants, hepatitis, genetic diseases, and chronic renal failure, among others.

All healthcare, health products, and diagnostic and monitoring supplies are provided in an integrated network of healthcare services, based on the national Clinical and Therapeutic Guidelines (*Protocolos Clínicos e Diretrizes Terapêuticas* (*PDCT*)).

For all medicines dispensed at SUS facilities, including over-the-counter (OTC) drugs, a prescription is mandatory, and most municipality health managers opt to dispense medicines only for prescriptions written at a public health facility. However, antiretrovirals (ARVs) and specialized component medicines are dispensed under prescriptions that come from both private and public healthcare providers.

The majority of SUS medicines are dispensed free of charge in PHC facilities. However, there are also specific dispensing facilities mainly for specialized medicines. Public hospitals and emergency facilities are used to dispense medicines to outpatients as well.

The procurement of medicines is undertaken at all the levels of SUS according to federal regulations. These involve several procedures that are usually bureaucratic and not agile. In many cases, it takes around 9 to 12 months between the time a procurement list is prepared and until medicines are delivered to the warehouse. With the exception of some large hospitals with managerial autonomy, public procurement is always centralized at one of the three central levels of SUS.

All government purchases are done through an open bid, and the complexity of the process varies according to the total value of the purchase [67, 68]. For low-cost purchases, invitations must be sent to at least three suppliers at least 5 days in advance, assuring that the other suppliers access the invitation as well. Since 2002, it is possible to carry out electronic procurement through a reverse auction, which is recommended for any purchases irrespective of cost. Typically, contracts include a 1-year price agreement and clauses permitting specific needs in purchase orders [67].

Spending on medicines at each federal level in 2009 was US$ 3.25 billion (MoH); US$ 943.98 million (states) and US$ 942.28 million (municipalities), amounting to US$ 5.13 billion in total [69]. SUS's expenditures on medicines increased 61.6% from 2006 to 2009, but this increase in drug expenditures was higher for the states (112.4%) than the MoH (65.3%) or municipalities (22.7%).

Part of the efforts to reduce the costs of medicines and ensure the sustainability of access to life-saving medicines includes the use of compulsory licenses (see Box 7.1).

Box 7.1. Compulsory License for Efavirenz

Brazil's world-renowned HIV/AIDS program is based on human rights commitments and strong partnerships with the state. These factors help explain the program's successes in guaranteeing access to life-saving antiretroviral medicines [70]. While international health experts emphasized that

middle- and low-income countries should invest scarce resources only in prevention, Brazilian officials and activists balked and insisted that their citizens also have the right to treatment that transforms the deadly infection into a chronic disease and cuts transmission rates. Transnational drug companies in the 1990s, however, charged over US$10,000 per person per year for the antiretroviral (ARV) combination therapy. In response, local Brazilian firms, including both public labs (or government-owned) and private companies, began to produce generics of off-patent ARVs, dramatically cutting the price of triple therapy to US$2,767 per patient/year by 2000 compared to lowest price of US$10,439 offered by originator companies. The next challenge was to remain abreast of technological innovation in medicines and keep costs at a minimum so that an additional 10,000–25,000 people a year could be included in the program and patients experiencing resistance could migrate to newer treatments.

As a result of its membership in the World Trade Organization founded in 1994, Brazil had to adjust domestic laws governing patents to be in line with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). In the decades leading up to the WTO, Brazil like many other countries had not extended patent protections for pharmaceuticals given the costs on public health budgets and threats to access. However, lawmakers anticipated TRIPS commitments with the approval of Law No. 9279 of May 14, 1996 (Industrial Property Law) instead of waiting until the 2005 deadline for becoming TRIPS compliant. In light of this situation, Brazil's strategy to address high-cost, patented medicines included aggressive price negotiations using the threat of compulsory licenses and local production of medicines [70]. TRIPS permits the use of compulsory licenses – a legal devise allowing other producers to market a drug under a patent and to effectively rescind a monopoly – in cases of government use, emergency situations, and other situations. In 1999–2001, Brazil first threatened a compulsory license during price negotiations for nelfinavir with Roche and for efavirenz with Merck Sharpe & Dohme (MSD). Although the companies agreed to a price reduction, the United States government initiated a WTO Dispute Settlement Body questioning Brazil's new patent legislation and use of compulsory licenses. In response to pressures from the United States and transnational drug companies, Brazil spearheaded a coalition of like-minded countries and health activists to push the right to health in various international and United Nations venues [71]. These efforts culminated in the Doha Declaration on TRIPS and Public Health, which stipulated that WTO-member countries have the right to decide the criteria for issuing compulsory licenses and other TRIPS safeguards to address public health needs.

From a strengthened position, Brazil successfully negotiated price negotiations on patented ARVs in 2003, but within a few years, the number of Brazilians in treatment had reached 165,000 people and ARV

expenditures, US$500 million. To ensure the sustainability of the program, Brazilian negotiators demanded price cuts for MSD's efavirenz, Gilead's tenofovir, and Abbott's ritonavir/lopinavir. In 2005, these three ARVs accounted for one-third of all treatment costs. Merck and Gilead conceded price discounts, but Abbot remained intransigent. Despite vocal support from civil society activists, Brazilian negotiators backed down from issuing a compulsory license and accepted a limited price reduction locked in over several years. Government officials voiced concerns about the local capacity to produce the ARV, the limited time to ramp up production in order to fulfill domestic demand, and potential quality concerns of imported generics. In response, the state initiated several industrial policies seeking to bolster local production of pharmaceuticals, especially in the crucial area of active pharmaceutical ingredients (APIs) [70].

On May 7, 2007, Brazil finally issued a compulsory license for MSD's efavirenz. At the time, 70,000 of the total 200,000 people in treatment were taking the ARV. Brazilian negotiators asked the company to reduce unit prices from $1.65 to $0.65, but the company refused to lower prices beyond US$1.10 a pill. But use of the compulsory license allowed Brazil to cut unit prices by two-thirds. AIDS officials estimated a total savings of US$104 million from 2007 to 2011 with annual government expenditures falling from US$40 million to US$12 million [72]. Initially, Brazil imported a generic version of the ARV from India certified by the World Health Organization until a public-private partnership of Brazilian public labs and local API makers produced their first batch of the medicine in February 2009. A formidable treatment coalition, involving activist health officials, civil society groups, and domestic drug manufactures, has played a central role in overcoming political pressures not to issue compulsory licenses and in ensuring the sustainability of Brazil's treatment program [70]. This treatment alliance has not only successfully challenged Gilead's application for a patent on tenofovir in 2009 but has helped reduce spending on patented drugs as a proportion of the ARV budget. Between 2008 and 2012, annual ARV expenditures increased from US$294 million to US$380 million, but acquisitions of foreign/patented medicines fell from US$192 million to US$162 million. Meanwhile, purchases of locally produced generic versions increased from US$102 million to US$218 million over the same period, and per patient per year costs of first-, second-, and third-line treatments fell.

As the right to health and the duty of the state are clearly established in the Brazilian Federal Constitution, people with HIV/AIDS and other disease groups have sued the government since 1991 at all federal levels [73]. Most court decisions have favored patients in what is called the health litigation phenomenon (*judicialização da saúde*). By 2011, there were about 241,000 health-related lawsuits, mainly against SUS, and 50% of all litigation involves medicines [74] and other health-related issues including access to hospital beds, private insurance, etc. [75].

7.5 The Popular Pharmacy Program

Created in 2004, the Popular Pharmacy Program (*Programa Farmácia Popular* (PFP)) is a government program to provide subsidized medicines to low-income patients who obtain drug prescriptions mainly from private clinics (but patients from SUS clinics can also participate in the program).

The program began in government-owned facilities, where 79 medicines from 38 therapeutic groups were sold at lower prices. In 2006, the program expanded to private pharmacies where 14 medicines from eight therapeutic groups distributed through a co-payment system. The government pays 90% of reference price of the medicine, while patient pays 10% of the sales price of medicines under this program. This program is called the "Popular Pharmacy is Available Here" (*Aqui tem Farmácia Popular* (*ATFP*)). Since 2011, a subset of items, antihypertensives, antidiabetics, and antiasthma medicines are provided free of charge in both government-owned and ATFP pharmacies. This program is called "Health Has No Price" (*Saúde Não Tem Preço*).

7.6 Out-of-Pocket Expenditures on Medicines

Out-of-pocket purchases of medicines occur in about 78 thousand private pharmacies and drugstores across the country [76]. Retail pharmacies' total sales reached US$ 25.2 billion in 2014 with the majority (51.9%) in the Southeast region, and medicines accounted for 77% of sales [77].

Overall, 88.8% of all patients with NCDs had access to all medicines (obtaining all medicines prescribed in the last 30 days) [78]. Nevertheless, except for hypertension, diabetes, and hypercholesterolemia, most people paid out of pocket for their medicines [78].

7.7 Medicines Use Issues

In Brazil, most of medicines are obtained from prescriptions only, and regulations define the entire list of over-the-counter medicines [79], but it is not uncommon to obtain prescription-only medicines without a prescription. In SUS-dispensing facilities as well in the Popular Pharmacy Program, all medicines, including OTCs, are only dispensed under prescription. Physicians and dentists are the main authorized prescribers, but nurses, nutritionists, and pharmacists may prescribe specific products under certain circumstances.

In 1964, Brazil elaborated its first essential medicines list, calling it "Basis and Priority List of Biological Products and for Human and Veterinary Use (*Relação Básica e Prioritária de Produtos Biológicos e Matérias para Uso Farmacêutico Humano e*

Veterinário)." Since 1975, this list has been called as National List of Essential Medicines (*Relação Nacional de Medicamentos Essenciais* (RENAME)) [80]. The current ninth edition comprises 840 items addressing all levels of healthcare, including medicines, medicinal herbs, and health products, such as strips for blood glucose and male and female condoms [64]. The National Committee for Technology Incorporation in SUS (CONITEC)[9] regularly updates RENAME using evidence-based criteria. All CONITEC dossiers are available for public consultation, and any member of the public can contribute by filling out an online form. All procedures, including the CONITEC meeting schedule, are published on its website. All medicines and health products on RENAME are available free of charge at SUS facilities. Since SUS is decentralized, states and municipalities may have their own essential medicines list.

Brazil has invested heavily on resources to improve information systems specific to medicines and pharmaceutical services. For example, the Drug Logistics Management System (SICLOM) addresses supply chain information for antiretrovirals from procurement to dispensing at a health facility level. *Horus* is an another medicine logistic system in Brazil developed by the MoH [81]. When fully implemented, Horus in the future would be able to provide logistics information of medicines throughout at federal level.

In 2005, a national assessment study was undertaken at the healthcare facilities level. This study was undertaken by using WHO indicators [82, 83]. The indicators showed low performance in percentage of prescriptions completely filled (46%), prescriptions containing antibiotics (40.1%), availability of RENAME in healthcare facilities (70%), and of standard treatment protocol (STP) for tuberculosis (43.3) in healthcare facilities.

Recently, Brazil developed Survey on Medicine Access, Utilization, and Rational Use of Medicines (PNAUM) 2013–2015. The survey has two arms: one is to sample population of households, and the other is to sample PHC facilities. The household survey arm included 41,433 interviews at 20,404 households [78]. The PHC facilities survey, encompassing 1175 clinics in 273 municipalities, interviewed 1,585 physicians, 1,139 pharmacists, 8,870 patients, and 507 pharmaceutical services managers [84]. The intention is to repeat this survey every 5 years.

The survey found out that the 50.7% (95% CI 49.3–52.2) of the population uses medicines, and consumption is higher among women 61.0% (95% CI 59.3–62.6) than among men 39.3% (95% CI 37.5–41.1). Some other results can be seen in Table 7.3.

Advocating the appropriate use of medicines in Brazil has gained momentum and includes backing from various stakeholders including the MoH, federal and state pharmacist councils, and undergraduate and postgraduate pharmacy courses. May 5 is the national day for the rational use of medicines. Also, there is a national committee for the rational use of medicines.[10]

[9] http://conitec.gov.br/

[10] http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/sctie/daf/urm

Table 7.3 Indicators of rational use of medicines. Brazil, 2015

Indicator	Median Brazil (%)
There is always/repeatedly a health professional for patient education regarding medicines use	77.5
Medicines use without a prescription	38.9
Polypharmacy (five medicines or more)	23.7
Physicians are aware about procedures to request the inclusion/exclusion of medicines in the municipal standard list	27.2
Total access to prescribed medicines to treat noncommunicable diseases	88.8
General prevalence of use of medicines	50.7
Prevalence of medicines use for acute conditions	
Prevalence of medicines use in the 15 days prior to the interview for the treatment of pain	21.1
Prevalence of medicines use in the 15 days prior to the interview for the treatment of fever	2.11
Prevalence of medicines use in the 15 days prior to the interview for the treatment of infections	4.9
Prevalence of medicines use in the 15 days prior to the interview for the treatment of respiratory diseases	4.5
Prevalence of medicines use in the 15 days prior to the interview for the treatment of acute gastrointestinal disturbances	6.9

Source: Brazilian Survey on Medicine Access, Utilization and Rational Use of Medicines (PNAUM) [66, 78]

7.8 Conclusions: Summary and the Way Forward

Brazil has made considerable progress implementing inclusive social policies that have improved the quality of health services and the population's quality of life. The country has a health system that provides universal access to medicines and other health technologies and has upgraded its regulatory capacity. However further work is needed to improve the situation.

Many challenges remain to be addressed for a country of more than 200 million people, but Brazil has shown that its development model and public policies can be adopted by other middle-income countries. Strongly committed to international standards and regulation, Brazil works in close association with other several like-minded countries and regional blocs, thus ensuring a better quality of life for its citizens. Either through joint efforts or by country-specific actions, we must continue to find our way forward, and with each success, future generations will receive the heritage of having better conditions of health and life.

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Chapter 8
Pharmaceutical Policy in Bulgaria

Ruth Lopert

Abstract Bulgaria is experiencing rapid growth in expenditure on medicines but without obvious improvements in health outcomes. Many current policy settings appear designed to limit the National Health Insurance Fund's outlays rather than ensure financial protection for patients, and medicines make up three quarters of all out-of-pocket costs in health. Existing mechanisms for selecting and pricing medicines are not promoting value for money. Current pricing policies do not encourage competition in the off-patent market and prices for some medicines compare unfavorably with those in wealthier countries. The application of Health Technology Assessment for selecting medicines for the Preferred Drug List together with restricting the use of non-cost-effective medicines, promoting generic uptake, and encouraging greater competition in the off-patent medicines market could improve value for money. Developing clinical treatment guidelines that consider cost-effectiveness, and promoting rational prescribing and dispensing could also improve efficiency and create fiscal space to improve affordable access for patients.

8.1 Bulgarian Health System and Context

Like many former Soviet-bloc countries, Bulgaria has gradually moved away from a centralized *Semashko* system to a social health insurance model. However, unfavorable demographics over the last two decades – an aging and shrinking population, low fertility and birth rates, significant net out-migration, growing levels of poverty and a declining tax base – are undermining the publicly financed health system. By mid-century, it is estimated that the current population of approximately 7.2 million

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(at January 2015) will decline to less than six million, 30% will be 65 and over, and only just over half will be of working age [1].[1] The combined effects of the shrinking working-age population and declining tax base are made worse by a large informal labor force, estimated to be worth more than one-third of GDP [2] and involving over 16% of the workforce [3]. In addition, poverty levels have been increasing since 2008 and in 2015 over 40% of the population were either poor, or vulnerable to falling into poverty [4] and thus largely unable to pay for health care services out of pocket [5].

The National Health Insurance Fund (NHIF) is the compulsory national health insurer and single risk pool for the entire population. Established in 1999, it is the single largest payer in the country, purchasing services from both public and private providers. In theory, the entire population is covered with workers (and their employers) paying social health insurance contributions based on their incomes, while the poor, unemployed, children, pensioners, the disabled and other socially disadvantaged groups are exempt and their contributions are paid by the government. Health insurance coverage is compulsory for all Bulgarians, via an employer/employee mandate for the formal sector and an individual mandate for the self-employed including informal sector workers, with the rest of the population including children, pensioners, the disabled, the unemployed and other socially dependent groups covered by the state. However in reality, at any given time it has been estimated that 7–8% of the population are not covered, the bulk of whom are poor, working-age but unemployed [5].

While per capita health spending in Bulgaria remains well below the EU average, overall spending is higher than other countries of similar GDP, and public spending is comparable [5]. Total expenditure grew from 5.2% to 8% of GDP (from 8.5% to nearly 12% of the budget) between 1995 and 2012, and (unadjusted for purchasing power parity) per capita health spending increased from $US82 to $US566 [5]. In 2012, public health spending represented 51% of total health spending and 4.1% of GDP. Bulgaria is, however, a significant outlier with respect to private expenditure, particularly out-of-pocket payments – 47% of total health spending and 3.8% of GDP [5]. The share of the household budget spent on health is relatively high, at 5.3% in 2013, compared to about 3% on average in Western Europe, [6] with almost 20% of households spending 10% or more of their total outlays on health care, well in excess of the EU-15 average of 5.8%. Moreover, medicines overwhelmingly constituted the largest component of OOP, amounting to between 75% and 80% [7].

In terms of health outcomes, Bulgaria has been unable to reduce gaps in health outcomes and has failed to catch up with EU15 countries[2] since its EU accession in 2007. On life expectancy and disability-adjusted life years (DALYs) per capita, Bulgaria's performance is comparable, and in some cases slightly better than other

[1] Defined as between 15 and 65 years of age.

[2] The term EU-15 refers to the 15 member states of the European Union prior to the accession of ten additional member states on May 1, 2004. The EU15 member states were Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.

countries with similar levels of income and health spending per capita. However, compared with EU averages, Bulgaria performs poorly on most mortality and morbidity indicators, falling well short of the EU15 in overall life expectancy, having improved only slightly since the 1960s and now trailing Croatia, Hungary, and Romania [8].

Poor outcomes in life expectancy may be explained at least in part by Bulgaria's underperformance in managing the growing burden of non-communicable diseases (NCDs). In 2013, the standardized death rate (SDR) from circulatory disorders, at 1086, was the highest in the EU and nearly three times the EU average, [9] accounting for almost 2/3 of reported deaths. Ischemic heart disease, cerebrovascular disease, and chronic obstructive pulmonary disease (COPD) were the three leading causes of premature death (highest number of years of life lost, YLLs). In terms of morbidity, high systolic blood pressure, dietary risks, and high body-mass index were the leading risk factors in 2013) [10].

Unfortunately, the health system structure is not well geared to Bulgaria's disease profile and does not provide the optimal mix of services [5]. There are a number of significant key structural inefficiencies evident in the health system, particularly an emphasis on inpatient services at the expense of primary care and prevention, with both hospital capacity and hospitalization rates above average among countries of similar levels of income and health spending [5]. The hospital-centric focus is ill-suited to the growing burden of non-communicable diseases (NCDs), so that while at 4.2% of GDP, current public spending is consistent with other countries of similar income, private out-of-pocket spending is exceptionally high, to the point of impoverishing 4% of the population each year. In 2011, Bulgaria spent 52% of health expenditure on inpatient services, nearly 20% more than in other EU countries, and hospitalization rates were nearly 40% higher than in other recent EU members. In the same year, outpatient visits were relatively low, averaging 5.5 per person per year, well below the average of 7.23 in countries joining the EU after 2004 [5].

To some extent, this imbalance in expenditure reflects the circumstances of service provision. Health services are delivered by a network of public and private providers, and virtually all have contracts with the National Health Insurance Fund (NHIF). In fact, the NHIF cannot refuse to contract any facility approved by the MOH, irrespective of whether the NHIF agrees that it is needed [5]. Hospitals operate as commercial enterprises and are mainly owned and controlled by central and local governments, with around 10% of the beds and a third of hospitals privately owned [7]. They are paid on the basis of around 300 clinical care pathways (CCPs), which are case-based payments and create an environment in which there are strong incentives to overservice. The list of CCPs and their prices are negotiated annually and not based on costing data; they have not been assessed to determine whether they reflect efficient resource allocation; they even specify minimum (not maximum) length of stay to be eligible for payment [5]. As the numbers of facilities and beds has grown, the same number of cases must be shared among the providers, thus reinforcing incentives to do more and limiting facilities' ability to achieve economies of scale [5]. Further, Bulgaria has no standard criteria for hospital admission,

with the result that facilities admit any and all patients, many of whom self-refer via the emergency department. Not only are there no incentives that exist to encourage patients to seek more cost-effective and appropriate primary care, in many cases, a hospital admission involves lower out-of-pocket costs for the patient [7].

General practitioners (GPs) are paid on the basis of a mix of capitation and fee for service, while outpatient specialists, laboratories, and dentists are paid on a fee-for-service basis. For private patients, whether they purchase services directly or are privately insured, providers are generally paid fee for service. A National Framework Contract is negotiated every year between the Bulgarian Medical Association and the NHIF, together with a price-volume agreement that sets the conditions for provider participation and the prices and volumes of services that may be provided by all categories of medical professionals [7]. While Bulgaria has no overall shortage of physicians (398 per 100,000 population in 2013 [11]), both general practitioners (GPs) and nurses are in short supply. Only around 5% of GPs have been trained in family medicine, and the average age of the existing workforce is over 50. Among European countries, Bulgaria ranks among those with the lowest number of nurses per capita, and in recent years, there has been significant out-migration of young health professionals [7].

8.2 The Bulgarian Pharmaceutical Market

Although the Bulgarian pharmaceutical market is one of the smallest in the EU, it has expanded rapidly in recent years, and the pharmaceutical industry is one of the fastest-growing sectors of the economy [12]. In 2011, the Bulgarian market was valued at BGN 2.1 billion, an increase of 12% over 2010;[12] by 2015, it had grown to BGN 2.71 billion and is expected to be worth BGN 2.89 billion by end 2016, an average annual growth rate of approximately 7.5% [13]. The growth has been attributed in part to increasing consumer spending on over-the-counter (OTC) products, as well as increased NHIF expenditure on oncology and other high-cost medicines. It is also thought to be partly the result of the opening of the market brought about, at least to some degree, by the harmonization of the Bulgarian regulatory framework with EU standards of regulation, a prerequisite for Bulgaria's accession to the EU in 2007 [14].

Large multinational pharmaceutical companies are the biggest players in the market, with *Novartis* (7.1%, BGN 179 million in sales), *GSK* (6.0%, BGN 152 million), *Actavis* (6.0% BGN 152 million and the largest pharmaceutical manufacturer in Bulgaria), *Roche* (6.0%, BGN 151 million), and *Sanofi-Aventis* (4.5%, BGN 114 million) being the top five by value of sales in 2014 [15]. The Association of Research-based Pharmaceutical Manufacturers in Bulgaria (ARPharM), established in 1996, represents the interests of 26 pharmaceutical manufacturers from Europe, the United States, and Japan. Many foreign companies operate via local subsidiaries, often licensed as distributors or wholesalers [7].

The domestic industry comprises around 30 companies with a sizeable manufacturing base, of which the largest Bulgarian-owned manufacturer is *Sopharma* (4.4% market share, BGN 111 million in 2014) [15]. The main domestic pharmaceutical manufacturers

began as former state-owned enterprises that were restructured and privatized. Domestic production accounted for 30–40% of the pharmaceutical market in 2009 [7]. Today, Bulgaria is one of the largest producers of pharmaceuticals in Eastern Europe and exports have increased substantially over the past few years, accounting for 3% of Bulgaria's overall exports in 2013 [12]. Actavis and Sopharma have developed substantial export channels particularly to former Soviet-bloc countries, with Russia (27% of total exports), Romania (11%), Croatia (8%), Ukraine (7%), Germany (6%), and Serbia (6%) the main destinations in 2011 [12]. Bulgaria's pharmaceutical trade remains largely in favor of imports, however, reflecting the country's historically small manufacturing base but has improved dramatically since its EU accession, with the export value increasing from 20.3% of import value in 2004, to 62.0% in 2010.

8.3 Regulatory Framework

The establishment of EU standards of drug regulation was largely the result of the implementation of the Law on Medicinal Products in Human Medicine (LMPHM) in 2007 [16]. Among other things, the Act sets out the role and responsibilities of the regulatory authority, the Bulgarian Drug Agency (BDA), and includes provisions for centralized, decentralized, and national medicines registration procedures. The agency is funded in part from the budget of the Ministry of Health, with the remainder derived from fees for laboratory analyses, application and evaluation fees, annual registration charges, and GMP inspections. Fees and charges are determined by the Council of Ministers.

The BDA reports to the Ministry of Health and is responsible for the following:

- Marketing authorization of medicines
- Authorization and oversight of manufacturing, import, wholesaling, and retailing of medicines
- Authorization and oversight of clinical trials
- Regulation of advertising
- Pharmacovigilance and drug information
- Classification (scheduling) of medicines

The regulatory framework continues to evolve in line with EU directives. In June 2012, Bulgaria introduced amendments to the LMPHM to provide for enhanced pharmacovigilance capability, requiring the Bulgarian Drug Agency (BDA) to establish and maintain a system for the monitoring of the safety of medicines, and of the risks to patients' health arising from the use of medicines. The BDA should also maintain a national internet portal to be shared with the European gateway for medicinal products [17]. Consistent with the EU Medicines Directive 2010/84/EU, the amendments require the BDA and others to submit reports of actual or suspected adverse reactions to the *Eudravigilance* database. Marketing authorization holders have new safety obligations such as creating and maintaining a system for the monitoring of the safety of medicines, appointing a qualified person responsible for

pharmacovigilance, introducing a risk management system for each product, and submitting regular periodic safety update reports. In addition the BDA is empowered to suspend or terminate the marketing authorization of a product on safety grounds, as well to require post-marketing safety studies [17].

In February 2016 Bulgarian legislation was enacted to give effect to the EU Falsified Medicines Directive[3] requiring all pharmaceutical companies selling products in the EU to introduce Serialization and Track and Trace Systems, by 2019. The legislation introduced new requirements for sale or purchase of medicinal products, including specific obligations with respect to packaging and labeling to enable verification of authenticity, and to identify individual packages. All participants in the supply chain are obliged to record consignment numbers of supplied products and to prepare a plan for an emergency, including measures to remove products from the market if directed to do so by the BDA, the manufacturer, or the MAH [17].

In July 2015, the BDA signed a memorandum of cooperation with the Agency for Drugs and Medical Devices of Serbia (ALIMS) with the aim of assisting Serbia in enhancing its standards of medicines regulation to support its integration into the European Union. This is said to reflect the mission of the BDA to promote EU policies in the area of quality assurance, safety, and efficacy of medicines and control of medical devices [18].

8.4 Medicines Pricing

The primary price-setting mechanism is international (external) reference pricing. For new prescription medicines, the Bulgarian ex-factory price is set at the level of the lowest "official" price in any of ten primary (Romania, France, Latvia, Greece, Slovakia, Lithuania, Portugal, Italy, Slovenia, and Spain) and seven secondary (Belgium, the Czech Republic, Poland, Denmark, Hungary, Finland, and Estonia) EU member states. Notably, all the reference countries have substantially higher per capita GDP than Bulgaria, so in each case the drug price will be less affordable in Bulgaria than in the reference country.

Wholesale and retail margins are set by the Ministry of Health and are proportional to drug prices. Wholesale mark-ups range from 4% to 7%, with a maximum of BGN 10. Retail mark-ups vary from 16% to 20%, with a maximum of BGN 25. These, plus 20% VAT, are added to the ex-factory price to form the maximum retail price [19].[4]

For generic medicines, the ex-factory price of the first generic version of a medicine listed on the Positive Drug List (PDL) may not exceed 80% of the ex-factory price of the reference product included in the PDL. Thereafter, generic prices are subject to external referencing, so although a statutory price reduction is applied at

[3] Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011.

[4] Bulgaria is one of the few EU member states without a concessional VAT rate for medicines. The United Kingdom, Ireland, and Malta do not apply any VAT to medicines; in Spain, France, Croatia, Cyprus, Lithuania, and Hungary, the rate is 5% or less.

the point of initial generic market entry, there is no mechanism to drive further price reductions within the off-patent market.

As a result of these listing and pricing mechanisms, the prices of some medicines on the Bulgaria PDL are as high – and some even higher – than in countries that are much wealthier. Insufficient consideration of cost-effectiveness when listing and pricing medicines, together with potentially inadequate or ineffective restrictions on prescribing, result in fast-growing expenditures on some very high unit cost and potentially non-cost-effective medicines. For multisource and particularly high volume medicines for chronic conditions, some prices also compare unfavorably with, for example, prices in the United Kingdom. At the same time, discounting in the supply chain suggests scope for lowering prices and clawing back some of the savings currently accruing to pharmacies [20].

8.5 Drug Selection and the Positive Drug List

Although originally drafted to ensure the alignment of the Bulgarian regulatory framework with European standards for EU accession, the scope of the LMPHM is much broader, covering the pricing of prescription and over-the-counter (OTC) medicines, and the establishment and maintenance of the PDL. The LMPHM is complemented by various other laws and ordinances addressing medicines pricing, payment, prescribing, and dispensing diseases for which the NHIF pays for outpatient care and the basic package of services covered by the NHIF budget.[5]

The LMPHM has also been amended more than 20 times since its inception. In particular, a 2011 amendment established the National Council on Prices and Reimbursement of Medicinal Products (the Pricing Council), conferring on it the responsibility for listing and pricing of medicines on the PDL, as well as for setting maximum prices for all other medicines. While the price-setting mechanisms and processes are broadly outlined in the LMPHM, the details may be found in the 2013 Ordinance on the Terms, Rules and Procedure for Regulation and Registration of Prices for Medicinal Products (the Pricing Ordinance) [21]. The Pricing Council's role also includes approving, revoking or modifying pharmaco-therapeutic guidelines, as well as recommendations for treatment algorithms proposed by national consultants, various medical societies, and experts. However, to date, only six such guidelines have been finalized, though others are currently under development.

[5] Of particular relevance are: Health Law (1 January 2005); Ordinance on the Terms, Rules and Procedure for Regulation and Registration of Prices for Medicinal Products (30 April 2013 and amendments); Ordinance № 4 on the terms and conditions for prescribing and dispensing of medicines (4 March 2009); Ordinance № 34 on the terms and conditions for payment from the state budget for the treatment of diseases outside the scope of mandatory health insurance (25 November 2005);Ordinance № 38 defining the list of diseases for which medicines, medical devices and dietary foods for outpatient treatment fully or partially paid for by the NHIF (16 November 2004); and Ordinance № 40 for determining the basic package of health services guaranteed by the NHIF budget (24 November 2004).

The Pricing Council comprises a chair and six members, three of whom must be physicians or pharmacists, plus two economists and two lawyers, all with experience in their specialties of not less than 5 years [22]. It meets on a weekly basis and direct updates to the PDL fortnightly, mainly involving changes to prices, available brands, and levels of reimbursement for existing medicines. The LMPHM also sets out timeframes for the Pricing Council's decision-making, which are:

- 60 days for listing and pricing of new prescription medicines to be included in the PDL[6]
- 30 days for listing and pricing of generic medicines
- 30 days for setting maximum prices for over-the-counter (OTC) products and prescription medicines not subject to reimbursement

The PDL comprises four lists or Annexes:

- Annex I (referred to as the Reimbursement List): contains outpatient medicines subsidized in full or in part by the NHIF and the levels of subsidy they receive, as established by the Health Insurance Act (HIA).
- Annex II: lists medicines funded from the budgets of 'medical-treatment' facilities and paid for in full from NHIF funds.
- Annex III: includes medicines for the treatment of HIV/AIDS and certain other communicable diseases outside the scope of the HIA, as well as vaccines for compulsory immunizations.
- Annex IV: lists the ceiling prices of all medicines in Annexes I, II and III.

The Pricing Ordinance sets out the criteria for inclusion of medicines in the PDL. To be considered for listing, a medicine must be registered in Bulgaria and have evidence of coverage by health insurance programs in at least five of the ten primary reference countries. However, this does not require or imply evidence of satisfactory health technology assessment and thus is not an indicator of cost-effectiveness or value for money. A range of clinical characteristics and pharmacoeconomic indicators are then examined, based on an application dossier submitted by the manufacturer or supplier. Pharmacoeconomic indicators include the cost of therapy; the cost of therapy compared with available alternatives; the cost-benefit ratio; an economic evaluation of the additional benefits offered by the therapy; and an analysis of anticipated budget impact. The application is then scored; a medicine may score up to 95 points for "clinical factors" and up to 40 points for "pharmacoeconomic factors". However, a minimum of only 60 points is required for approval, and as a result, a clinically effective drug may be listed even with a low score on economic factors and without showing evidence of cost-effectiveness [20].

[6] The EU Transparency Directive No 89/105/EEC specifies a series of procedural requirements to ensure transparency of pricing and reimbursement measures adopted by the Member States, including specific time limits for pricing and reimbursement decisions (90 days for pricing, 90 days for reimbursement, or 180 days for combined pricing and reimbursement decisions). The Directive also requires competent national authorities to provide a statement of reasons based on objective and verifiable criteria for each of their decisions and to provide appropriate legal remedies to applicants.

Table 8.1 Prices and projected expenditure for selected drugs listed on the PDL on 1 January 2015; comparison with UK prices

INN	Brand	Dose/Qty	Bulgarian price (€)	UK NHS price (€)	2015 Forecast expenditure (€ 1000s)
ruxolitinib	Jakafi	5 mg × 56	2144	2143	5810
pertuzumab	Perjeta	520 mg	3089	3055	4522
axitinib	Inlyta	5 mg × 56	4052	4486	1694
aflibercept	Zaltrap	100 mg	381	377	906

Notes: Bulgarian prices from Annex II dated 2 May 2016 from http://ncpr.bg/bg/регистри/приложение-2 UK prices from British National Formulary, May 2016. Exchange rates as of 1 May 2016 from www.oanda.com. Analysis reproduced from Lopert [20] based on data provided by NHIF and updated to reflect prices as at May 2016

It is perhaps illustrative to consider some of the 13 new medicines added to the PDL in January 2015, with a collective expenditure estimate of BGN 34.6 million in the first year of listing (notwithstanding some of the costs of these new medicines will be offset by reductions in the use of older products). The prices of these drugs in Bulgaria are generally comparable with those in the United Kingdom (see Table). However, in the United Kingdom several of these medicines have been subject to Health Technology Assessment (HTA) by the National Institute for Health & Care Excellence (NICE) and found to be either not cost-effective (and therefore not recommended for use in the National Health Service) or significantly restricted on cost-effectiveness grounds. They are therefore highly unlikely to be cost-effective in Bulgaria. For example, in the United Kingdom *ruxolitinib* (Jakafi) was recommended by NICE in only a limited subset of its approved indications and subject to a discount on the listed price [23], while *pertuzumab* (Perjeta) was not recommended because the incremental cost-effectiveness ratio (ICER) was in excess of £125,000 per quality-adjusted life-year (QALY) [24]. NICE recommended *axitinib* (Inlyta) only in limited circumstances and subject to a discount on the listed price [25], while *aflibercept* (Zaltrap) in combination with irinotecan and fluorouracil-based therapy was not recommended by NICE for the treatment of metastatic colorectal cancer resistant to, or having progressed after an oxaliplatin-containing regimen [26] (Table 8.1).

The PDL is published on the Pricing Council website (www.ncpr.bg) [27] and is updated on the 2nd and 16th day of each month. New products may only be added on the 1st January each year, and the Pricing Council may change the level of reimbursement of a medicine only once a year, although price changes can occur much more frequently. Ceiling prices can be increased only 12 months after the last approval of the price [19]. Importantly, reasons for the Pricing Council's decisions are not made public. To date, applications for inclusion of new drugs on the PDL have rarely, if ever, been rejected; however, any decision to refuse an application to include, change, or exclude a medicine, or to endorse a proposed price, is appealable to the Transparency Commission (TC).[7]

[7] The Transparency Commission is also established under the LMPHM, with members appointed by the Council of Ministers from nominations from the Minister of Health, the Ministry of Health,

For each multisource medicine on the PDL, a notional reference or benchmark price is set at the level of the lowest cost per defined daily dose (DDD) for any brand or presentation of that medicine.[8] Benchmark pricing is also applied across molecules within the same ATC subgroup where the products are considered to be of similar efficacy and safety for a particular indication. The benchmark price within the "cluster" of drugs is set at the level of the lowest cost/DDD for any of the drugs within that cluster. The level of reimbursement is then set as a proportion of the benchmark. As a result of this therapeutic reference pricing, there are few incentives for competition in the off-patent market. As long as the ex-factory price of a multisource medicine is not higher than 80% of that of the originator and the price is shown to be no higher than the lowest price for the same presentation in any of the specified reference countries, the actual price can substantially exceed the current benchmark in terms of cost/DDD, with any excess becoming an OOP cost to the patient.

Section 264.2 of the LMPHM sets out notification requirements for suppliers of products whose prices form benchmarks, but it is unclear whether any guarantee of supply is required, or how lack of availability of a benchmark-priced product would trigger a revision of the benchmark price. More broadly, it is also unclear whether mechanisms exist to ensure that benchmark-priced products are either available for supply or stocked by pharmacists. In a recent announcement, it was stated that where no amount of an outpatient product has been procured by the NHIF in the preceding 6 months or the amount paid by the NHIF is less than 1% of the total amount paid for the reference pricing group, the product may be deleted from the PDL by the NHIF. This is expected enable the exclusion of products listed on the PDL but either unavailable in the market or with only a very small market share, from setting the benchmark price [28].

8.6 Levels of Reimbursement and Patient Out-of-Pocket Costs

The Pricing Ordinance sets out procedures for establishing the level of reimbursement paid by the NHIF for products in the Reimbursement List (Annex 1). It states that these should be determined according to perceived clinical significance, but at best this seems to be inconsistently applied. All products in Annex III, as well as

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the Ministry of Labour and Social Policy, the Bulgarian Drug Agency, the National Health Insurance Fund, the Bulgarian Physicians' Union, the Bulgarian Dentists' Union, the Bulgarian Pharmacists' Union, and from patient and pharmaceutical industry organizations.

[8] The defined daily dose (DDD) is a statistical measure of drug consumption, defined by WHO and used to standardize the comparison of drug usage between different drugs or different health care environments. It is generally the assumed average maintenance dose per day for a drug used for its main indication in adults. Importantly, the DDD does not necessarily reflect the recommended or actual prescribed dose. Moreover, an observation that two drugs in a given class have the same DDD for a given indication does not imply that they are of equivalent efficacy.

those in Annex I for chronic diseases causing "severe disruptions in the quality of life or disablement and requiring prolonged treatment are said to be subject to full (100%) reimbursement. However, the levels of subsidy for oral anti-diabetic agents, for example, range from 25% to 100%. Medicines for chronic diseases with widespread prevalence are said to be subsidized at 75% of the benchmark price; for all others, reimbursement is up to 50%, according to a complex assessment of various factors that include whether use of the product is considered to be essential, preventive, palliative, symptomatic, or for maintenance therapy; the social significance of the condition; the duration of treatment; "accepted" treatment algorithms; the number of patients with the condition; expenditure in the preceding year; and available budget. For some products reimbursement may be as little as 10% of the benchmark price.

As described earlier, for multisource products containing the same INN in the same pharmaceutical form, the benchmark price is set at the level of the cheapest version of the product as determined by cost per DDD. This is then prorated across all pack sizes. Benchmarking is also applied across different molecules within the same ATC subgroup, where the products have been shown to be of similar efficacy and safety for a particular indication, in which case the benchmark or reference price is calculated according to the lowest cost/DDD within the cluster.[9] Importantly, irrespective of how therapeutic referencing is applied (i.e., for multiple brands of the same molecule or a therapeutic class of medicines grouped in a cluster) the level of NHIF reimbursement is only a *proportion of the benchmark price*, not the actual price. Consequently, the OOP cost for a drug subject to, for example, 75% reimbursement may be considerably higher than 25% of the product's price, if that product is priced above the benchmark (see Box 8.1 for an example).

Box 8.1 An Example of Variable Out-of-Pocket Costs

Ranitidine, used in the treatment of esophageal reflux and peptic ulcer disease, carries a reimbursement level of 25%. It is available in three different brands.

For a treatment course corresponding to 30 days of 300 mg/day (30 DDDs), the NHIF contributes 25% of the benchmark price per DDD, or BGN 1.99 across all presentations.

Depending on the brand dispensed, the patient will pay either BGN 5.96, 15.17 or 13.61 in OOP costs for the same quantity.

(Example using Annex 1 data, Sept. 2014)

Adapted from Lopert [20]

Thus, the patient's OOP costs consists of the reference price minus the NHIF contribution (the minimum co-payment), *plus* any difference between the reference

[9] Therapeutic reference pricing is not used for medicines considered to have narrow therapeutic indices (e.g., anti-convulsants, immunosuppressants).

price and the retail price of the product. In many cases, the actual OOP is several times the benchmark price, and the NHIF contribution only a small fraction of the total. This has been reported to be a key driver of patients seeking medicines without prescription, as the levels of reimbursement are often so low that it is cheaper to pay for the entire product OOP than to add the co-payment to the cost of seeing a doctor to obtain one [7]. Reducing OOP costs would not only improve financial protection but potentially improve adherence to treatment for chronic conditions as well and in so doing, reduce downstream costs in the health care system. This has been shown empirically in several chronic conditions, particularly diabetes [29]. Yet, despite the very high rates of cardiovascular disease and diabetes, the NHIF subsidizes only 25% of the benchmark price of key medicines like statins. It is perhaps not surprising then that in 2013, statin use amounted to only 31.8 DDDs/1000/day,[10] low even within Eastern Europe and very low compared with the OECD average of 95 DDDs/1000/day in the same year [30].

Two recent announcements signal a potential easing of the burden of OOP costs to some degree. Following a 2015 amendment to the Pricing Ordnance, from September 2016 pharmacies may not charge patients more than 60% of the value of the benchmark price over and above the minimum co-payment for the product (the minimum co-payment being the benchmark price minus the NHIF contribution) [25]. However, it is not clear how this will be enforced, and given that the minimum co-payment varies as often as the benchmark-priced product changes, it is unclear how patients will be able to know whether they are being charged the correct amount. In addition, in March 2016, the Minister of Health announced that treatment for essential hypertension would be made available free of charge, with the NHIF fully subsidizing at least one drug in each therapeutic class of anti-hypertensive agents [31].

8.7 Procurement and Payment

Procurement procedures for medicines used in inpatient facilities (Annex II) fall within the scope of the Public Procurement Act. Each public hospital undertakes the procurement annually. Prices cannot exceed those established by the Pricing Council. The costs of medicines used in hospitals are ostensibly captured in the estimations of the costs of the clinical care pathways (CCPs), so in theory medicines used in inpatients should be fully covered by hospital budgets. In practice, however, patients with chronic diseases for whom medicines subsidized by NHIF are prescribed in outpatient settings are frequently expected to bring their medicines with them when admitted to hospital.

For outpatient medicines, the NHIF is responsible for payment in accordance with the determinations made by the Pricing Council. In 2012, the Ministry of

[10] Author's calculations based on IMS data for total statin sales in Bulgaria in 2013 of 84.4 million statin DDDs and population of 7.285 million.

Health assigned responsibility for payment for a list of specialty medicines to the NHIF. All of the medicines are fully reimbursed and include several oncology drugs funded outside the CCPs, as well as various drugs for orphan diseases and post-transplant immunosuppression. Despite additional funds being allocated to the NHIF to pay for these medicines, the amounts have increasingly fallen short of the demand, and the NHIF has only limited means by which to moderate prescribing. Expenditure on oncology medicines is one of the fastest growing areas of expenditure (56% growth rate over 2011–2013) and demand routinely outstrips the amounts budgeted (see Table 8.2).

Even with recent rapid growth, Bulgaria remains a small market. Despite the external reference pricing methods, prices for many new medicines are as high, and at times higher than in countries with much greater capacity to pay. The NHIF has the ability to leverage considerable market power as an effective monopsony but does not currently utilize this. While the option to reject a medicine on the basis of inadequate cost-effectiveness would create indirect leverage on price, until HTA mechanisms currently being developed are fully operational, some form of pooled procurement to increase market size would be advantageous in price negotiation

Table 8.2 Magnitude and growth in NHIF medicines reimbursement over 2011–2013

Group	Reimbursement value 2011 (000 s, BGN)	Reimbursement value 2012 (000 s, BGN)	Reimbursement value 2013 (000 s, BGN)	Growth 2011–2013
Digestion and metabolism	92,808	104,748	117,120	26%
Blood & blood forming organs	32,825	31,318	43,739	33%
Cardiovascular	85,978	92,560	85,447	−1%
Genitourinary system	7365	9542	9439	28%
Hormonal drugs for systemic use	4275	6078	6803	59%
Anti-infectives for systemic use	9586	13,760	14,695	53%
Antineoplastic and immunomodulatory drugs	57,207	72,331	88,998	56%
Musculoskeletal system	1484	1582	1647	11%
Nervous system	76,840	70,245	61,120	−20%
Anti-parasitics	143	164	157	10%
Respiratory system	70,172	79,307	82,691	18%
Sensory organs	9159	9434	7797	−15%
Various	5237	7740	8484	62%
Monitors and test- strips	8758	8814	9094	4%
Dietary foods	1142	1336	1521	33%
Medical devices	10,184	10,652	11,253	10%
Total	*473,163*	*519,612*	*550,005*	*16%*

From: Lopert [20]

and would expand purchasing power by increasing the market size. In June 2015, the Health Minister announced that by the end of 2015, Bulgaria would enter into arrangements with Romania for joint procurement of "high-value" pharmaceuticals [32]. With an anticipated focus on vaccines and oncology medicines, the objective is to obtain lower prices and reduce shortages. However, to date, arrangements have not progressed beyond the discussion phase, and further development may first require amendments to Bulgaria's procurement laws.

8.8 Distribution and Supply Chain

In Bulgaria, all levels of the medicines distribution chain for medicines are regulated. Vertical integration (manufacturer – wholesaler – retailer) is theoretically prohibited. However, the largest local producer Sopharma, a founding member of the Association of Bulgarian Pharmaceutical Manufacturers (ABPhM) (supplying both originator and generic products and the only local manufacturer of sterile injectables) is in fact one of several entities reportedly heavily vertically integrated with a wholesaling operation as well as owning a large number of pharmacies. There is also a substantial degree of horizontal integration. While by law, any one individual is permitted to own a maximum of four pharmacies, that same individual may own multiple entities, each of which may, in turn, also own up to four pharmacies, thereby controlling a substantial network. In reality, one network of around 300 pharmacies is owned by a single entity, which also owns a wholesaler [20].

Although the wholesale supply of medicines can be carried out by entities holding permits issued by a regulatory authority of any EU Member State, warehouses located in Bulgaria must be licensed by the BDA [7]. There are approximately 190 wholesalers currently licensed by the BDA and some 27 importers. Despite this, five wholesalers supply more than 80% of the market. As of May 2016, there were 4195 registered pharmacies in Bulgaria, including those in health care facilities [33]. Prescription-only medicines may only be dispensed and sold in registered pharmacies, but over-the-counter medicines are available in both pharmacies and drug stores of which there were around 960 in 2010. Only about half of the registered pharmacies hold contracts permitting them to dispense fully reimbursed medicines, as this is often perceived as commercially unattractive; they do not attract a retail margin and pharmacies receive only a fee of 2 BGN per prescription. Around 15% of Bulgarian municipalities have no pharmacy dispensing *any* NHIF-subsidized drugs, and patients must travel to regional centers for their subsidized prescriptions, or pay for them OOP. Pharmacies do not receive dispensing fees for their professional services, so they are heavily reliant on retail margins, OOP prescriptions charges, and sales of OTCs and non-medical consumer goods [20].

Parallel export is significant issue in Bulgaria. The NHIF is legally obliged to buy at lowest prices available among producers in the EU and once they have agreed to sell to the NHIF suppliers have no right to refuse sales of medicines at the same low price. Wholesalers are reported to purchase and repack products for

sale in countries where prices are relatively higher. In 2012, parallel export sales were valued at BGN 300 million BGN, three times the amount of the preceding year [12].

8.9 Promotion, Prescribing, Dispensing, and Rational Use of Medicines

To date there has been little apparent attention paid to the rational use of medicines in Bulgaria. While direct to consumer, advertising of prescription medicines is not permitted in EU member states; industry promotion directed at providers is thought to be influential in motivating the prescription of more expensive medicines. Anecdotally, there is frequent criticism of the BDA's capacity to adequately control advertising in the market. Although the Pricing Council's remit has included review and authorization of clinical (pharmaco-therapeutic) guidelines since its inception, the first six were only promulgated in late 2015 and early 2016. Moreover, none of the six appears to take into account cost or cost-effectiveness in guiding treatment and could conceivably increase existing growth in the use of high-cost medicines.

Prescribing by International Non-Proprietary Name (INN), though permitted, is rare [34] and is seemingly discouraged in most institutional settings. For NHIF-subsidized prescriptions, pharmacies are supposed to dispense only the brand specified by the prescriber. In practice, however, there is anecdotal evidence that because of the proportional nature of retail margins, substitution often occurs in favor of higher-priced products. The latter also tend to be favored when medicines are dispensed without a prescription. Substantial dispensing of prescription-only medicines to patients without prescriptions in part reflects the low rates of NHIF reimbursement and unpredictable OOP costs but also that patients who go directly to the pharmacy can avoid the time and expense of a physician consultation [35]. While this reduces costs to NHIF, it may well be adding to the burden of medication-related adverse events.

Yet despite near universal prescribing by brand and the theoretical prohibition on substitution at pharmacy for NHIF-subsidized drugs, generic utilization is not insubstantial, though it has declined in recent years. In 2011, the generic share of the market was estimated at 75% by volume and 44% by value [12]. This decline in part reflects the effects of promotional activities focused on new medicines but also concerns about the quality of generic products. In a 2012 study assessing patients' attitudes towards generic medicines in Bulgaria, 94% of respondents expressed beliefs that generic medicines were inferior to brand medicines in quality, safety, and efficacy but also that their views were heavily influenced by the recommendations of medical professionals [36]. By specifying originator brands, prescribers believe their patients can avoid "inferior" generic products. However, when medicines with prices above the benchmark prices are dispensed, patients must pay the difference out of pocket,

8.10 Conclusions

At the present time, Bulgaria lacks a cohesive national medicines policy framework and as a result, policy evolution has, to some extent at least, been reactive and seemingly *ad hoc*. Many current policy settings appear to be more concerned with limiting NHIF expenditure, rather than delivering financial protection for patients. Out-of-pocket costs for medicines are exceptionally high and make up around three quarters of all OOPs in health.

While the regulatory framework has been largely brought into line with EU standards, existing mechanisms for selection, pricing, and subsidizing medicines are not promoting efficiency or value for money and are giving rise to rapid growth in expenditure. Current pricing policies do not promote competition in the off-patent market and prices for some medicines compare unfavorably with countries with far greater capacity to pay. Several high-cost medicines contributing significantly to rapid expenditure growth are unlikely to be cost-effective in Bulgaria. Of perhaps greatest concern is that the growth is taking place without obvious improvements in health outcomes.

If rigorously applied, the introduction of formal HTA for selecting medicines for the Preferred Drug List should enable better estimation of value for money from novel medicines and at the same time strengthen the market power of the Pricing Council. Identifying and delisting or restricting the use of non-cost-effective medicines, promoting the use of generic medicines, and encouraging greater competition in the off-patent medicines market could improve value for money, while developing clinical treatment guidelines that consider cost-effectiveness and a range of measures to address demand and promote rational prescribing and dispensing could significantly improve efficiency in pharmaceutical expenditure and create fiscal space to facilitate improved access for patients.

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Chapter 9
Pharmaceutical Policy in China

Yu Fang

Abstract The Chinese government is implementing a systematic plan to achieve universal access to health care by 2020. One of the key pillars of this policy is to establish the National Pharmaceutical Policy. The aim is perhaps to ensure drug safety, quality, supply, and affordability. The China Food and Drug Administration have established regulatory systems to monitor the drug production process from manufacturing, distribution to safety monitoring, and medicines use. Although China has aspired to be a global manufacturer in the past decades, innovative drug development and generic medicines promotion policies are urgently needed to push China to become a true innovator in global pharmaceutical market. In China, the hospital pharmacies sell about roughly four fifths of all retail medicines sales. Economic incentive from prescribing medicines has been regarded as a factor influencing irrational and over use of drugs. In response to the rapid growth of drug prices and the ineffectiveness of previous price setting policy, the National Development and Reform Commission eliminated price ceilings in June 2015. To improve people's access to low-cost and high-quality essential medicines, a zero-markup policy will be introduced to all public health care institutions by 2017. With the implementation of Separation of Dispensing from Prescription policy, retail pharmacy will play a much bigger role in drug supply chain. However, pharmaceutical care provision has not been a priority for routine community pharmacy practice; multiple measures are needed to improve the contribution of pharmacists to pharmaceutical care.

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9.1 China's Health System

9.1.1 China Health Profile

China has a population of more than 1.37 billion people, with approximately seven million added annually. More than half of the population lives in urban areas (56.10%). Life expectancy at birth rose from 35.0 years before 1949 to 76.3 years in 2015, which has resulted in population aging. In 2015, people aged 60 and over accounted for 16% of the total population. It is expected that by 2020, the proportion of population aged 60 years and over will reach 18%, further increasing to 26% by 2030 [1].

Noncommunicable diseases (NCDs) (cardiovascular diseases, cancer, diabetes mellitus, and chronic lung diseases) are the main cause of mortality in China. More than 85% of mortality in China is attributed to NCDs. Although the main disease burden has evolved from communicable diseases to noncommunicable diseases, communicable diseases remain a problem in some western provinces. China's total health expenditure in 2015 was 4058.77 billion RMB (about US$635.5 billion). It accounted for 6.0% of GDP, lower than the average for all middle-income countries (6.6%). Per capita health expenditure is 2952.0RMB (about US$462.2). China operates a three-level medical service system: national level, province level, and county level. At the end of 2014, China had a total of 981,432 medical institutions and 4.84 medical institution beds per thousand residents. However, there is a marked difference between urban and rural areas, with 6.24 hospitals and health center beds per thousand people in urban areas, and only 2.80 in rural areas. In 2014, there were 9.70 health technical personnel per thousand in urban areas, more than twice the number for rural areas (3.77), with an average of 5.56 [2].

9.1.2 China Health Reform

The health care system reform was launched full scale in 2009 as the Central Committee of the Communist Party of China (CPC) and the State Council issued the Opinions on Deepening the Health Care System Reform. The State Council issued the Implementation Plan for the Recent Priorities of the Health Care System Reform (2009–2011). The overall goal of health care reform is to establish and improve the basic health care system covering urban and rural residents, and providing the people with secure, efficient, convenient, and affordable health care services. The government identified five priority areas for reform and established a committee across ministries to coordinate the policy formulation and implementation. Five priorities are accelerating the establishment of the basic medical security system, establishing a national essential medicines system, strengthening health services at grass roots level, promoting the equalization of basic public health services, and promoting pilot projects for public hospital reform.

1. Insurance
   The Chinese medical insurance system comprises mainly the basic medical security, supported by many forms of supplementary medical insurance and commercial health insurance. The basic medical security system covers basic medical insurance for working urban residents, basic medical insurance for non-working urban residents, a new type of rural cooperative medical care, and urban–rural medical aid, which cover, respectively, the employed urban population, unemployed urban population, rural population, and people suffering from economic difficulties. Much progress has been achieved since the implementation of the new health care reform in 2009. By the end of 2015, 1.325 billion urban and rural residents were insured [3].
2. Basic medical and health services system
   The basic medical and health services system includes county hospitals, community health organizations, township health centers and village clinics. The central government has invested about 63 billion RMB (approximately 10 billion USD) to support the 33,000 county hospitals and grassroots level of medical and health institutions. Local governments have also increased capital inputs. Besides the infrastructure, the central government also allocates funds to train healthcare professionals working in grass root-level health institutions. In this context, 36,000 primary care providers from 127 health centers were trained.
3. Essential public health services
   Essential public health services comprise ten types of basic public health services and seven categories of major public health services, including residents' health records, health education, immunization, communicable diseases, maternal and children health, chronic disease management, and mental health. Other important programs includes providing hepatitis B vaccine free of charge for people under the age of 15, prenatal services to rural women, including early pregnancy folic acid supplements, services for poverty-stricken cataract patients, and support for water quality laboratories.
4. Public hospital reform
   Health services in China are provided mainly by the public system, which covers 90% of emergency and inpatient services. Public hospital reform is currently in progress, and 17 national pilot cities and 37 provincial pilot cities are included in the program. China government has decided to put emphasis on comprehensive reform of county-level public hospitals and plan to complete the staged reform by 2015. Official statistics shows that, in the pilot areas, the out-of-pocket health expenditure as a percentage of total health expenditure has dropped from 40.4% in 2008 to less than 30.0% in 2015.

   China's county-level hospitals are leading the country's reform on public healthcare facilities since 2012. A pilot program was introduced, and this program covers 300 county-level hospitals. This would undergo reforms in finance, management, and human resources by 2015 to enhance their capacity. The program plans to wipe out the existing financing mechanism of Chinese hospitals relying heavily on medicine sales while their services are undervalued. County hospitals are known as the backbone of the country's health care network in rural

areas and directly serve over 900 million Chinese. Rural patients, however, tend to flood into major hospitals in cities to seek better quality services. The program has set a goal of restoring people's trust in county-level medical facilities and serving 90% of all the patients within each county [4].

According to the government policy, Chinese hospitals obtain about 15% markup by prescribing and dispensing medicines to patients. The unit price and prescription volume of a specific drug determine the amount of revenues generated from that drug. It is argued that financial incentive drives physicians (i.e., employees of hospitals in China) to dispense more prescription drugs, especially high-priced medications [55]. China has restricted around 2000 county-level hospitals to not to increase markup on drug prices. This has been done by introducing heath care reform in 2014. Public hospital reform has been carried out in all counties starting from 2015. The goal is that the hospitals reduce their dependability on revenues generated from drug sales. This is indeed a source of high public dissatisfaction for the patients. In due course, a centralized medicine procurement platform will be set up to boost transparency [5].

5. Essential medicines

The national essential medicine system is seen as an important innovation in health reform in China. A policy for the sale of essential medicines with zero markup (ZMU) has been introduced in public medical and health institutions since July 2011. Primary care facilities have almost universally implemented ZMU. By the end of 2015, all county-level hospitals and dozens of urban pilot hospitals have also implemented this policy. The State Council called for all urban hospitals to introduce this policy by 2017 [6].

At the beginning of 2009, a list of essential medicines was confirmed, and the system of drug supply was strengthened. Policies have been promulgated, including making use of the market mechanism, promoting improved medicines production, developing unified delivery systems, strengthening the quality of drugs, and fixing drug prices. Reform of the basic drug system is the key aspect of the reform of medical and health institutions. This was completed at the end of 2011.

9.2 Pharmaceutical Situation of the Country (Key Statistics, Pharmaceutical Industry, Trade Import Export)

As of the end of 2009, China had 6807 pharmaceutical companies; the top three pharmaceutical companies captured a 20% market share (compared to 90% in the USA and 73% in Japan). Wholly owned foreign or Chinese-foreign pharmaceutical companies accounted for 30% of the total number of registered pharmaceutical manufacturers and 27% of total market revenue. By the end of 2015, China hopes to have at least five pharmaceutical companies that post RMB 50 billion or more in

annual revenues and 100 pharmaceutical companies that post RMB 10 billion or more in annual revenues. Also the top 100 pharmaceutical companies are expected to be responsible for 50% of industry revenue [7].

Asia has the world's highest rate of pharmaceutical sales growth, increasing at an average annual rate of 15% between 2007 and 2012. This is well ahead of the USA and Europe, experiencing low single-digit growth over the same period.

In China, healthcare spending has more than doubled from $156bn in 2006 to $357bn in 2011 and is estimated to reach $1tn by 2020. This is about 6% of the country's GDP. As a result pharmaceuticals sales have increased from $21bn in 2008 to around $50bn in 2012. By 2015, pharmaceuticals sales will hit $63bn. This figure is bigger than the total sales in the combined markets of Brazil, Russia, and India [60].

It is expected that this phenomenon is set to continue in the future. Key drivers are the emergence of an increasing middle class in the country – second only to the USA in absolute terms – together with the government reforms.

However, healthcare spending is still relatively low on a per capita basis. The World Trade Organization (WTO) estimates that the USA spends about 30 times more than China on healthcare – accounting for about a fifth of its GDP, whereas in China spends about5% of its GDP on health.

In the past, China has aspired to be a global manufacturer, rather than an innovator. As a consequence, generic medicines dominate as follows: only 9 percent of domestic pharmaceutical sales is attributed to nongeneric brands, and only four drugs a year have been approved for marketing in the past 10 years [56].

Chinese research and development (R&D) spending is low. Total R&D expenditure for all sectors was about $220bn, or 1.7% of estimated 2013 GDP according to research by Battelle and R&D Magazine [57]. The equivalent figure in the USA was 2.7% and in Japan almost 3.5%. China is not reinvesting its revenues back into research. However, it is expected that this would change in the future. Government spending on R&D is expected to reach 2.5% by 2020 as it strives to get in line with the developed economies.

Sales in China amounted to less than 3% of sales for companies such as Pfizer, AstraZeneca, and Sanofi. However, the growth opportunities, which China offers, are not to be underestimated. The other issues included declining R&D productivity and the ongoing expiration of patents for many blockbuster drugs, and they pose serious threats to the industry [8].

9.3 Country's Regulatory Environment

9.3.1 Medicines Regulatory Authority

The China Food and Drug Administration or CFDA is the Chinese agency for regulating food, drugs, and medical devices [10]. The predecessor to the CFDA was founded in 1998 to initially oversee drugs and medical devices. When it was given

jurisdiction over food in 2003, it was renamed the State Food and Drug Administration (SFDA). Following a series of scandals in 2008, the regulatory body was put under the supervision of the Ministry of Health (MoH). Formerly known as the State Food and Drug Administration, the CFDA was restructured in March 2013 and elevated to a ministerial-level agency.

The China Food and Drug Administration is now part of the State Council of the People's Republic of China, the country's highest regulatory body that oversees the introduction of food, health products, and cosmetics in mainland China. Its responsibilities include drafting laws and regulations for food safety, drugs, medical devices, and cosmetics. It also established medical device standards and classification systems [9].

Here are main drug related responsibilities of CFDA:

1. The CFDA draft laws, regulations, rules, and policy plans on the administration and supervision of drugs [including traditional Chinese medicines(TCM) and ethnomedicines, the same below] and medical devices and so on. It has also established the direct reporting system for critical drug information. It also takes measures to reduce risks on regional and systemic drug safety.
2. To organize the formulation and publication of the national pharmacopeia, other drug and medical device standards, and classification system, and supervise their implementation. To develop good practices on research, production, distribution, and use of drugs and medical devices; supervise their implementation; and undertake drug and medical device registration, supervision and inspection. Also, to establish monitoring system for adverse drug reactions and it also undertakes monitoring and response activities. It also improves regulations and qualifications for licensed pharmacists and participates in formulating the national essential medicine list and assists in its implementation.
3. To formulate the investigation and enforcement system for drugs, medical devices, and cosmetics; organize their implementation and the investigation and punishment on major violations; establish recall and disposal system for defected products; and supervise the implementation. To establish drug emergency response system, organize and guide the emergency response and investigation on drug safety incident, and supervise the implementation of investigation and punishment. To formulate science and technology development plans for drug safety; organize their implementation; and accelerate the construction of drug testing system, electronic supervision tracking system, and information system. To undertake the public communication, education and training, and international exchanges and cooperation in the field of drug safety and promote the establishment of credibility system. To guide drug administration works of local governments, regulate administrative activities, and improve the interlocking mechanism between administrative enforcement and criminal justice [10].

9.3.2 Quality Control

In recent years, the CFDA has highlighted the importance of innovative drug development and safety surveillance by establishing and improving regulatory systems covering preclinical and clinical research, registration, supply, adverse drug reaction (ADR) monitoring and medicine recalls system. A relatively comprehensive system monitoring the whole drug production process from manufacturing and distribution to safety monitoring has gradually been established, including quality control of active pharmaceutical ingredients, postmarketing surveillance, and implementation of guidelines such as "Good Manufacturing Practice for Drugs" (GMP), "Good Clinical Practice"(GCP), and "Good Pharmacovigilance Practices" (GVP). Other approaches to maximize public protection in terms of medication safety and effectiveness include upgradation standards of drug testing, disseminating, and implementing the newly revised GMP, promoting the development of the national electronic drug regulatory system to track the quality of pharmaceutical products, strengthening ADR monitoring and drug reevaluation. According to CFDA in-house information, there are more than 4500 pharmaceutical manufacturers and about 180,000 approved products in China. Various pharmaceutical companies, including state-owned TCM/western medicine companies, small biotechnology firms, foreign-owned and joint ventures are also involved in drug research, development, and production. In the last few years, some multinational pharmaceutical companies have increased investment in drug development in China, especially the development of biological drugs.

9.3.3 Pharmacovigilance

Development of the pharmacovigilance system in China can be described in four stages: the preparation period between 1989 and 1999; the initial development period between 1999 and 2004; the rapid development period between 2004 and 2011; and a period of stability following implementation of the revised version of the Adverse Drug Reaction Reporting and Monitoring Provision. After more than 20 years of working and development, a relatively mature regulatory, management, and technology system has now been established.

There are four administrative levels in the pharmacovigilance system – national, provincial, municipal, and county – forming a technical support system to carry out ADR monitoring, and assessment at each level. The Department of Drug and Cosmetics Surveillance (DDCS) of the CFDA takes full responsibility for the surveillance of the manufacturing, supply, distribution and utilization of drugs, cosmetics, and special drugs or formulations. The DDCS also supervises the implementation of GMP, GSP, "Good Agricultural Practice" (GAP), and ADR

monitoring regulations, and responds promptly to urgent safety issues. The National Centre for ADR Monitoring (NCADRM) (also known as the Centre for Drug Re-evaluation, which is affiliated with the CFDA) is the technical supporting institution for the DDCS, which monitors ADRs and re-evaluates marketed pharmaceutical products, thus providing evidence for risk-management decisions made by the CFDA. As of 2013, one national center, 34 provincial centers, and more than 400 municipal centers for ADR monitoring were included in the four-level pharmacovigilance network, with more than 200,000 grassroot organization users, forming the foundation for further development of pharmacovigilance in China.

In 2003, a nationwide online spontaneous reporting system was established. To adapt to the rapid development of pharmacovigilance in China, the national ADR monitoring and updating platform was officially launched online on 1 January 2012. Based on daily routine requirements, the new management modules on the online platform included (1) individual ADR case reports; (2)"group adverse event reports" (reports for mass incidents); (3)foreign ADR reports; (4) periodic safety update reports; (5) quality evaluation; (6) early warning; (7) gathering structured data; and (8) category analysis.

Currently, healthcare professionals and pharmaceutical companies mainly report ADRs online. Patients/consumers can request their healthcare professionals, pharmaceutical companies, or local center staff to submit their ADR reports. ADR case reports from rural areas can be submitted on paper or by telephone, and are then sent to regional or national centers by mail or fax. The information is subsequently entered into the central system electronically.

In 2011, the role of pharmaceutical manufacturers in pharmacovigilance was highlighted in the revised Adverse Drug Reaction Reporting and Monitoring Provision, with the aim to promote the reporting from manufacturers. For instance, manufacturers are required to report serious ADRs incurred abroad within 30 days via the China Adverse Drug Reaction Monitoring System. The manufacturers are also required to submit written reports to the CFDA and NCADRM within 24 h if any overseas pharmaceutical products are suspended or withdrawn from the market.

By the end of 2015, the NCADRM had received more than 9.3 million reports, averaging 1044 reports per million in 2015. In that year alone, 1,398,000 case reports were received, of which almost 393,734 (28.2% of the total) were new or serious case reports. Of the total case reports in 2015, western drugs, TCM, and biological products accounted for 81.2%, 17.3%, and 1.5%, respectively [11, 12].

9.3.4 Counterfeit Medicines

Coupled with the lack of medical care, counterfeit medicines are also a serious problem in China. China is currently the world's top producer of both legitimate and counterfeit pharmaceuticals. An example of China's production capacity: the country can produce over a billion doses per year of over 40 different types of vaccines.

The medicines are produced by almost 7000 registered drug manufacturers, reaching the domestic market via a network of 341,000 pharmaceutical retailers. Total pharmaceutical output rose from RMB 1.37 billion in 1998, to RMB 667.9 billion in 2007. However, lack of consumer education, high medicines prices, and protectionist local governments' support for counterfeit industries has created a vast underground market of counterfeit pharmaceuticals. As a result, by some estimates, China is now the world's leading exporter of counterfeit drugs and bulk chemicals [13].

It is estimated that in China, between 200,000 and 300,000 people die each year due to counterfeit or substandard medicine. Due to many consequences stated above, counterfeit medicines are one of the deadliest businesses, but it can make an enormous profit for those who ignore the legislation and morality. This is the reason why its revenue keeps growing every single year.

In 1984, the Standing Committee of the National People's Congress adopted the Drug Administration Law of the People's Republic of China and introduced legal responsibility for the production and sale of counterfeit drugs. The law was amended in 2001, further explaining the counterfeit drug provisions by providing broad definitions of "counterfeit" and "inferior", as well as clear legal liability for production and sale of counterfeit medicines. According to this law, production (including dispensing) and distribution of counterfeit medicines are prohibited [14].

According to Article 141 of the Criminal Law of the People's Republic of China, anyone caught producing or selling counterfeit pharmaceuticals that are sufficient to seriously harm human health could face serious legal actions. As one of the leading exporter of counterfeit medicines, China has a responsibility to crack down on the production, distribution, and export of fake drugs. In addition, the safety and health of Chinese consumers require a nationwide and sustained commitment to keep counterfeit pharmaceuticals off the shelves [15]. Recent regulatory revisions and draft amendments are a step in the right direction.

9.4 Medicines Supply System (Procurement, Distribution, Etc.)

Due to the changing economic system, the Chinese government has reformed its pharmaceutical distribution network. It has been changed from a centrally controlled supply system to a market-oriented system. The competitive mechanism has been introduced into the pharmaceutical market, which improves the availability of medicines. Figure 9.1 shows the new pharmaceutical supply chain in China.

Under this supply chain, domestic pharmaceutical production grew dramatically while numerous imported drugs began to enter in the Chinese market. This supply chain is different from the drug supply mechanism under central planned economy. Whereas earlier pharmaceutical manufacturing firms could only sell drugs to wholesalers, now they are able to sell their products not only to the drug wholesale stations and drug stores but also directly to the hospitals. Meanwhile, bigger distributors can sell drugs to smaller ones. The wholesale prices could be different because of the different purchasing volume. There is a considerable imbalance of retail market

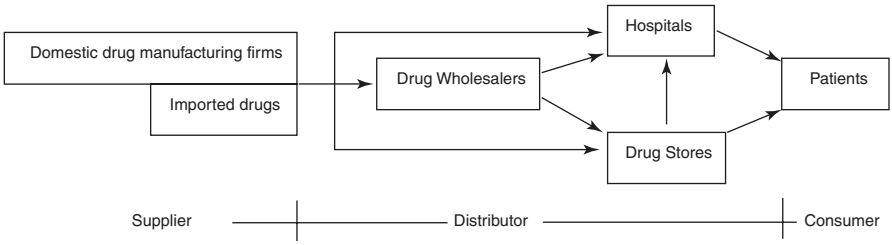

Fig. 9.1 Pharmaceutical supply chain in China (Source: Yu et al. [17])

sales within the supply chain: more than 80% of medicines are dispensed at the hospital pharmacies, while the remaining drugs are dispensed by retail pharmacies, including retail enterprises and rural drug supply outlets.

In China, most patient visits take place in the hospital, and patients typically fill prescriptions in the hospital's pharmacy. Patients prefer hospital pharmacies to retail drug stores for several reasons: convenience, physician recommendation, and greater assurance of pharmaceutical quality. Pharmaceutical sales are a hospital's main revenue source, typically accounting for over half of its total revenue. Hospitals account for roughly fourfifths of all retail pharmaceutical sales, even though retail pharmacies have been growing in recent years. By the end of 2015, China had 13,508 wholesale pharmaceutical enterprises, 448,057 retail pharmaceutical enterprises and chain store enterprises, and more than 550,000 rural drug supply outlets [16]. Most pharmaceutical manufacturers and large wholesalers have been actively promoting their products using a variety of strategies including hiring medical representatives to promote prescription in hospitals, advertising in public media for over-the-counter products, etc. These medical representatives often contact hospitals and doctors directly to sell their products. They use sales commissions, kickbacks, or gifts to hospital managers and/or doctors who purchase or prescribe their products.

The commercial promotion activities and profits for multiple layers of distribution are a substantial component of the total costs of pharmaceuticals [17].

9.5 Medicines Financing

9.5.1 Medicines Expenditures in General

The Chinese health financing structure has been constantly improving. China's health expenditure comes from the government's general tax revenue, social medical insurance, commercial health insurance and residents' out-of-pocket spending. In 2015, the total health expenditure (THE) in China reached 4058.77 billion yuan, 2952 yuan per capita. The total expenditure accounted for 6% of the country's GDP. In comparable prices, the health expenditure grew by an average annual rate

of 11.32% from 1978 to 2015. Individual "out-of-pocket" spending declined from 57.70% in 2002 to 29.97% in 2015, showing that health financing is working better in the areas of risk protection and redistribution [18].

Both total health expenditure (THE) and total pharmaceutical expenditure (TPE) have increased rapidly over the past few decades. Since 2000, THE growth has outpaced that of TPE. Thus, while TPE once made up close to 60% of THE, it has gradually fallen to around 40%. Nonetheless, drug spending makes up 2.28% of total GDP, a figure much higher than the OECD average of 1.5%. China's TPE/THE ratio is higher than that of Brazil (12%), Russia (18%), or India (26%). While health spending has increased across the country, there is significant interprovincial variation [19].

9.5.2 Pharmacoeconomics, Medicines Pricing and Access

Although multiple pricing mechanisms exist, drug pricing is largely determined through tendering for off-patent drugs or direct negotiations for on-patent drugs led by the National Health and Family Planning Commission (NHFPC). In both cases, drug quality plays a role in determining prices. We focus on hospital tendering, as this is the largest market. After the tender winners are announced, individual hospitals engage with manufacturers in a process known as "secondary negotiation." Secondary negotiation is where actual drug volumes are specified and hospitals usually secure a price that is lower than the listed tender winning price. At last, hospitals sell the drugs directly to patients and can charge a 15% markup. The supply chain from manufacturer to hospital can involve multiple distributors, each charging a markup. The process is slightly different for primary care facilities and pharmacies. Provinces will procure directly from tender winners for all their primary care facilities. Pharmacies are able to bypass the tender process and negotiate directly with manufacturers [19].

Following the rapid privatization of China's health care system, drug prices grew more than double digit rates annually [20]. In response, the government set price ceilings and price cuts on different products. Between 1997 and 2013, over 30 price controls were announced on a variety of drugs. Unfortunately, a substantial body of evidence has emerged showing that these policies were ineffective. While the prices of targeted drugs decreased by an average of 15–20%, total drug expenditure increased steadily. A study of price caps on antibiotics between 1996 and 2005 demonstrated a 47% decline in prices of selected antibiotics, but the overall expenditure on antibiotics was 205.7% higher [21]. Incentivized by the 15% markup rule, physicians evaded price ceilings by switching to more expensive antibiotics or prescribing higher volumes of medication. Due to their ineffectiveness, price ceilings were eliminated by the National Development and Reform Commission (NDRC) in June 2015 [22]. Even though price ceilings have officially been removed, price cuts are sometimes still used for tendering, with mandated cuts between rounds of tendering [19].

In the past 20 years, the rapid growth of the medical expense is a problem that both the developed and developing countries are facing. When the drugs are priced via drug economics, the drug clinical value must be considered to encourage enterprises to produce those medicines with the high clinical value. For example, in France, the clinical effectiveness level and the improved degree of clinical benefit must be evaluated before an innovator medicine is priced and determined into the medical insurance directory. Taking distinguishing pricing policies for different types of new drugs via the pharmacoeconomics evaluation system can enhance the management policy of innovative medicines and prompt new pricing policy to be in line with the drugs in innovation degree. The Chinese government should play the role of incentivizing drug innovation via price, such as setting up a pharmacoeconomics evaluation [23].

9.5.3 Generic Medicines

Like most other low-income and middle-income countries, China does not have a comprehensive national policy to promote use of generics; particularly, there are no progenerics insurance reimbursement policies.

There are more than 10,000 types of generic drugs in China, accounting for the vast majority of drug consumption market. Quality is becoming better and China's generic drugs can meet the treatment needs of most common diseases, and the market share has accounted for more than 85%. At the same time, the health care costs have become a large expense in China [24].

To further improve the quality of generic drugs, the China Food and Drug Administration issued a draft Working Plan for Quality Consistency Evaluation for Generic Drugs (Work Plan) on November 2012. As part of the 12th 5-Year Plan for Drug Safety, the Work Plan aims at elimination of generic drugs which fail the quality consistency evaluation in order to enhance the overall quality standards of generic drugs [18, 58].

The Quality Consistency Evaluation focused on consistency of composition and clinical efficacy between the test and reference products. CFDA intends to pilot the Quality Consistency Evaluation on the solid oral dosage forms of those essential medicines which have been applied widely in the patient population, with a large sales volume, produced by multiple manufacturers and that can be compared to a specific reference product.

Manufacturers of generic drugs are expected to conduct the Quality Consistency Evaluation on test products against the reference products based on the CFDA-published evaluation methods. They also need to submit the evaluation results as well as samples of the test products to the provincial FDAs where the manufacturers are located. The provincial FDAs shall subsequently organize an onsite inspection of the manufacturing facilities and collect three batches of the test products. Quality consistency can be established based on conformity with quality specifications set by the reference products and in-vitro in-vivo correlation. The evaluation results and

verification testing results can be forwarded by the provincial FDAs to the Project Office for an expert panel review. Failure to obtain a satisfactory opinion from the expert panel will result in test products to be withdrawn from the market [25].

9.6 Medicines Use (Issues Impacting on Rationale Medicines Use in the Country)

9.6.1 Medicines Use in General (In Community Pharmacies, Dispensing Doctors, and General Hospital Sector)

In China, the hospital pharmacies account for roughly four fifths of all retail pharmaceutical sales. The reminder of retail drugs are dispensed by drug stores, including retail enterprises and rural drug supply outlets. Patients can buy drugs from hospitals and drug stores [26].

9.6.2 Essential Medicine List, Selection of Essential Medicines, and Standard Treatment Guidelines

The Essential Drug System (EDS) is seen as one of five priorities that support the government's overall objective of establishing universal basic healthcare system that provides safe, effective, convenient, and low-cost healthcare services. This is to be achieved by 2020. Since the introduction of the official EDS concept in 2009, China has established the initial EDL and the supporting tendering policies, along with a purchasing and distribution system, and guidance on clinical usage. However, some significant challenges have remained unaddressed, including the lack of coverage of certain diseases and of certain patient groups, such as women and children. Furthermore, physicians' and providers' motivation to use more EDL products has been eroded by the implicit effect of decreasing revenues and profit for healthcare institutions.

The four areas of significant change in the new version of the EDL and its related policies demonstrate the government's bid to establish a more comprehensive and sustainable system. These four areas are listed below:

1. Expanded coverage of medicines
   The EDL coverage increased from 307 molecules to 520; the number of Western drugs increased from 205 to 317, and traditional Chinese medicines from 102 to 203. Disease coverage has broadened to include cancer and has been further expanded to include blood diseases and psychiatric disorders, with drugs in these three treatment areas accounting for approximately half of the newly listed Western molecules. The broadened coverage also includes more products for

women and children, for example, obstetrics/gynecology products and children specific formulations.

2. Standardized list, with tighter control of provincial additions.
   While the number of molecules on the EDL has expanded by an additional 70%, the number of formulations decreased by approximately 50% (from 2600+ to 1400+). The specification of formulation and dosage is part of the effort to build a standardized EDS. The central government also clearly requires local governments to strictly control provincial additions to the EDL. Provincial supplementing is still allowed to meet the rational needs of local populations but only after thorough scrutiny of the existing national EDL (NEDL) and provincial EDL (PEDL). Those products with similar clinical efficacy to drugs already on NEDL, products with unclear efficacy, and different formulations of NEDL drugs may not be added to the PEDL.
3. Broader medicines usage across healthcare institutions.
   To enforce the implementation of the EDS, the central government has extended the requirement for broader EDL usage beyond grassroots institutes and has expanded it to tertiary and secondary hospitals. More than 20 provinces have already published EDL-usage requirements for their hospitals. Most of these follow the requirements set by the central government on EDL revenue share (by value), which is 100% in grassroots hospitals, 25–30% in tertiary hospitals, at least 40% in secondary hospitals, and at least 50% in county hospitals that are participating in reform pilots.

   The government recognizes that there are clear challenges in achieving the EDL implementation goal, especially with respect to implementation in Class II and III hospitals: a deputy director of the National Health and Family Planning Commission (NHFPC) pointed out the that "only when physicians have incentives to prescribe, when patients have no doubts about the product quality, and when clearly favorable supporting policies are in place, then only EDL could be implementation in the large hospitals."
4. Increasing focus on medicines quality.
   In China, the current drug tendering practice considered both price and quality, which was first adopted by Anhui Province and then by other provinces. Under this tendering pattern, the manufacturers or wholesalers with high technical capacity and low-price products will have more chances to be the winning tenders. However, the resultant excessive focus on price – at the cost of quality – has widely been blamed for creating a market environment that is unsustainable for manufacturers. Due to excessive focus on pricing, it has resulted in producing low-quality medicines products in such province. With the emphasis on "quality first, appropriate price" in the State Council's No. 16 document(released in the same month as the 2012 EDL), the industry now expects more focus on the quality side of the price-quality balance. This is believed to be a long-term trend that is in line with the government's push to raise industry standards [27].

9.6.3 Prescribing Behavior in General (Factors Affecting Prescribing Behavior)

It is estimated that about half of antibiotic prescriptions in China were unnecessary . In China, economic incentive from prescribing medicines has been regarded as a factor influencing irrational drug use by 30% of studies. A survey on the health providers found that over 70% of the providers regarded bonuses as an incentive given to doctors to prescribe more or expensive services [28-34]. Studies in China showed that the lack of knowledge, especially from the patients' side was one of the important factors for irrational use. A study on the overuse of injections in China indicated that many people believed that injections were more effective than taking oral medicines [35].

9.6.4 Medicines Promotional Practices

Drug promotion presents a challenging dilemma for regulatory authorities. Physicians report that they often use promotion as a source of information about new drugs and this reliance increases as their career progresses. In developing countries, drug promotion is particularly crucial. Drug company sales representatives are often the most important source of information about new medicines, and studies have found that physicians rely heavily on industry-based sources of information.

China regulates the promotion and advertisement of drugs by two main statutes, the Advertisement Law (AL), promulgated in 1994 and revised in 2015, and the Drug Administration Law (DAL), promulgated in 2001, and the implementing and administrative regulations under these statutes. The China Food and Drug Administration and the State Administration for Industry and Commerce (SAIC) have concurrent jurisdiction over drug promotion. The regulation of drug promotion is currently dichotomous. The government closely oversees drug advertisements with clear rules on forum and content and with established penalties for violations, but largely ignores nonadvertising drug promotion. There are no regulations or standards for such promotion other than the general consumer protection requirement that promotion must not be false and misleading, the violation of which carries limited administrative penalties. China's biggest regulatory challenge is that it has a relatively underdeveloped regulatory regime but is faced with a high degree of regulatory noncompliance. In 2012, CFDA found over 179,000 illegal drug advertisements.

China prohibits direct-to-consumer (DTCA) advertising for prescription drugs. Advertisements of prescription drugs are limited to state-approved medical and pharmaceutical professional publications. China also strictly regulates advertisement content and requires approval prior to launch. Under Section 60 of the DAL,

drug advertisements, whether for prescription or OTC drugs, must be preapproved by the Provincial Food and Drug Administration of the province, or either by autonomous region or municipality in which the applicant is located. The main content requirement for an advertisement is that the statements must be true and legitimate and be based on information included in the approved package insert.

To curb inappropriate drug promotion, China relies a ban on DTCA for prescription drugs and a strict preapproval requirement for all drug advertisement but largely ignores nonadvertising promotion. Review and enforcement are mostly conducted at the provincial level, and not all provinces have the resources or expertise to monitor advertising activities. Because of these resource constraints, and the relatively light legal penalties available for advertising violations, illegal drug advertisements are common in China. Unethical nonadvertising promotion is also common due to the lack of regulation [36, 37].

9.6.5 Role of Pharmacist

China has two types of pharmacist qualification systems. The first is a professional qualification system, under which only pharmacists who pass the national pharmacist licensing exam can obtain a Licensed Pharmacist certificate. They are registered with a provincial regulatory authority and work in institutions where medicines are manufactured, distributed, or used. The minimum qualification to apply for the licensed pharmacist qualification examination is to attain a secondary technical school diploma and a major in pharmacy or related disciplines (e.g., medicine, chemistry, biology, or nursing). Meanwhile, working experience is also needed; this depends on the academic qualification. Currently, people with secondary, tertiary, Bachelors, or Masters degrees can apply for the examination after 7, 5, 3, and 1 year of experience, respectively. No work experience is required for candidates with Doctorate degrees. The CFDA and the Ministry of Human Resources and Social Security are the governing bodies charged with overseeing the licensing examinations, as well as the registration and mandatory continuing education of licensed pharmacists.

The second pharmacist qualification system is a specialized system, under which a pharmaceutical specialist is assigned a specific title, such as chief pharmacist, associate chief pharmacist, pharmacist in-charge, pharmacist, or assistant pharmacist, according to their educational background, work experience, and professional skills. This type of pharmacist works mainly in medical institutions overseen by the Ministry of Health [38].

At present, passing the licensure examination is not mandatory for pharmacists in medical institutions. As a result, the vast majority of pharmacists in medical institutions have specialized qualifications instead of licensed pharmacist qualifications. For example, by mid-2016, it is estimated that approximately 350,000 pharmacists work in Chinese medical institutions; of these, only 4126 were licensed [59]. There are also more than four million pharmacy technicians working in China's community

pharmacies [39, 40]. The role of the pharmacy technician requires a high school diploma or equivalent and also some training and certification at the college level, which takes between 3 and 6 months to complete. Under the direct supervision of a pharmacist, pharmacy technicians help dispense prescription medicines and perform other administrative duties in the community pharmacies.

Prior to 1990, the roles of pharmacists in community pharmacies mainly involved in the supply and dispensing of medicines, bulk compounding, administrative functions, and staff supervision and management. Since then, numerous developments have taken place in the various aspects of pharmaceutical education, legislation, and practice that encompass industry, hospitals, and community pharmacy [41]. The introduction and acceptance of clinical pharmacy and pharmaceutical care into the practice of pharmacy in China during the 1990s led to the involvement of some community pharmacists in related professional activities, such as drug information services and patient medication counseling [42].

The field of clinical pharmacy has grown rapidly since the introduction of the Temporary Regulations of Pharmacy Administration for Medical Institutions in 2002. Since then, the government required all hospitals to develop clinical pharmacy programs to promote appropriate drug use [43]. In January 2006, the MoH established 1-year clinical pharmacy training programs with both didactic and experiential components for practicing pharmacists [44]. However, to date, no standard working model for clinical pharmacists has been developed in China. This is because the establishment of the clinical pharmacist system has only recently been accomplished, and the pilot training of clinical pharmacists has just been completed [45].

The implementation of pharmaceutical care in Chinese hospital pharmacies continues to expand. However, pharmaceutical care provision as part of routine community pharmacy practice has not been a priority as the challenges include a shortage of pharmacists, lack of professional skills, lack of reimbursement systems for healthcare services, and poor public awareness of pharmacists [46]. The challenge in providing pharmaceutical care has led pharmacists to change their practices in community settings. Pharmacists from Shanghai Changhai Hospital were the first to extend pharmaceutical care from hospital patients to community residents, resulting in increased medication education across all levels with an expanded scope for pharmaceutical care [47]. The role of the community pharmacist in primary care has undergone significant changes, with a greater emphasis on providing patient-centered care and documenting healthcare services, which include counseling and providing medicines use reviews [48].

9.6.6 Pharmaceutical Care Interventions and Assessment of Community Pharmacy Practice

After the healthcare reforms in 2009, community pharmacies have come to play a significant role in China. In 2015, the number of community pharmacies reached 448,057. This is an estimated 6.0% increase from 2014. This increase was primarily

a result of the establishment of community retail pharmacy chains, which accounted for 45.7% of pharmacies in 2015, while the number of independent pharmacies decreased. Each community pharmacy in China caters for an average of 3057 people. In contrast, the number of licensed pharmacists was only 257,633 in 2015, equivalent to approximately 5317 people per licensed pharmacist. There is a lack of pharmacists in China, which has resulted in chronic shortages in rural areas in both hospital and community pharmacy sectors. A community pharmacist must register in a Provincial Pharmacists' Association to work. Two professional societies represent all Chinese pharmacists in community pharmacies: the Chinese Pharmaceutical Association (CPA) run by the Ministry of Civil Affairs, and the China Licensed Pharmacist Association run by the CFDA.

Both prescription and nonprescription medicines can be sold at community pharmacies. However, there are some exceptions which include narcotic drugs, some psychotropic substances, abortion drugs, anabolic steroids, peptide hormones, chemical products used in the production of narcotics, radiopharmaceuticals, and vaccines, which can only be prescribed and dispensed in designated medical institutions. Current regulations state that prescription medicines cannot be sold without a medical prescription [49]; however, because of the shortage of pharmacists and the profit-driven behavior of some retailers, the illegal sale of prescription medications (e.g., antibiotics) is very common, especially in the rural regions of China [50].

After the initial developments outlined above, a number of activities must now be initiated to further develop community pharmacy services in China.

1. Enactment of the Chinese Pharmacist Law
   Following the introduction of the provisional regulations of the Licensed Pharmacist Qualification System in 1994, and their revision in 1999 by the Ministry of Personnel and State Drug Administration, the number of licensed pharmacists (passing the national examination) in China has increased sharply from 98,310 in 2003 to 650,000 in 2015. With licensed pharmacists playing an increasingly important role in patient care, the legal and professional obligations of licensed pharmacists should be stipulated in law. However, no pharmacist laws are currently in place in China, thereby hindering the development of pharmacist skills for providing clinical pharmacy and pharmaceutical care services. In addition, pharmacists in China are of many different types, including licensed pharmacists in industry, hospitals, and community pharmacies, and pharmacists in medical institutions. Their responsibilities, as defined in the SFDA regulations [51], do not include the duty to maintain and proper care for patients. Thus, the Laws related to pharmacist involvement in patient care must be enacted.

   The adoption of standards for conducting pharmaceutical care activities is also an important step toward improving patient care throughout the nation. Pharmaceutical organizations, government, universities, and other healthcare stakeholders should work together in developing a nationally mandated standard to ensure quality pharmaceutical care practices in both hospital and community settings. Training programs delivered by health departments are also needed to ensure that the standard is correctly implemented by all pharmacists.

2. Development of the pharmacy workforce
   Pharmacists are expected to become more involved in pharmaceutical care in the near future [52]; hence, pharmacist development must be a priority to ensure an adequate supply of high-quality pharmacists. In February 2011, the MoH issued the Long-term Medical and Health Personnel Development Plan (2011–2020) [53] that projects that the number of Chinese pharmacists will reach 850,000 by 2020.
3. Increasing public awareness of pharmacists
   In line with the SFDA program to increase public awareness of healthcare issues, the China Pharmaceutical Association (CPA) carried out a "Pharmacist on Your Side" campaign [54]. This campaign aimed to increase public awareness about the vital role of pharmacists within primary healthcare team. Through increased awareness of the potential contribution of pharmacists to the Chinese healthcare system, more opportunities for educating pharmacists will be made available in the future to satisfy the public health needs of the patients.
4. Pharmacy services reimbursement
   The lack of third-party reimbursement for dispensing and advanced patient services provided by pharmacists is a barrier that must be addressed. To foster greater awareness of the value of pharmacist services and to ensure the long-term success of pharmaceutical care, policymakers need to focus more on remuneration for community pharmacy services. Ultimately, pharmacists will be able to enhance their revenues by increasing the range of patient care services, exploring innovative markets for pharmaceutical care services. This also includes getting remuneration from third-party payers (including private insurance companies, government programs such as the New Cooperative Medical Scheme in rural areas and basic medical security for urban residents.

9.7 Conclusions: Summary and Way Forward

China is reforming its health care system and committed to providing affordable basic health care for all by 2020. One of the key elements of this system was the establishment of a National Pharmaceutical Policy. In the past, China has aspired to be a global manufacturer, rather than an innovator. As a consequence, generic medicines dominate. The China Food and Drug Administration has highlighted the importance of innovative drug development and safety surveillance by improving regulatory systems. As a result, the drug production process from manufacturing and distribution to safety monitoring has gradually been established. Due to the changing economic system, the Chinese government has reformed its pharmaceutical distribution network, changing from a centrally controlled supply system to a market-oriented system. The competitive mechanism has been introduced into the pharmaceutical market, which improves the availability of pharmaceuticals. Under this supply chain, domestic pharmaceutical production has grown dramatically

while numerous imported drugs began to enter in the Chinese market. In response to the rapid growth of drug prices, the Chinese government set price ceilings and price cuts on different products since mid-1990s. However, this price setting policy was proved to be ineffective. As a consequence, the National Development and Reform Commission eliminated price ceilings in June 2015, while price cuts are sometimes still used for tendering. In China, the hospital pharmacies account for roughly four fifths of all retail pharmaceutical sales. To improve people's access to low-cost and high-quality essential medicines, a zero-markup policy has been introduced in public medical and health institutions since 2009. This policy will be implemented in all public hospitals by 2017. The implementation of pharmaceutical care in Chinese hospital pharmacies continues to expand. However, pharmaceutical care provision has not been a priority for routine community pharmacy practice. A number of activities must now be initiated to further develop community pharmacy services in China, including enhancement of number and quality of licensed pharmacists, improving professional skills, implementation of a reimbursement systems for healthcare services, and increasing public awareness of pharmacists.

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Chapter 10
Pharmaceutical Policy in Colombia

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Abstract This chapter aims to provide an overview of Colombia's pharmaceutical sector from 1993 to 2016. The 1993 Colombian Health Sector Reform was a radical change and led to the implementation of a compulsory social health insurance scheme covering essential medicines and use of generic products and International Nonproprietary Names for prescription and dispensing. This chapter provides valuable information about current country pharmaceutical achievements and challenges in the implementation of the General System of Social Security in Health (SGSSS). Over the past 22 years, health insurance coverage expanded from less than 20% in 1993 to over 97% in 2015. However, access and rational and effective use of health services and medicines are still burdened by inequality and inefficiency. Ensuring effective access to medicines in so-called scattered areas is one of the country's major challenges. The Government is currently working on developing a special health model for these areas. The 2012 National Pharmaceutical Policy has promoted positive scenarios of specific policies such as pricing system, biologics regulation, and interesting joint initiatives between the health sector and research on drug use, which may provide useful future interventions in the rational use of

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medicines. In 2015, a Statutory Law was also enacted to ensure the fundamental right to health. Currently, shifting to an implicit approach that involves the definition of an explicit exclusion list instead of the explicit inclusion list has become the medicines coverage challenge for the health system.

10.1 General Context

Colombia is located in South America and has a surface of 2,070,408 km^2, with an estimated population of 48.2 million (2015). More than 75% of its inhabitants live in urban areas [1, 2]. Colombia is a unitary, decentralized Republic consisting of 32 departments currently comprised of 1101 municipalities and districts [3].

Colombia's epidemiological transition has witnessed predicted increases in chronic, noncommunicable diseases. However, the burden of communicable diseases persists. Health improvements were observed nationally, but with large regional gaps. For example, the infant mortality rate (IMR) has been declining nationally, reaching 17.23 in 2014. However, the largest IMR is over four times higher in the Amazon department (48.96) compared with the Quindío department (11.83) [4].

Colombia is significantly affected by global economic changes and blatant inequalities. Colombia is classified as an upper middle income country. Its Gross Domestic Product (GDP) was US$ 292.08 billion in 2015 [5]. Monetary poverty and extreme monetary poverty levels show reductions at the national level during the period 2005–2014, from 45.0 to 28.5% for monetary poverty and from 13.8 to 8.1% for extreme monetary poverty, but with large regional gaps. In 2014, poverty incidence in rural areas was 1.7 times greater than the urban areas, and extreme poverty incidence was 3.5 times greater [6]. Moderate income distribution improvements were measured by the Gini index, from −0.557 in 2005 to 0.538 in 2014, but large inequalities remain [6], as the wealthiest 1% of the population accounts for 20% of revenue and about 40% of total wealth [7].

10.2 Health in Social Protection: The Policy Context

In 1991, Colombia's new constitution states that the social security is a public service to be provided under the coordination and control of the State, subject to efficiency, universality, and solidarity and under the terms established by the Law. Social security may be provided by public or private entities and resources allocated to these institutions may not be used for other purposes [8].

In 1993, the National Health System (1974–1993) was radically reformed; the General System of Social Security in Health (SGSSS) began to operate as part of the Comprehensive Social Security System. In 2007 and 2011, incremental changes were introduced to the SGSSS. In 2015, Colombia established health as fundamental

right, whose protection has to be regulated and established by designing and implementing mechanisms to structure national health benefits [9–12].

The SGSSS developed the "Structured Pluralism Model", which is based on managed competition with financing for a comprehensive package of personal health services [13]. Colombia was the first Latin American country to implement this model in its entirety in the 1990s. Published as a World Bank document, this model is recommended and promoted the main agencies and international organizations as the most effective model to attain the best levels of efficiency and equity in health systems [14–17]. However, its implementation has been a long and complex process with controversial results [18–21].

SGSSS key features can be described considering three parts [3, 13, 17]. First comes public financing, based on universal health insurance, which has two schemes. The "*Contributory Scheme* – RC" includes people with paying capacity: formal sector employees, informal sector workers, and freelance workers. Health insurance is mandatory for them. RC is funded by nontax resources, from compulsory employer and employee contributions. The other insurance scheme is the "*Subsidized Scheme – RS*", covering people with no paying capacity. Low-income individuals are identified by a means test. Its funding derives from fiscal, national, departmental, and nontax solidarity funds.

There is also another segment called "Noninsured low income individuals – PPNA". They are people with no paying capacity who are not affiliated with RS or RC and cared for by public health service providers. Their care is financed only from fiscal, national, and departmental public resources. The SGSSS does not apply to some other population segments. They are the so-called Exceptional and Special Schemes – R.E.E., such as military, workers of the Colombian state-run oil company – Ecopetrol, and teachers.

The second part is the institutional design with four separate health system functions: *modulation, financing, coordination, and delivery*. *Modulation*[1] is separated from financing and delivery of health services. Since 2012, the Ministry of Health and Social Protection (MoHSP) is the only legally responsible agency for SGSSS modulation [22]. *Financing* is separated from delivery of services with the establishment of the National "Solidarity and Guarantee Fund – FOSYGA". Funds are collected and solidarity is ensured between the schemes (RC and RS).

The delivery of health services gathers private and public "health service providers – IPS". Public health service providers are also called "*Social State Enterprises – ESEs"*. In both cases, they are funded by the sale of services (contracts). Actually, for many reasons, mainly or only ESEs are in place in many municipalities and departments, due to difficult geographic access and low population [23].

[1] Modulation is a broader concept: it involves setting, implementing, and monitoring the rules of the game for the health system, as well as providing it with strategic direction, according to Londoño and Frenk [13] p.8. During the period 1993–2012, two extinct boards were in charge of this function: the National Council of Social Security in Health – CNSSS (1993–2007) and the Health Regulation Commission – CRES (2007–2012).

Entities responsible for the *coordination* of services are separated from the delivery of services. Currently, there are public, private and mixed "Health Promotion Enterprises – EPSs". Legally, vertical integration between EPS and IPS is limited to 30% of the insurer's total expenditure [10]. In 2011, the EPS was called "Benefit Plans Management Entities – EAPB" [24]. The EAPBs have to ensure health services delivery, including medicines, through coordination and risk management with healthcare providers. EAPBs of the contributory scheme are responsible for collecting nontax contributions and retaining the "*Per-capita Payment Unit – UPC*" established by the SGSSS to offer the "*Individual Services Package – POS*". EAPBs of the subsidized scheme receive the "*UPC-S*" established by the SGSSS to finance the *individual beneficiaries' services package (POS-S).*

The third key feature is the definition of SGSSS benefit packages. Actually, there are four types of benefit plans [25]. The first one is the *Public Health Plan of Collective Interventions (PIC)*, defined as "basic care for all citizens", and has to be offered on a free and compulsory basis, it is financed by fiscal and public funds. The second is the individual services plan called *POS*, financed by the UPC. At the beginning of the SGSSS there were two plans, a contributory scheme (POS) and a subsidized scheme (POS-S). A single POS has been in place since 2012, while the definition of UPC is still being assessed [26, 27]. In 2015, the MoHSP initiated a 2-year pilot study for the temporary equalization of "pure premium", which corresponds to the premium net of administrative expenses of the per capita Payment Unit amount (for RC and RS) [28, 29].

The other healthcare plan is for accidents and catastrophic events for the entire population; it is financed by the compulsory insurance for road traffic accidents and the EAPBs, or by FOSYGA. The last plan is for urgent care and is for all citizens; it is financed by POS (RC and RS) via the EAPBs or other funds.

In the period 1993–2014, Total Health Expenditure (THE) ranged from 6.3 to 7.2% of GDP; individual out-of-pocket healthcare declined from 43.7 to 15.5% of THE in the same period, one of the lowest figures in Latin American region [30–32]. In 2014, health expenditure per capita was US$ 569 [33]. Over the past 21 years of SGSSS operation, the population's health insurance coverage expanded from less than 20% in 1993 to over 96.6% in December 2014, practically achieving universal coverage: 48% of the population under the subsidized scheme and 43.6% in the contributory scheme; it is estimated that 5% belongs to the R.E.E. However, inequalities and inefficiencies related to access, rational, and effective use of health services and medicines remain [28, 30, 34].

10.3 Pharmaceutical Policy Context

All the paramount health rules have involved direct or indirect changes related to the pharmaceutical sector. For example, in 1993, Law 100 states that "essential generic medicines" are part of benefit packages defined by the SGSSS and has been crucial for the promotion of essential medicines, use of generic products, and International

Non Proprietary Names (INN) for prescription and dispensation and subsequent efforts to establish a National Pharmaceutical Policy (NPP).

Laws have been the political and technical opportunity to create institutional arrangements (the National Institute of Food and Medicines Surveillance – INVIMA in 1993; and the Institute of Technology Assessment in Health – IETS in 2011). Similarly, in 1993, the MoHSP would again participate in the definition of a Medicines Pricing Policy with the creation of the National Commission on Medicines Prices (NCMP).

Thus, two NPPs were structured. In 2003, the MoHSP published the first NPP 2003–2008, focusing on rational use, essential medicines selection, and promoting competency [35]. However, it was not officially adopted and did not incorporate funding, monitoring, and evaluation mechanisms.

The approved NPP 2012–2021 had an intersectoral approach [36]. It identified issues related to nonrational use of medicines, inefficient spending, information problems, poor supply and dispensing system, and monitoring and stewardship weaknesses. It aimed at achieving equitable access to effective medicines and provision of quality pharmaceutical services under the principle of shared responsibility between sectors and stakeholders. Ten strategies were set to achieve these goals: reliable and timely information; governance; pharmaceutical human resources; pricing regulation; environmental sustainability and leverage biodiversity; strengthening inspection, monitoring, and control; design of pharmaceutical services networks; improved access to special medicines programs; and adapted medicines programs supply.

Currently, the Directorate of Pharmaceuticals and Health Technologies at the MoHSP created in 2011 is responsible for leading intersectoral NPP's monitoring and evaluation [37]. Important advances were achieved on pricing regulation, improving information, and regulatory framework for biotechnological medicines. The MoHSP also worked on an off-label use model in order to allow access and on the design of a medicines centralized bargaining mechanism.

Colombia has a specific approach to define SGSSS-financed benefit packages, which is the explicit inclusion list for individual healthcare services, including the list of medicines covered by POS and PIC. Recently, in 2015, shifting to an implicit approach that involves the definition of a specific exclusion list instead of an explicit inclusion list has become the medicines coverage challenge for the SGSSS [12, 38]. The MoHSP is currently designing the process to introduce this change without affecting rational use. This should be monitored by the NPP.

10.3.1 Pharmaceutical Market and Industry

In 2007, the NCMP legally defined two "channels" for the medicines market, considering the characteristics of the health sector [39]. The institutional channel represents all sales made by the institutions that comprise the SGSSS and R.E.E. The commercial channel represents all sales made by the commercial sector.

The size of these channels is not accurately established. However, recognizing that fact, the current NPP refers to estimates that can be made based on two sources [36]: (1) Intercontinental Marketing Services – IMS and (2) the Medicines Information System (SISMED) of the MoHSP.[2] IMS monitors the pharmacy and drug store market through standardized sampling. SISMED captures transaction reports for each medicine (in values and units) that sellers and buyers are required to make [40].

On the one hand, IMS estimated and characterized the domestic pharmaceutical market in December 2011 at approximately Colombian pesos (COP) $ 5.94 billion, or US $3.3 billion, the commercial or private channel at US $ 2.2 billion (COP $ 3.96 billion) and the institutional channel at 50% of the market, i.e., US $ 1 billion (COP $ 1.98 billion). The extrapolation and sampling methodology used by IMS in their estimates is characterized by uncertainty [36]. On the other hand, SISMED estimated the domestic pharmaceutical market at more than COP$ 8 billion. These data are not comparable with IMS estimates; it includes in-patient sector and real transaction reports from various stakeholders of the Colombian pharmaceutical supply chain [41].

The pharmaceutical industry sector in Colombia has approximately 143 industrial plants that are GMP-certified by INVIMA, 133 of which belong to national businesses and ten are foreign-owned laboratories. There is just one public manufacturer, which is part of the National Health Institute (NHI) and produces snake antivenom immunoglobulins [42].

The pharmaceutical industry represented 2.31% of industrial GDP and directly employs 22,264 people [43]. Both domestic and foreign laboratories mainly formulate medicines. Many of these medicines have been on the market for many years. There is no research or development of new molecules [44].

In 2011, domestic manufacturers reached a market share of 42% in terms of value, while their share in terms of volume produced (units) was 75% [45]. Colombia is highly dependent on pharmaceutical imports (both finished products and APIs, as well as, chemical, biological, and biotechnological products). Its deindustrialization process is reflected by the reduced value added to pharmaceutical production, total industrial and nonindustrial economic activity, as well as reduced net foreign investment in the pharmaceutical industry and loss of participation of foreign capital establishments in the domestic production of medicines [46].

In 2009, pharmaceutical products exports represented just 1.19% of total exports, while pharmaceutical products imports reached 3.36% of total imports. For that same year, total country imports and exports of APIs, excipients, and finished and semifinished products were US$ 1.105 billion and US$ 391.21 million, respectively, showing a foreign trade balance deficit of US$ 714 million. Regarding these totals,

[2] SISMED is part of the Integrated Information System for Social Protection - SISPRO. SISPRO is a tool for obtaining, processing and consolidating necessary information for decision-making for policy development, regulatory monitoring and management services in each of the levels and essential processes in the sector: insurance, financing, supply, demand, and service use. This information is available to all citizens http://www.sispro.gov.co/.

APIs and excipients represented roughly US$ 234 million of imports and US$ 19.3 million of exports, respectively. Finished and semifinished pharmaceutical products imports were US$ 656 million and US$ 214 million, respectively, whereas finished and semifinished products exports reached US$ 370 million and US$ 1.5 million, respectively [43].

10.4 Medicines Regulatory Environment

The *MoHSP* is the highest level health authority. The *National Health Superintendent-Supersalud* is the head of SGSSS Inspection, Monitoring and Control (IMC). Two of SGSSS' seven areas are specially relevant for medicines as regards Supersalud's role: insuring the population and providing individual and collective healthcare [47]. Surveillance agencies for the production of goods and services for use and human consumption, supplies, facilities, and processes across the production chain are divided into three categories: health authorities, producers, and suppliers and consumers of these goods and services. Health authorities are the Ministry of Health and Social Protection, National Narcotics Fund-UAE, INVIMA, NHI, and the Territorial Entities (ETs) through the Territorial Directorates of Health (DTS).

The *National Health Institute – (INS)* is an autonomous entity linked to the MoHSP. It is responsible for epidemiologic surveillance. Since 2011, it is classified as a National Institute of Science and Technology of the General System of Social Security in Health and the Science, Technology and Innovation System. The INS also promotes, guides, implements, and coordinates scientific research in health and biomedicine; it is a national reference laboratory and manufactures biological products of interest to public health. The National Health Observatory is part of the INS and is responsible for the surveillance of public health information and provides policy recommendations [48].

The *National Institute of Food and Medicines Surveillance*, *INVIMA*, is an autonomous entity linked to the MoHSP. It is responsible for implementing IMC for medicines and other supplies that may impact individual and collective health. INVIMA has the power to issue regulations to develop the regulatory frameworks established by the MoHSP.

The *Territorial Directorates of Health – DTS* (departmental, district, and municipal level) is required by INVIMA to perform IMC of distributors and retailers of medicines establishments, such as pharmaceutical specialty agencies, warehouses, pharmacies, drug stores, and health food stores. Under the SGSSS Obligatory System for Quality Assurance in Health (SOGCS), the DTS is also in charge of IMC for health service providers (IPS and ESE), including pharmaceutical service providers.

The *Institute of Technology Assessment in Health (IETS)* is a nonprofit corporation with mixed public and private participation and own assets. Among their main functions is conducting health technology assessments based on scientific evidence, taking into account issues of safety, efficacy, effectiveness, and economic impact;

developing recommendations, guidelines, protocols, and generating information to facilitate decision making in the health sector, all at the request of the MoHSP [49].

10.4.1 Medicines Regulatory Authority

INVIMA is in charge of marketing authorization; it regulates advertising and conducts postmarketing surveillance throughout the lifecycle of health products. It ensures the traceability of medicines from production to final consumption to prevent counterfeiting and drug smuggling. As part of postmarketing surveillance, the pharmacovigilance program examines efficacy, safety, adverse events, and contraindications. In addition, INVIMA certifies Good Manufacturing Practices, Good Clinical Practices for medical research in humans, and operates the country's quality control reference laboratory.

In 2010 for the first time and in 2016 for the second one, INVIMA was recognized as a reference national regulatory authority (NRA) for the Americas [50, 51]. It means INVIMA adequately performs its regulatory functions to ensure efficacy, safety, and quality of medicines. It is one of the six reference NRAs in the region. This section offers an overview on some of the main medicines regulatory functions, according the regulatory assessment tool [45]. Colombia has made important progress in the strengthening of regulatory systems for medicines and other technologies. Nevertheless, local improvements are required in specific areas such as pharmacovigilance.

10.4.1.1 Good Clinical Practices

Legal provisions are in place for biomedical research mainly to protect human rights and welfare of enrolled individuals. Clinical trials require prior authorization and approval of an ethics committee and must be reported in INVIMA's clinical trials database. Research sponsors have to meet Good Clinical Practice standards and healthcare providers involved must have certified health service quality standards. INVIMA oversees every instance involved in this type of research. Information about clinical trial requests and approvals for the period 2008–2016 and other related document are available at the institutional website.

10.4.1.2 Medicines Licensing

Specific marketing authorization criteria are publicly available, as are exemptions, such as special imports, donations, emergency, orphan drugs, among others. There are no foreign license recognition mechanisms. Following the current government's development plan, the MoHSP and INVIMA are analyzing the medicines authorization process in order to include IETS inputs. In 2011, there

were about 17,000 pharmaceutical products licensed by INVIMA. The institutional website provides current technical information about approved products in Colombia [45].

10.4.1.3 Quality Control

In Colombia, legal provisions ensure the quality of pharmaceutical products as per GMP standards. INVIMA has a national reference laboratory for medicines quality control where inspectors collect samples for quality testing in postmarketing surveillance.

A local program called "Demuestra la Calidad" (Demonstrate Quality) has been in place, since 2004, in which samples are collected at wholesalers and retail pharmaceutical establishments. As of 2011, more than 765 samples had been collected and 22.5% did not meet quality standards [45].

10.4.1.4 Pharmacovigilance

The country's pharmacovigilance network is led by INVIMA, with important results in monitoring adverse drug reactions (ADRs) and medication error notifications. In 2011, INVIMA's database included 35,398 ADR notifications. New efforts are required on risk management and regarding decision making.

Worth highlighting are some specific efforts made according to strategies of the current NPP (2012). A recent study describes medication errors reported to a pharmacovigilance system by 26 hospitals for patients in the Colombian healthcare system from 2008 to 2013: there were 9062 medication errors in 45 hospital pharmacies. Real errors accounted for 51.9% of the total, of which 12.0% affected the patient and caused harm to 17 individuals. The main error-prone process was prescription, followed by dispensation, transcription, and administration. Administration-related errors were 45.2 times more likely to affect patients [52].

Another study following ADR associated with the use of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis recommends patients monitoring to reduce the risks observed. The highest numbers of ADRs were reported following the use of tocilizumab, rituximab, and infliximab, and the most frequently reported ADRs were elevated transaminase levels and dyspepsia. Overall, 73.2% of patients who experienced an ADR stopped taking their drugs [53].

10.4.1.5 Generic Medicines

Generic medicines policies in Latin America have aimed to improve access to medicines by promoting competition in the pharmaceutical market; there is scarce evidence about the effect of these strategies in the region since the 1990s. Furthermore, for other subregions, and even for the United States and Canada, policies promoting

generic drugs are mainly focused in replacement policies restricted to deprescription conditions and dispensing of generic versions of a specific pharmaceutical product, and these concessions are strictly related to the guarantee of equivalence between the competitors and innovators. Colombia does not have any registration, financial or deprescription incentives to promote the use of generic medicines [54].

Generic drug-use policies have been in place in Colombia since the late 1980s. In 1991, during the National Health System, the Ministry of Health established the mandatory use of INNs for the prescription of medicines [55]. This has been reinforced in all regulations on medicines coverage since the beginning of the SGSSS to date [56]. NPPs medicines supply chain rearrangement strategy have been the promotion of generic drugs competition in the pharmaceutical market.

Perception studies on generic medicines continue to show controversial outcomes. A recent study showed a good level of perception in a sample of prescribers in Bogotá: 5 out of 5 questions were answered as "adequately perceived" by more than 50% of cases. Outcomes for this realm coincided with Shrank, in which 45.8% of individuals who stated that generic and brand drugs are equally effective. Actually, INVIMA has structured an advertising campaign about myths and realities about generic medicines [57–59].

10.4.1.6 Patents and Data Exclusivity

Since the 1970s, patent protection has been regulated in Colombia through the Andean Community Decisions. Because of its membership, decisions directly affect the country. The World Trade Organization TRIPS Agreement (Trade-related Aspects of Intellectual Property Rights) was incorporated in 2000 by Decision 486 [44]. Colombia has been a WTO member since 1995 and has never exercised the right to use any TRIPS flexibility (e.g., parallel imports or compulsory license) or the Doha Declaration (2001) as safeguards to protect public health from patent rights' holders abuse. Instead, Colombia introduced data protection for an exclusivity period by Decree [60]. This is a controversial decision because of its impact on the generic market: it delays the entrance into the market of competitors of the protected product, regardless of the patent protection's status. Subsequent free trade agreements celebrated by Colombia with the United States and EU adopted the same standard, laying down an obligation to provide for a 5-year term of regulatory test data exclusivity. The Decree has established a highly effective entrance barrier [44].

Only two processes have requested drug compulsory licenses (Kaletra® started in 2008 and Glivec® in 2014); both initiatives stemmed from civil society organizations and none of them has resulted, in a compulsory license so far. Fortunately, Kaletra® process achieved a price reduction of around 80% due to a price control mechanism ordered by a judge to the Government. Glivec® process is still ongoing [61] (Fig. 10.1)

Kaletra® and Glivec® processes have contributed to improve stakeholders' understanding and technical capacity to increase access to medicines in Colombia. Civil society will continue to insist on the need and urgency to use the compulsory license mechanism for Glivec®, knowing that a favorable outcome is difficult to obtain.

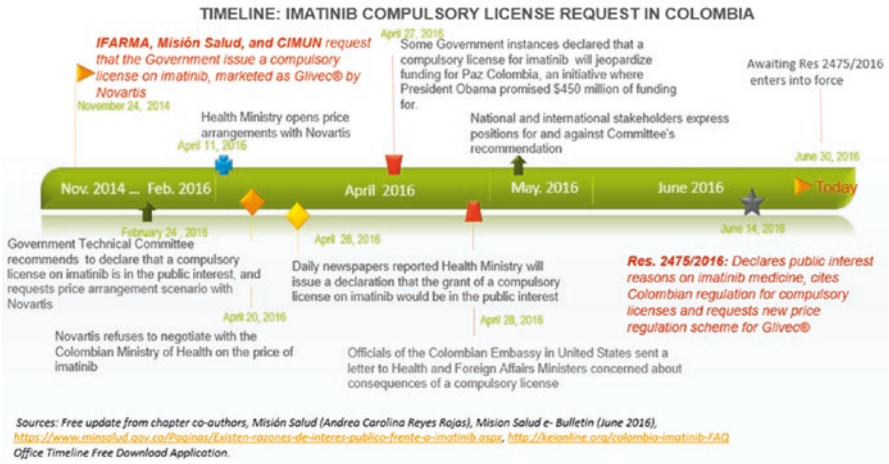

Fig. 10.1 Timeline: imatinib compulsory license request in Colombia, 2014–2016 (Source: Elaborated by authors)

Thus, Government's support is needed, and future initiatives to grant compulsory licenses will evolve from the Government. This would help to achieve lower prices for those medicines. [61].

10.5 Medicines Supply System and Pharmaceutical Services

In general, there are three medicine supply systems: the institutional sector, the private sector, and the Government supply for diseases and conditions of public health interest and controlled medicines.

10.5.1 Institutional Sector

This sector corresponds to the marketing and distribution of medicines in the institutions that compose the SGSSS and the R.E.E. There is no single network for supply chain distribution within the country. The chain network consists of three groups with specific roles.

The first group is composed by *manufacturers and importers*. They manufacture or import medicines as a finished product. They are responsible for registering the product at INVIMA. Then we have *distributors and retailers*, they act as brokers purchasing directly to agents in Group 1 or other distributors and sellers of the same group, to sell to the IPS (public or private). It is important to note that it has not been possible to establish the level of intermediaries in the supply chain or the approximate

number of stakeholders. This is because Colombia lacks mechanisms to measure registration of companies and organizations whose purpose is to purchase, sell, and/or distribute medicines.

The existence of companies generically called "logistics operators" in Colombia is also highlighted here. These companies have outsourced pharmaceutical services of the public (ESEs) and private IPSs and contracted insurers (EPS) for dispensing medicines to members of the SGSSS (in RC and RS). For the Adapted Entities (EA), they dispense medicines to the R.E.E. Logistic operators even perform other types of assistance activities at the hospital and outpatient areas. Some of them are Third Party Logistics (3PL) and Fourth Party logistics (4PL) operators. 3PL outsources one or more logistical processes, while 4PL outsources logistical strategy design and its processes. These operators integrate pharmaceutical processes, including logistic and pharmaceutical operations like compounding, pharmaceutical care, and other clinical activities.

Decreased direct purchases by health service providers (IPSs) – private and public (ESEs) – to Group 1 stakeholders has been observed. Actually, purchases by insurers (EPS) via intermediaries and pharmaceutical outsourcing services have been increasing. For example, in the case of cancer medicines, in 2009, 85% of oncological IPS were purchased directly, while it fell to 52% in 2012 [62]. This occurs especially in the contributory regime of the SGSSS and R.E.E. in large cities. In 2014, approximately 72% of the population in the contributory regime received their outpatient medicines from the large EAPBs or outsourced major logistics operators (*source based on* [63]). The situation of the subsidized scheme differs between capitals and other municipalities. In capitals, there is a similar pattern of intermediation, but EAPBs contracts are with small intermediaries or hospital cooperatives[3] (or other types of cooperatives); in cities or intermediate and small municipalities, contracts are made according to accessibility or availability – with intermediaries, the public hospital (IPS-ESE), or drug store (private).

Private and public health service providers in charge of dispensing medicines form the third group. For hospitalization, IPSs contract pharmaceutical services with the EAPBs directly or via outsourcing (partial or whole service). Those agreements follow the same practices described above or they also buy its products from agents of the first or second group depending on its financial capability. In this area, a new type of outsourcing appears, namely, the "Compounding center", which also has become important in facilitating compliance with defined quality standards for pharmaceutical services in the Obligatory System for Quality Assurance in Health (SOGCS).[4]

Very few services perform the full technical processes for dispensing medicines. In most cases, they are simply limited to medicines delivery, without providing information to patients or meeting the quality standards established by pharmaceutical service regulation.

[3] Public hospital Department cooperatives are organizations under private law where public hospitals (currently called ESE) collaboratively purchase medicines and devices [62].

[4] Principles and requirements for the provision of quality health services were established from the beginning of the SGSSS and are regularly reviewed. SOGCS currently consists of four components: Training, Auditing, Accreditation and Information System for Health Quality.

The distribution of SGOCS pharmaceutical services is heterogeneous; they are concentrated in the capitals. Only 38% of the municipalities in the country have SGOCS-compliant pharmaceutical services [65]. This, in part, is due to geographical barriers and poor road infrastructure (Grade 2/7) [66].

Contract rules are governed by type of medicine product; those included in the benefit packages and ambulatory supplies (excluding high-priced medicines) are contracted by capitation: the EAPBs deliver a fixed amount on a regular basis, the IPS is contracted to cover supply for a period of time, regardless if the user requests them or not [67]. High-priced and hospital medicines are purchased per event. In recent years, for certain health conditions, contracting is done comprehensively, including medical care, provision of medicines, and other health technologies, as well as providing complementary services such as pharmaceutical care with payments through fee for service and diagnostic related groups (for both outpatient and inpatient) [67]. This is commonly seen for the treatment of diabetes, chronic heart disease, breast cancer, and hemophilia.

10.5.2 Medicines Managed by Government

Through the MoHSP, the national government performs centralized management of the medicines supply for the following diseases of public health importance: malaria, leishmaniosis, Chagas disease, and tuberculosis. In addition, there are vaccines and supplies through the Expanded Immunization Program. The Public Health Plan of Collective Interventions (PIC) provides guidelines and the MoHSP directly performs the supply, storage, purchase, and distribution of these medicines and vaccines.

The MoHSP uses international procurement mechanisms such as PAHO Strategic Fund for the purchase of medicines (TB, malaria, Chagas, and leishmaniosis) and PAHO Revolving Fund for vaccines and syringes. In some cases, the MoHSP makes local purchases. The level of compliance with quality standards for the processes of demand management, storage, distribution, and dispensing is homogeneous within each department; however, there are large differences between departments. The development of these processes is influenced by local government policies. Some departments show significant improvements regarding processes and human resource stability; in others, there is a high turnover of human resources, which does not allow for continuity in quality compliance [68].

Despite efforts of national and territorial authorities, poor coordination between central level and departments is an issue that impact supply; which, therefore, impacts access to medicines. During the implementation of the SGSSS, public health indicators related to vaccination coverage and management of diseases of interest to public health (i.e., malaria, tuberculosis, Chagas disease, and leishmaniosis) also suffered significant deterioration.

The lack of an information system that makes real time and traceable information available for medicines is clear [68]. Given the geographic diversity of rural versus urban and low and highly populated areas, it is important to establish

a decentralized logistics model with different distribution centers to optimize supply [69].

10.5.2.1 Medicines Under Special Control

"Special control" medications are managed by the Government through the National Narcotics Fund, UAE-FNE. Departmental Narcotics Revolving Funds (FRE) were legally created to ensure availability in the country. The network involved the UAE-FNE, the FRE, wholesalers, IPSs, ESEs, drug stores, and other pharmaceutical establishments that are legally authorized to manage these types of medicines. One of the access-related challenges is the weak coordination between central and departmental levels, the lack of resource allocation at department levels for the FREs and the lack of pharmaceutical services or drug stores trained to handle these medicines in remote areas [70].

10.5.3 Private Sector

This sector includes large drug store chains and cooperatives that sell medicines. In this case, there is only one supply chain: the laboratory, chain, or cooperative drug store. The State, through the Territorial Health Entities, conducts inspection, monitoring, and control (IMC) on products and processes. The end user (patient) purchases medicines via out-of-pocket expenditures.

Some of these chains also operate in the institutional channel, with the same infrastructure and human resource processes, but with different sales prices. There is no official source stating the number of medicine stores. In 2011, 12,441 drug stores and 178 pharmacy drug stores were reported in 20 of the 36 Territorial Health Entities, according to the MoHSP [45]. In 2014, 10,945 drug stores were registered nationally, which corresponded to 2.5% of all companies in the country [71].

Colombia has regulations on standards for the provision of pharmaceutical services, specifically for the selection, purchase, storage, distribution, and dispensing of medicines. However, the application, interpretation and strictness of regulators actually vary across regions and type of stakeholders [70].

Ensuring effective access to medicines in so-called scattered areas is one of the country's major challenges. Population dispersion stems from the country's poor infrastructure and geographical, socioeconomic, and cultural characteristics. The Government is currently working on developing a special health model for these areas. The idea is to have a single operator in charge of insurance and service delivery in all municipalities [72].

There are large gaps in infrastructure and technology for supply chain management between territorial entities and institutions. Few services are automated or have comprehensive and robust information. Most services are performed manually with intermediate-level information systems, such as Kardex manuals. The challenge

is also to articulate supply chain management with appropriate standards and rational use.

Throughout the implementation of the SGSSS there have been many attempts to develop a negotiation strategy [11] for centralized procurement. Although legislation exists for certain high-priced medicines for HIV/AIDS, cancer, or orphan diseases [73], the government has not been able to implement centralized procurement. The principle of risk sharing has prevailed among insurers against consolidation of needs and centralized procurement. By 2016, the Government will renew this initiative to legislate and implement a centralized bargaining process [74].

10.6 Medicines Financing

All medicines covered by the SGSSS are financed according to the benefit packages rules (POS and PIC). There is a special authorization process for medicines nonpart of POS (non-POS). The current benefit packages consist of 673 medicines and 13 pharmacological groups; this represents about 710 active principles. The subgroup of medicines for Public Health Special Programs (under PIC) represents 25 products and about 19 active principles [56]. Most medicines included in "WHO Model Lists of Essential Medicines" are included in the current list.

Besides the extension of benefit packages, the big challenge for the government is to ensure rational use of medicines. It considered that the prescription will be established under the principles of doctors' self-regulation and transparency.

The provision of medicines for the PIC is free-of-charge through all the SGSSS and the R.E.E. For the CR, POS medicine prescription requires user rates according to individual income. There are no user rates for the RS. Amounts collected from this matter are EAPBs. User rates are not considered a financing mechanism, but this payment at the point of service could be considered a barrier for access.

The authorization process for non-POS medicines is changing, due to the transition from an explicit plan of benefits to an implicit plan with exclusions, as referred to in Sect. 10.3. EAPBs is responsible for this procedure until September 2016, then after this period it would go through an online prescription system without any special authorization [75].

One last consideration is the judicial order for non-POS medicines, which is a dramatic situation. The MoHSP estimates that between 1997 and 2000, reimbursement requests for medications not included in PB totaled 387 and there were 701 judicial orders that mandated the reimbursement of medication not included in PB. By November 2009, the health system received 1,412,462 requests for non-POS medication reimbursements and 945,406 judicial orders. In an attempt to accommodate the increased request for non-POS medicines, the Colombian Government enacted a new law to increase POS coverage. The

Constitutional Court, however, ruled it as unconstitutional as it favored only certain parts of the population [44]. In 2014, there were 36,510 judicial orders to supply medicines: this constituted 62.82% non-POS orders, while the rest were POS 37.18% related orders [76].

Contributory scheme expenditure had a noticeable rise from 2009 to 2011, mainly due to increased members, but also due to the significant growth in payments by FOSYGA to the EPSs regarding reimbursements of non-POS medication. In addition, FOSYGA lost several lawsuits[5] initiated by patients for medicine reimbursements. The amount of reimbursement payments (in billions of Colombian pesos) in 2009 was 1925.4, 2429.0 in 2010, and 2154.8 in 2011 [77].

Subsidized scheme expenditure has grown much more than any other area. According to the MoHSP, this has occurred due to government decisions to expand scheme membership, as well as POS (RS and RC) equalization, which began gradually in 2009. This was in order to implement the Constitutional Court decision (ST-760-CC) [77]. This MoHSP report does not show the breakdown of reimbursements or lawsuits related to RS expenditures. The studies have also shown that the number of reimbursements and lawsuits are much less among subsidized schemes, compared to the contributory scheme due to (among other reasons) patients' lack of knowledge of their rights [78].

10.6.1 Medicines Pricing

High medicines prices were observed in Colombia when compared with other countries. Consequently, national pharmaceutical expenditure showed increase in prices during the 2008–2011 period [79]. This scenario was addressed during the NPP formulation. As a result, external and internal reference pricing methodologies were implemented in 2013, which are described in detail in Fig. 10.2.

Following external reference pricing policy, as of March 2015, 1086 medicine prices have been regulated given their market power and national average price (higher than setting reference prices). Andia et al. [80] demonstrated in 2014 that average price reductions due to price regulation was 41% and regulated medicines represent 80% of expenditure from one of the main financing mechanism.

[5] Lawsuits allow anyone to state their case before a judge; this legal action serves to immediately protect the individual's fundamental constitutional rights when they are violated or threatened by the action or omission of any public authority. The protection consists of an order to the public authority in question to act or refrain from doing so. The ruling is immediately enforceable and can be contested before a competent judge. The maximum time allowed by law for an entity to respond to a lawsuit is 10 days from the date of receipt thereof (Colombia, 2000). This is an important mechanism created by the current Constitution in force (1991). For example, 89,762 lawsuits occurred in 2010 to demand services not included in the POS. Ombudsman, 2011 (Defensoria del Pueblo, 2011).

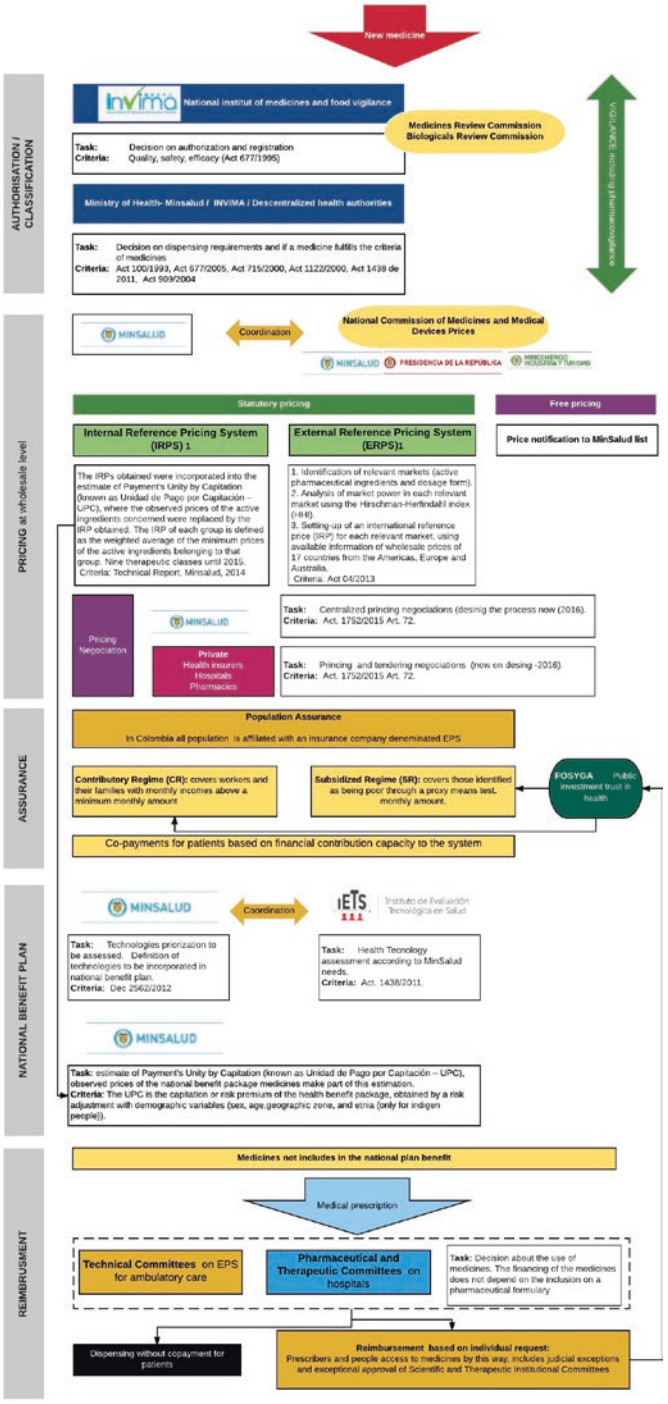

Fig. 10.2 Pricing and reimbursement policies scheme in Colombia

Adapted from: Third Pharmaceutical Pricing and Reimbursement Policies Meeting: Challenges beyond the Financial Crisis (12–13 October 2015, Vienna, Austria). Acosta A. Rapid Oral Presentation.

However, policymakers are aware of the short-term impacts of these policies, therefore, MoHSP has identified other strategies to implement other pricing policies, such as Risk Sharing Schemes and Value-Based Pricing.

10.7 Rational Medicines Use

The rational use of medicines and other health technologies have to consider all levels and stakeholders, including the end users, the consumer. Essential medicines' concepts and the definition of a national list of medicines were established by the SGSSS, but were not sufficient to ensure the incorporation of good practices and rational use of medicines by key stakeholders (health workers, IPS, EAPB, consumers, and communities) in the health system.

At the national level, it is important to note that the institutional arrangements to ensure an appropriate selection process of medicines covered by the SGSSS suffered many modifications and hardships between 1993 and 2015. However, the list of essential medicines has been periodically updated and it was last updated in December 2015. The current challenge is to shift the approach from explicit to implicit National Benefit Package (as described in Sect. 10.6).

In 2012 the NPP diagnosis the lack of information on prescription patterns in Colombia, and scarcity evidence about appropriate use of medicines. Since then to nowadays a significant progress has been made, more specifically from a pharmaceutical service provider and a pharmacoepidemiology research group joint with access to a representative database of different health centers from all the country [81–89].

Since 2015, the MoHSP is implementing activities in order to set up a National Program, including the participation of INVIMA and IETS; the program considers the establishment of the National Formulary, pharmaceutical advertisement regulation and antimicrobial resistance control [49]. Nevertheless, it is relevant to note that, with the NPP, public-private initiatives started to target rational use of medicines strategies [52, 53]. Fifty national Clinical and Therapeutic Guidelines have already been published and some are currently being developed.

Box 10.1 illustrates the pharmaceutical regulatory framework that covers diverse fields and regulations (Box 10.1)

Box 10.1 Legal Bases and Stakeholders (Authorities, Market and Health System Players of the Pharmaceutical Sector), Colombia, 2015

Field	Legal basis	Scope	Authority	Actors
Market authorization	Law 100/1993, art 245 Dec.677/1995 and main modifications	Decision on medicines authorization and registration under quality, safety and efficacy criteria	MSPS Invima	Pharmaceutical manufacturers and importers, holders of market authorization

Field	Legal basis	Scope	Authority	Actors
Medicines coverage by the Health System (SGSSS) Financing and reimbursement	Law 100/1993. Title III Decree 806/1998 Res. 5592 /2015	Medicines coverage by the benefit packages for: (1) individual services, UPC financed (POS); (2) special Programs (for PIC), MSPS funded. Description by active ingredient (INN), strength and dosage form. A specific use included on case basis	MSPS	Mix, and private health insurers – EAPB, public, and private healthcare providers (IPS, ESE) Prescribers and health workers
	Law 1122/2011, art. 33 Res. 518/ 2015	Directions on Public Health management and PIC operation (focus on coordination: Territorial entities, EAPB and IPS). Medicines for PIC described by Public Health program, INN, strength, and dosage form	MSPS	EAPB, IPS, ESE; prescribers and health workers; MSPS and Territorial Health Directorates (Department and Municipal)
	Decree 2562/2012	MSPS legal mandate for SGSSS key components definition (e.g., BP and financing)	MSPS	MSPS, IETS, and other stakeholders based on MSPS request
	Law 100/1993, art 187; Law 1122/2007 art 14 Cuervo CNSSS 260/2004 and 365/2007 Acuerdo CRES 30/ 2011 Circular 16/2014	Copayments and user rates User rates values include medicines prescription Exception for copayments and user rates based on regime (RS) or legal protection or criteria (e.g., displacement population, indigenous)	MSPS	EAPB, IPS, ESE; prescribers and health workers
	Res. 5395 de 2013	Legal procedure to claim medicines not included in the benefit plan package (POS)	MSPS	EAPB, IPS, ESE

(continued)

Field	Legal basis	Scope	Authority	Actors
Pricing	Law 04/2013 Res. 5592 de 2015	External Reference Pricing System (ERPS) Internal Reference Pricing System (IRPS)	NCMP	Manufacturers and importers, holders of market authorization, wholesalers, logistic operators, EAPB; IPS, ESE; prescribers and health workers
Purchasing	Laws 80/1993, 1150/2007 Decree-Law 4170/2011	Regulation on Public purchases and contracts Colombia efficient purchasing		ESE, mix EAPB, MSPS, Invima, ETs
Distribution	Decrees: 919/2004, 1950/1964, 2200/2005	Medicines donations, medicines storage, commercialization, distribution, dispensing	MSPS, Invima	ET's, EAPB, IPS, logistic operators, wholesalers and retailers.
Human resources	Law 212/1995, Decree 1945/1996	Provisions related to chemical pharmacist profession in Colombia	MSPS	Health professionals
	Law 485/1998 Decree 3616/2005	Provisions on other types of workers in the pharmaceutical field: "Tecnólogo en Regencia de Farmacia" – TRF and technicians (Auxiliar en Servicios Farmacéuticos)		Technologists and technicians professionals
Postmarketing surveillance	Laws 100/1993, 715/2001, 1122/2007, 1438/2011, Law 909/2004. Decree 677/1995	Dispensing requirements, pharmacovigilance and compliance of medicines quality criteria	MSPS, Invima, ETs	Pharmaceutical companies, holders of Market authorization Wholesalers, Logistic Operators, Health insurers, Health care providers, Hospitals, Pharmacies, Prescribers

Field	Legal basis	Scope	Authority	Actors
Services provision Surveillance	Decree 1011/2006, Res 1403/2007; Decree 2200/2005	Directions on the Obligatory System for Quality Assurance in Health (SOGCS) & IMC; pharmaceutical services	MSPS Supersalud	ETs public and private IPS-ESE pharmaceutical services
Intellectual property and public health	Andean Agreement Law Decisions 486/2000; Decree 2085/2002 Decree 1313/2010	WTO TRIPS Agreement adopted by Andean countries; data exclusivity; medicines parallel importing for SGSSS (TRIPS flexibility)	Andean Community; MSPS, SIC	Invima Manufacturers and importers. Holders market authorization, wholesalers, EAPB, IPS, ESE

Sources: Elaborated by authors based on regulation of MSPS and Invima; Supersalud and SIC. R.E.E. specific regulations not included

10.8 Final Considerations

This chapter provided an overview of the key features of the health system reform that Colombia implemented, and also presented the main progress and challenges of the country's pharmaceutical policy.

Achieving universal coverage for "nominal" healthcare of the Colombian population in 2014 and equalization of the subsidized and contributory schemes of the *Individual Services Package* – POS must be recognized together with the persistent challenges of equity, quality and sustainability. It is encouraging to know that the Statutory Law on the right to health opens the possibility of a renewed debate for all sectors involved to define a health policy and structure that responds to the characteristics of the country and the population.

The right of access to medicines as part of the right to health is a big challenge for the current pharmaceutical policy of the SGSSS, since there is a gap between nominal insurance coverage and the actual use of medicines. The valuable lists of essential medicines coverage by the SGSSS, along with Colombian low rates of out-of-pocket expenses, are elements favoring access to medicines.

The country has taken great strides in medicines regulation, through the strengthening of INVIMA. The local capacity for pharmaceutical manufacture has to be reinforced; there are competent human resources, but challenges persist to formulate and apply an industrial policy considering research, development, and production of medicines to meet population and health sector needs.

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Chapter 11
Pharmaceutical Policy in Ecuador

Carlos E. Durán, Ruth Lucio, and Joan Rovira

Abstract Ecuador has a heterogeneous health system. The 2008 Constitution signaled the start of a process that aims at attaining universal, publicly financed healthcare, including medicines. This has lead to a systematic increase in the use and expenditure on medicines. Between 2008 and 2015, the total Ministry of Health pharmaceutical budget more than doubled, from USD 106.9 million to USD 235.6 million. The National Agency for Regulation, Control and Surveillance of Health (ARCSA), the new medicines regulatory agency, shows several shortcomings in its capacity to ensure the efficacy, safety, and quality of the drugs marketed in Ecuador. The National Essential Medicines List is being updated every second year; however, the introduction of new medicines by means of *ad hoc* tracks has become a norm during the last years in order to introduced publicly funded high-cost drugs. Price regulation of new drugs is trying to move from the traditional cost of production criterion to more updated mechanisms, based on international price referencing and value-based pricing, but there is still a long way ahead, as there is still not enough technical capacity in health technology assessment and economic evaluation analysis. The local pharmaceutical industry only has a small share of the domestic market, and exports are not substantial, which might be partly caused by the concerns on the quality of locally manufactured medicines. Moreover, local production is highly dependent on the importation of active pharmaceutical ingredients and other inputs, that is, it has a rather low added value. In conclusion, there is a dire need to design and

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implement a pharmaceutical policy that primarily aims at public health goals but also takes into account the industrial and economic objectives and constraints.

11.1 Health System of the Country

Ecuador is located in South America. It has a population of 16.5 million in 2016 [1]. It is classified as a middle-income country with a gross domestic product (GDP) per capita as of USD 6010 for 2015 [2]. In 2014, the crude birth rate was 14.3 births per 1000 population, the infant mortality rate 8.3 deaths per 1000 live births, and the total mortality rate was 3.9 deaths per 1000 population. [3] These indicators have recorded a significant and sustained improvement in the last decade and are well positioned within the Latin American landscape.

The health expenditures recorded a sharp increase during the last 5 years. In 2015, the total health spending was USD 8125 million, which amounted to 8% of the GDP. This figure reached up to 5.9% in 2007 and 9% in 2014 [4]. It is estimated that 52.3% corresponds to public health spending and the remaining 47.7% to the private sector expenditures (Fig. 11.1). The average health expenditures as percentage of GDP in the South American countries were 7.3% in 2014. [4]

The country's health system comprises two healthcare sectors: the public and the private. The public sector is built on the basis of healthcare facilities run by the Ministry of Health (MoH) and also facilities in three social security subsystems, including (i) the Ecuadorian Institute of Social Security (IESS), covering civil servants, private employees, rural peasants, fishermen (including the closest relatives in all cases), and retirees from these subgroups, (ii) the Social Security of the Police Force (ISSPOL), and (iii) the Social Security of the Military Force (ISSFA), in both cases with similar coverage schemes [5–7].

The private sector comprises a diversity of nonprofit and for-profit hospitals, small clinics, and out-patient physician's offices. Majority of payments in the private sector are out-of-pocket, while some correspond to voluntary prepaid insurance schemes covering 5% of the population. Nonprofit institutions include nongovernmental organizations with focus on particular health issues or specific geographical regions, such as, the Ecuadorian Society to Fight against Cancer (SOLCA) and the Guayas Welfare Board (JBG). These institutions receive a mix of public funding, donations, and fees from the patients [6].

The Ecuadorian Constitution guarantees access to universal health coverage [8]. All citizens and residents are entitled to get healthcare free of charge in the facilities run by the MoH. Although this policy was implemented in 2008, there is still an important part of the population attending private facilities, which implies that some people are simultaneously attending both, public and private services. This makes it difficult to get precise figures of coverage; hence, Table 11.1 presents estimates, and those should be treated with caution.

The public health sector accounts for 49% of 4223 healthcare facilities, 18% (765) are inpatient centers and 82% (3458) outpatient settings [9]. Between 2011 and 2014, the number of medical doctors increased from 31,929 to 32,618 [10].

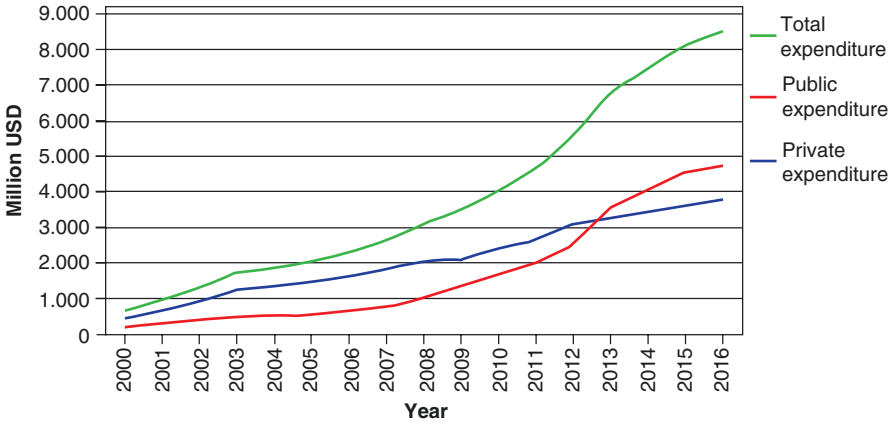

Fig. 11.1 Ecuador: Health Financing 2000–2016

Table 11.1 Ecuador: Health coverage and budget per subsystems in 2014

Subsystem	Covered persons (millions)	Percentage	Budget (USD millions)	Budget Per capita per subsystem (USD)
MoH	10.60	60%	2287	216
IESS	6.50	33%	2115	324
ISSFA	0.15	1.5%	55	358
ISSPOL	0.10		47	458
Private insurance	0.88	5.5%		

The MoH and the IESS are theoretically assumed to cover 100% and 55% of the population, respectively, which in fact is not feasible with the existing institutional capacity. The estimated coverage is, therefore, calculated by considering the number of beneficiaries and the effective access they would have under the actual resources and capacity constraints.
Data source: INEC [27, 34], MoH, ISSFA, ISPOL. Own figures estimated based on the cited sources.

However, the percentage of medical doctors working in the private sector decreased from 50% (15.015) to 37% (12,191) [9]. Most of the healthcare employees work in centers located in urban areas (91%) [10]. The total population living in urban areas was recorded as 64% in 2014 [2].

11.2 Pharmaceutical Situation of the Country

11.2.1 Pharmaceutical Industry in Ecuador

The origin of the pharmaceutical industry in Ecuador can be traced back to the 1930s. It subsequently evolved along the following three phases:

1. From 1930 to 1970, medicines´ consumption was completely reliant on import of finished products.

2. From 1970 to 1990, a national industry emerged. However, the domestic pharmaceutical consumption continued to be import dependent.
3. From 1990 to present, the industrialization process continued. It incorporated basic manufacturing technology, but it still requires importation of pharmaceutical active ingredients, other raw materials, and finished products.

Nowadays, there are 64 local firms and 53 production plants operating in the country [11]. In 2012, the estimated value of the local pharmaceutical production was USD 276 million [12]. It is often stated that approximately 80% of the medicines sold in Ecuador are produced abroad and only the remaining 20% by the local industry [13]. However, this estimate is not supported by official data or reliable sources.

Table 11.2 presents the value of medicines imports/exports through a period of 15 years. Import values have grown at an annual average rate of approximately 13%. Imports mainly consist of finished pharmaceutical products. The reported import/export differences are consistent with the limited volume of local pharmaceutical production. In 2014, finished medicines and pharmaceutical raw materials are the top non-oil import items. The 2015 policy that imposed imports' restrictions resulted in a reduction of pharmaceutical goods.

Table 11.2 Exports and imports of pharmaceutical products in the period 2000–2014

Year	Exports (FOB USD in thousands)	% Variation	Imports (CIF USD in thousands)	% Variation
2000	30,192		183,263	
2001	32,880	8.9	238,708	30.3
2002	36,447	10.8	268,402	12.4
2003	93,997	157.9	362,341	35.0
2004	88,718	–5.6	445,005	22.8
2005	77,599	–12.5	524,821	17.9
2006	129,244	66.6	605,755	15.4
2007	115,844	–10.4	707,456	16.8
2008	122,083	5.4	859,222	21.5
2009	118,691	–2.8	822,313	–4.3
2010	190,229	60.3	951,519	15.7
2011	204,826	7.7	1,102,444	15.9
2012	254,139	24.1	1,188,536	7.8
2013	194,585	–23.4	1,233,256	3.8
2014	154,684	–20.5	844,040[a]	–31.6
2015	170,375	10.14		

Source: Central Bank of Ecuador [35], SENAE (Imports 2014) [36]

[a]In 2014, the record system of the Central Bank did not provide the level of breakdown in the data previously used. Therefore, it was necessary to change the source of information to continue the series. It should be noted that the fall in importations in 2015 is consistent with the commercial policy implemented by the government and should not be necessarily attributed to the change of the source.

Investment in fixed assets in the pharmaceutical sector amounted to around USD 160 million between 2007 and 2010. The Ecuadorian Association of Pharmaceutical Laboratories (ALFE) reports that between 2010 and 2013, their members invested 32% in infrastructure, 57% in machinery and equipment, 8% in research, and 3% in training and certifications. [14]

According to ALFE [14] and the Superintendence of Companies of Ecuador, in 2011, the business of "manufacturing medical substances for human consumption" directly employed 5871 people. This implied a 16% increase from 2010, strongly outpacing the growth rate of the manufacturing sector that was 1.6%. Furthermore, the report also mentioned that during 2013, some of the companies increased their workforce between 5% and 10%.

In 2009, the central government decided to open the *Public Pharmaceutical Enterprise* (ENFARMA). Its mandate included research, production, import, and marketing of medicines (human and veterinary) and products for agriculture activities, all publicly funded. ENFARMA had successfully undertaken the process of compulsory licensing of the biologic drug infliximab. Unfortunately, after 7 year, it was not able to define its role within the pharmaceutical sector and consolidate a clear development plan to solve critical issues on the medicines availability, especially in the public sector. In May 2016, the closing of ENFARMA was announced by the Presidential house.

11.2.2 Medicines Regulatory Authority

In the last decade, the Ecuadorian government has taken several initiatives to strengthen the pharmaceutical regulatory capacity. The establishment of a new regulatory agency, the National Agency for Regulation, Control and Surveillance of Health (ARCSA) in August 2012 is the most important step [15]. Prior to the establishment of ARCSA, the National Hygiene Institute was the medicines regulator for 71 years.

From an administrative point of view, the new regulator was conceptualized as an autonomous body attached to the MoH. The agency's functions include regulation, control, and vigilance of healthcare products and food. According to the foundational decree [15], the agency's main goal is to improve the quality of medicines and to strengthen the local production of pharmaceuticals. Due to its role in promoting local production, there is an ongoing debate on whether the agency should be brought under the auspices of the Ministry of Industry. This has led to a political conflict between the MoH and the Ministry of Industry, and it has also influenced the agency's decision-making processes.

At present, the ARCSA has approximately 250 employees. In 2015, the agency's budget was USD 22.4 million [16]. Figure 11.2 depicts some milestones in the establishment of the agency.

Key challenges faced by ARCSA are described in the following sections.

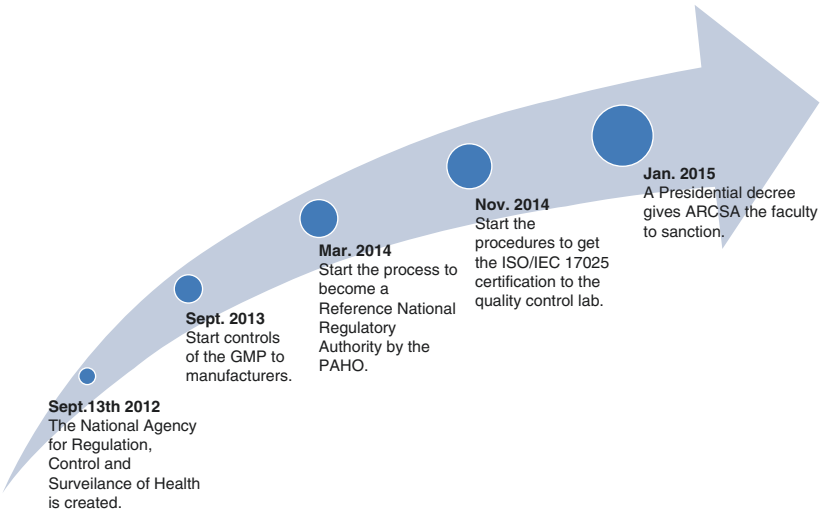

Fig. 11.2 Milestones of the establishment of ARCSA

11.2.3 Quality Control

11.2.3.1 Premarket Review and Authorization Process

ARCSA inherited a problematic registration procedure from its predecessor. An important step to overcome this hurdle was the adoption of an automated online registration process. This online system has saved time and has prevented face-to-face contact between the ARCSA officials and the industry representatives.

An *ad hoc* committee reviews the efficacy, safety, and quality of the drugs. However, little is known about the procedures and the criteria applied by the committee. The evaluation reports, registration files, and other related documents are not publicly available. According to law, all new drugs must be evaluated through a laboratory analysis. [17] However, medicines already approved by a reputed regulator recognized by the agency can skip this step and follow a simpler approval process. At present, Ecuador has approximately 18,000 pharmaceutical products, identified by a single registration number[1] [18].

11.2.3.2 Postmarketing Control

Postmarketing control is the weakest aspect of the quality assurance of pharmaceuticals in the country. Although the regulation for postmarketing control exists [17], the regulator is yet to implement a strong control program. There is no information available on the ARCSA website on this issue.

[1] A registration number is allocated to each product with a different active ingredient, pharmaceutical form, strength, pack size and manufacturer.

The main ARCSA's quality control laboratory is located in Guayaquil, the largest industrial city, with two branches in Quito, the capital, and Cuenca. In 2014, the laboratory started the ISO/IEC 17025 certification process [19], which is an ISO standard for test and calibration of laboratories, Fig. 11.1.

11.2.3.3 Good Manufacturing Practices (GMP)

Under the Ecuadorian legislation, obtaining the Good Manufacturing Practices (GMP) certification (WHO technical report N° 32) is a prerequisite to manufacture and market pharmaceutical products in the country [20]. In 2011, a formal plan was discussed by the government and the local pharmaceutical industry for all companies to obtain the GMP certification in the next few years. As a result, in January 2013, the MoH launched a new GMP regulation and allowed the companies up to 6 months to get the GMP certification. This goal has not yet been achieved. In August 2015, 44 of the 53 plants had a GMP certification [19]. The remaining non-GMP certified companies are still manufacturing and marketing their products.

11.2.4 Pharmacovigilance

The pharmacovigilance system was officially launched in August 2011 [21]. The National Pharmacovigilance Center (NPhVC) was created to coordinate the activities. During the first two years, the MoH was in charge of starting up the center. In May 2013, it was completely transferred to the regulatory agency.

Lack of human capacity is a major challenge in establishing a sound pharmacovigilance system. The first steps for implementing the system include intensive training to the NPhVC and local committees´ personnel, and promote the spontaneous detection and reporting by healthcare professionals, particularly in the public sector. According to the agency's web site, approximately 600 healthcare providers from 52 hospitals have been trained till May 2015.

11.2.5 Falsified Medicines

Sanctions against falsification activities were introduced for the first time under the penal law in 2014 [22]. Several initiatives have been undertaken under the guidance of the regulatory agency to strengthen the capacity to deal with this problem. A special police force unit has been established, and public prosecutors have been trained on crimes related to falsified healthcare goods.

Several cases of falsified products have been reported. The most remarkable became public in 2011, when it was reported that a company had changed the expiry dates of expensive cancer drugs. During 2015, approximately 7000 units of suspicious products were confiscated. In late 2016, the first judicial judgment for a crime of medicine falsification was taken with a sentence of 6 year in prison.

11.3 Medicines Supply System

Seven companies control the wholesale distribution of medicines. During the last years, most of them have also expanded their operations to the private retail sector, leading to the conformation of larger companies integrating both aspects of the distribution, wholesale and retail sales [23]. Total profits rose from USD 43.1 million in 2011 to USD 69.3 million in 2013. They are among the largest companies in the country by 2015 [24].

Out of the total units available in the Ecuadorian pharmaceutical market, up to 57% is placed on private pharmacies through the wholesale companies; 36% is distributed by the manufacturers (national or international) under direct transaction channels, mainly to the public sector; and the remaining 7% goes through the wholesalers to private and public healthcare institutions, mainly hospitals [23].

Due to the centralized procurement process implemented by the government over the last 6 years (i.e., inverse bidding, where preapproved manufactures or wholesalers bid downwards), the government became one of the strongest players in the pharmaceutical market. In 2014, the public procurement reached USD 400 million amounting to 26.6% of the total pharmaceutical market value for that year [25]. Once a company gets the best price in the bid, it becomes the exclusive supplier for the public sector during a period of 2 years. The winning companies are also in charge of the distribution according to a preapproved schedule. Particular procurement and distribution systems are applied to certain drugs such as antiretrovirals, TB drugs, or vaccines. Procurement through the Strategic Fund by the Pan American Health Organization [26] has become an outstanding tool for this kind of drugs.

Medicines are dispensed in private community pharmacies and pharmacy outlets within public and private healthcare centers. In 2001, there were 7654 private pharmacies registered in the country; however, due to the process of consolidation, the number of pharmacies decreased to 5362 in 2006. Recent data from the Ministry of Industry pointed to 4649 pharmacies in 2013, while MoH reported the existence of 5738 pharmacies in 2014. Available data are apparently inconsistent, and it is difficult to validate them. The current figures suggest the existence of one pharmacy per 2800 to 3400 inhabitants.

11.4 Medicines Affordability and Financing

According to the Constitution [8], the Ecuadorian government is the main source of financing for healthcare in the country. Constitutional articles 47, 362 and 363 establish that the state is responsible for universal and free provision of medicines to all citizens, at all levels of care.

11.4.1 Medicines Expenditures in General

Between 2008 and 2015, the total MoH budget on medicines increased from USD 106.9 million to approximately USD 250 million, experiencing an annual growth rate of 10.8%. As previously stated, the medicines expenditure of the two largest public providers (MoH and IESS) was USD 400 million in 2014, amounting to approximately 0.5% of the GDP. The total value of the Ecuadorian pharmaceutical market was USD 1500 million in 2014 [25].

In 2012, the estimated monthly average household income was USD 893 [27]. Average global spending reached USD 810, of which 24.4% was allocated to food, 14.4% to transportation, and 7.5% to healthcare (8.1% in rural areas). The average monthly out-of-pocket spending on health was about USD 50, and medicines constituted 53% of the total health expenses [27]. This proportion varies from 51% for households in the highest decile (wealthier families) to 67% for those in the lowest decile [28].

11.4.2 Pharmacoeconomics

Many countries are increasingly relying on economic evaluation as a criterion to justify the assignment of resources in the health sector. In Ecuador, the MoH has undertaken some economic evaluation analyses, usually as a component of broader technology assessments of (new) technologies that were commissioned by policy makers for multiple purposes. Until recently, there have been no norms specifying the situations or decisions for which economic evaluations must or can be conducted. Also, it is not clear how the results of the evaluations should influence resource allocation decisions. Some studies were undertaken in recent years when MoH was asked to fully cover certain high-cost medicines which are not part of the National Essential Medicines List.

The MoH recently developed Methodological Guidelines for Economic Evaluation of Health Technologies in the public sector. If followed, they will ensure the comparability of the economic evaluation studies carried out in Ecuador and the consistency and coherence of the resource allocation decisions made within the health sector.

More recently (end 2014), the Technical Secretariat of the Council for Medicines Prices (STFP) has also started using the economic evaluation approach as part of the assessment of the therapeutic value of new medicines. The price regulation for the private sector establishes that the new medicines that have no therapeutic advantage over existing medicines for the same indication, will get a price not higher than the existing competitors. Moreover, the new medicines that can be shown to have a therapeutic contribution, will be priced according to the external reference pricing approach, which in principle allows a higher price than in the former case. In that

sense, although the regulation does not explicitly state that economic evaluations should be used for pricing purposes, in practice it is being applied as an initial step in the pricing procedure.

11.4.3 The Regulation of Medicines Prices in the Private Sector

Medicines prices in Ecuador have been regulated since 1964 (Supreme Decree N° 163, Drug Price Control Act). [29] The next few paragraphs summarize the regulations applied in the country during the last decade.

The Ecuadorian Health Law (articles 159 to 163) launched in December 2006 assigned the responsibility of medicines prices regulation in the private sector to the National Health Authority. The National Council for Fixation and Revision of Medicines Prices is the agency in charge of the implementation of the regulation. In May 2011, the Presidential Decree 777 established a price regulation system that introduced three regimes: regulated regime (for strategic medicines), controlled regime (for non-strategic medicines), and direct price setting (as a sanctioning/emergency regime). It kept the cost-plus or cost-of-production approach to drugs in the regulated regimen as applied in the 1990s.

The local manufacturers claimed that this regulation system was detrimental for local production as it was very stringent for locally produced medicines. The local manufacturers had to present a comprehensive and detailed set of information on the production costs. On the other hand, the system was much more flexible for imported products. In that case, the maximum price was derived from the FOB/CIF price declared by the importer, hence, it was difficult for the regulator to monitor and verify the acquisition costs. This approach produced a large dispersion of prices of products assumed to be therapeutically equivalent, that is, products with the same active ingredient, pharmaceutical form, and potency. Price differences sometimes even reached the range of 1:5. An example of this situation was omeprazole, which retail unit price from local manufacturers was as low as $0.25 cents whereas the highest internationally sourced price was about $1.70. [30]

A new Presidential Decree (N° 400) was approved in July 2014 in order to set up a new Medicines Price Regulation System. The Decree aimed to reduce the large variations between equivalent and similar medicines. Although it applied the same three pricing regimes as the previous Decree 777, it moved the regulation scheme from cost of production (cost-plus) to international (external) reference pricing and eventually to other pricing approaches, such as value-based pricing[2] for new molecules (see section 11.4.2 *Pharmacoeconomics*). For the products already in the

[2] Value-based pricing means that the pricing criterion is related to the estimated contribution of a new medicine over existing alternatives for the same indication, as assessed by economic evaluation (cost effectiveness/pharmacoeconomic) studies.

market at the time of enforcing the regulation and for new generic medicines, the regulation aims to set up a maximum retail price in each equivalent market segment.[3]

The maximum prices were officially announced during the last quarter of 2015, and 6 months later, they became effective. As an example, syrup of amoxicillin/clavulanic acid from an international company was priced at USD 26.00 before the regulation. The new price for this product had to be set below or equal to the maximum fixed price. Under this rule, it was fixed at USD 9.80.

Multinational pharmaceutical companies claim that the system envisaged in Decree 400 is unfair, as there are no rigorous quality controls of medicines in Ecuador. The companies argue that in this context, the corresponding production costs could not be always meaningfully compared across the products. This has been a recurrent topic of debate between local/generic and international/originator pharmaceutical companies.

11.5 Medicines Use

11.5.1 Medicines Use in General

It has been estimated that 86.4% of the registered drugs are prescription drugs and 13.6% are OTCs [31]. In the private sector, by 2011, prescription products with the highest volume of sales were Mesigyna® (parenteral contraceptive), Neurobion® (vitamin B complex), and Acrovastin® (atorvastatin), respectively. Among OTC drugs, the top ranked were Apronax® (naproxen), Pharmaton® (multivitamins and minerals), and Redoxon® (vitamin C) [31].

In relation to the market share of generic medicines in the private sector, unbranded generics accounted for 23.5% in 2011, in contrast to the 11.4% in 2001. Branded generics shared up to 51.5% in 2011, 5.5% less than 2001. [32]

Prescription by International Non-Proprietary Name (INN) is compulsory for both, the public and the private sector. However, this does not mean that the user is receiving the cheapest generic drug in the private community pharmacies; on the contrary, it has become a rather common practice that the first offered option by pharmacies is a branded expensive medicine. Among others factors, the lack of incentives for generic substitution might be the main reason for such behavior. Unfortunately, economic incentives for dispensing generics at retail level were withdrawn in 2011. The Law for Regulation and Control of the Market Power removed the generic profit markups for distributors and pharmacies previously established in the Generic Medicines Law (2006).

[3] A market segment is defined by 1) the active pharmaceutical ingredient, 2) route of administration, and 3) potency.

11.5.2 National Essential Medicines List (NEML)

Ecuador has a long history on selecting essential medicines. The first attempt was made in 1975 as a joint effort to select medicines for the Andean countries. Thereafter, during the 1980s, the first National Medicines Commission was established [29]. Since then, the Commission has published nine editions of the list; the 10th edition will be published in 2017.

The National Commission of Essential Medicines and Medical Devices (CONAMEI) is composed of representatives from institutions of the national health system. The NEML is updated every second or third year. Once released, the public institutions centrally procure most of these medicines. The latest edition of the NEML has 397 active ingredients leading to 533 pharmaceutical dosage forms. As an attempt to contain the country's growing pharmaceutical expenditure, the 9th edition included a special chapter on high-cost drugs, which are linked to specific indications.

In 2012, an alternative mechanism was implemented to allow the procurement of certain medicines not included in the NEML. This was done under the rationale to speed up the access to important medicines, especially for catastrophic conditions. During the first year of implementation, the rather flexible requirements lead to a substantial amount of medicines selected and procured through this mechanism. As a result, up to 60 medicines, most of them, new high-cost drugs, were approved between 2014 and 2015.

11.5.3 Factors Affecting Prescribing Behavior and Medicines Promotional Practices

In general, there is a lack of incentives, assessment, and control activities aimed to improve prescription patterns among public and private prescribers. With the exception of some initiatives [30], the lack of independent health and therapeutic information sources is evident. The industry-sponsored compendiums are still the main source of drug information. The use of the National Essential Medicines List in the public sector contributes to rationalize prescribing practices; however, it has a limited impact.

Ecuador's legislation allows direct advertising to the consumers only for over-the-counter (OTC) medicines. The regulatory agency approves all promotional material before it is delivered. Although the regulation exists, the *ex-post* control activities are weak leading to frequent unethical promotion messages in mass media.

In 2013, a law was enacted to regulate communication activities of different areas. The Ministry of Health (MoH) was given the responsibility to produce a list of drugs that could be directly advertised in mass media. It was an opportunity to strengthen the regulation by shortening the list of drugs which could be advertised.

However, the MoH never used this option, and recently, the Ecuadorian Parliament has decided to revoke said regulation.

Pharmaceutical representatives are not allowed to visit the public healthcare services. It is difficult for company representatives to get access to healthcare professionals within public hospitals in largest cities, but access is rather easier in smaller cities and remote regions.

11.5.4 Role of Pharmacist

Since approximately a decade ago, there was a tendency to hire pharmacist in every hospital and healthcare administrative zone in the public sector. Nowadays, hospital pharmacy activities have been reinforced as part of the MoH plan to achieve international quality certification in public hospitals.

Pharmacists have a very limited role in private community pharmacies. Pharmacists do not have a direct patient care role, they work few hours a week in the community pharmacies, sign the psychotropic drugs report, and perform few other duties. It is a well-known practice that pharmacists are simultaneously hired at more than one community pharmacy to fulfill the legal requirements.

The personnel on duty in private pharmacies are not pharmacists; in most cases, they have been trained by the pharmacy owner on basic concepts related to the pharmacy management. There are no standard recognized programs for pharmacy technicians in the country; thus, this role is nonexistent.

11.6 Challenges

The main challenge in coming years will be the quality assurance of the medicines either locally produced or imported. The quality of medicines has become a crucial aspect of the Ecuadorian regulatory issues and a recurrent topic in the national political scenario. It must be solved to improve the patients' safety, to increase the confidence on health and regulatory authorities and to promote the local pharmaceutical industry.

Regarding the promotion of the local pharmaceutical industry, the future stages planned by the Ecuadorian government include the increase of volume and quality to being able to supply both national and regional markets and investment in research and development of new drugs. The legal, political, institutional, technical, and technological frameworks are being developed to achieve these goals. Explicit references to these goals can be found in the Ecuadorian Constitution and in the National Development Plan [33].

Regarding the implementation of policies such as "free medicines for all" the out-of-pocket spending on drugs in 2012 amounts to 53% of the average monthly spending on health. This percentage is even higher among the poor and those living

in rural areas. This shows that policies applied are not equitable, and this will be a continuous challenge in coming years.

As most middle and low-income countries, Ecuador is experiencing big challenges in accessing high-cost medicines. Among other actions, the NEML selection process must be strengthened. This could be done by improving the technical capacities of the Commission, by implementing health technology assessment reports in the decision making process, and by enforcing the conflict of interest and transparency regulations.

Although several policies have been implemented during the last years, no evaluation has been performed to assess these policies. A plan to independently analyze and evaluate the different pharmaceutical polices is needed, academics can play a key role in this context.

11.7 Conclusion

The pharmaceutical environment of the country has kept moving during the last decade, from a new regulatory agency to new public procurement systems, improvements on the price regulation, and strengthening of human capacities. The main goal has been to address the challenges in improving access to affordable quality medicines. However, these strategies lack a global view and a coordinated implementation plan. Taking in consideration the above, Ecuador needs an integral pharmaceutical policy that balances public health and production goals of relevant stakeholders. These actions must be implemented following the Ecuadorian constitutional mandate that prioritizes health over economic interests.

The data available to assess health and medicines situation in Ecuador are scarce and often inconsistent. Thus, it is fundamental to develop an information system in health and pharmaceutical sectors. In order to improve policy decisions and their monitoring, this information system must be comprehensive, transparent and publicly available.

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Chapter 12
Pharmaceutical Policy in Jordan

Faris El-Dahiyat and Louise Elizabeth Curley

Abstract For many patients, it is essential to have consistent and regular access to treatment to prevent complications and premature death. In light of this, every country aims to improve availability, affordability and utilisation of essential medicines through the endorsement of good governance and management practices in the pharmaceutical sector. Like other countries, Jordan aims seriously to ensure an uninterrupted availability of essential medicines. This is of particular significance recently after increased stress on the Jordanian pharmaceutical sector as a result of the Syrian refugee crisis. In addition, Jordan has also upgraded its legislation, to govern the conduct of pharmaceutical market, prohibit common forms of misconduct and protect the rights of all parties involved in the pharmaceutical industry. This chapter, thus, explores the main challenges that the pharmaceutical sector may face in the future in Jordan and discusses the current pharmaceutical pricing policy and whether it provides adequate protection to Jordanian patients. Furthermore, this chapter briefly explores the supply and distribution of essential medicines in Jordan and addresses what changes could be made to legislation to ensure the trust and the predictability needed by the relevant parties involved in the pharmaceutical industry in Jordan.

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12.1 Country Profile

12.1.1 Population Numbers and Composition

In 2014, the population of Jordan was 8,117,564, out of which the number of non-Jordanians living in there reached approximately 2.5 million, including 1.4 million Syrian refugees. However, only one-fifth of Syrian refugees live in refugee camps. The remaining refugees live throughout the Kingdom, particularly in the northern governorates of Jordan [23].

12.2 Health System of Jordan (Health System and Health Indicators)

Jordan has three different healthcare delivery systems. The Ministry of Health (MoH) that provides basic primary and secondary health services, by means of a network of 29 hospitals and numerous health centres. These services are available for the whole population to use. The Royal Medical services (RMS) provide insurance and services through ten hospitals to military and government personnel and their dependents. Finally, there is the extensive private sector that includes 61 private hospitals and many private clinics [4, 11].

In addition to these systems, there are two large public university hospitals: University of Jordan Hospital and King Abdullah University hospital. Moreover, there is a specialised centre for diabetes and Endocrinology and Genetics [4]. There are a number of international and charitable sectors that provide services through United Nations Relief and Works Agency (UNRWA) for Palestinian Refugees, in the Near East, the United Nations High Commissioner for Refugees (UNHCR) and King Hussein Cancer Centre in addition to other charity association clinics [4].

The Jordanian Government has stated that it aims to provide a comprehensive healthcare system that includes the services of the private sector, to ensure preventative, tertiary and rehabilitative care for all. Nevertheless, the formulation of a healthcare strategy and policy has been hindered in Jordan due to the disjointed nature of the healthcare system and lack of accurate health statistics data [13].

There are private healthcare insurance providers that either sell insurance policies to the individual or work with large companies to provide private insurance for their employees. According to Brosk et al., the private sector is the largest source of health funding in Jordan, which accounts for 47% of the health funding. The public (45%) and other donors (8%) are the next largest source [13]. Private healthcare is mainly confined to the urban areas, and it is primarily utilised by the wealthiest Jordanians residents [19]. Fifty-seven percent of the total annual health expenditure in 2008 in Jordan was covered by the Government, with the remaining 37.5% and 5.5% being covered by the private and donor sectors, respectively [22].

Each of the healthcare subsectors in Jordan has its own financing and delivery system that reflects directly on its delivery of services among these sectors. The drawback of this varied system is problems related to accessibility, equality, duplication of services, poor coordination among major providers, unregulation of the private sector, low utilisation rates in the private sector, limited quality improvement programmes, inefficient use of available resources, poor management and an inappropriate health information system. These problems form the main challenges facing all providers of healthcare in Jordan [23]. According to a WHO study conducted in 2010, 74% of the Jordanian population is covered by a health service (MoH 34%, RMS 23%, UNRWA 9% and Private Health Insurance 8%). However, the remaining 25% of the population are without any form of health insurance [3].Thus, while the healthcare system appears to function well overall, there are still subpopulations at risk of substandard access to healthcare and severe financial burden, such as the poor, the elderly and the unemployed [2].

12.2.1 The Impact of Syrian Refugees on the Health Sector in Jordan

Jordan has recently hosted hundreds of thousands of refugees from neighbouring countries such as Iraq and Syria. This influx was mainly due to Jordan's relative safety and political security compared with surrounded countries. This has caused a high growth rate of the population and subsequently considerable pressure on the health system. This burden has been felt especially in health services provided to citizens, infrastructure and health institutions, particularly in the public sector. In view of the already scarce financial and natural resources available, the entry of huge number of refugees has negatively reflected on social, economic and health development [5].

12.2.2 Health Services Provided to Syrian Refugees

From 2012, the large number of Syrian refugees presented a challenge and an increased burden on the health system, especially concentrated in the Northern governorates. Various health services have been affected, such as immunisation and infectious diseases screening [23]. Jordan remains committed to providing humanitarian aid to Syrian refugees, despite the limited funding in the health sector, the limited number of healthcare workers and the lack of necessary facilities to provide health services for the Syrian refugees. This has had a serious impact on the health system in the public sector. Figure 12.1 illustrates the number of Syrian refugees who have received health services at MoH centres and hospitals up to the end of August 2013 [23].

As seen in Table 12.1 below, the spread of communicable diseases among the Syrian refugees is much larger when compared with Jordanians. In addition to the health burden in the refugee population, this high number could further spread

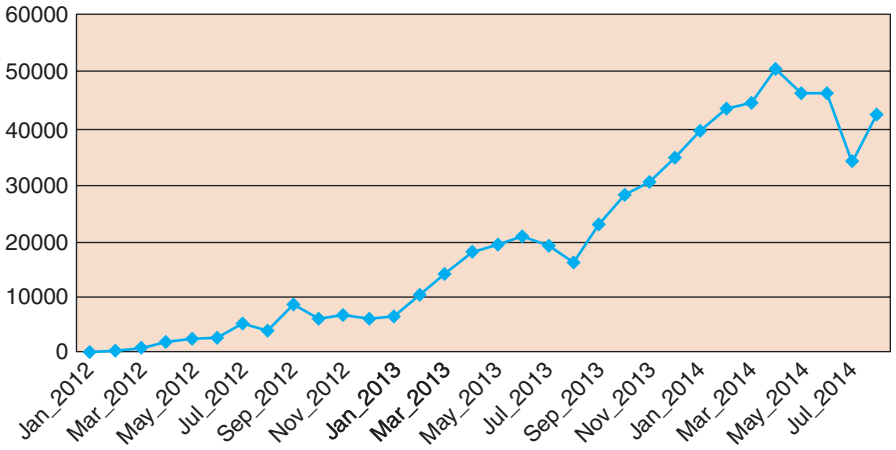

Fig. 12.1 The number of Syrian refugees who were served by MoH health centres during the period January 2012 to August 2013 (Source: The Higher health Council [23])

Table 12.1 Annual incidence rate of some communicable diseases among Jordanians and Syrians refugees

Disease	Incidence rate among Jordanians	Incidence rate among Syrian refugees
Pulmonary Tuberculosis	5 per 100.000	13 per 100.000
Measles	2.8 per million	51.2 per million
Leishmaniasis	3.1 per million	158.1 per million

Source: Ministry of Planning and International Cooperation [39]

diseases within the refugee population, and subsequently, it increases the risk for Jordanian nationals. The MoH provides healthcare services to all Syrian refugees free of charge. These services include immunisation, monitoring of infectious and communicable diseases, reproductive health, health control on foodstuffs, monitoring epidemics, recording injuries and registration of births and deaths, as well as supplying hospitals in the refugee camps with blood, serums and the correct control and disposal of medical waste, food control, hygiene and water and sanitation [39].

The number of cancer cases recorded among Syrian refugees in the National Cancer Registry has also increased from 135 cases in 2010–265 cases in 2014. This increase in turn reflects an added burden for the MoH [23].

12.2.3 The Impact of the Syrian Refugees on the Health Sector

According to the National Strategy for Health Sector in Jordan 2015–2019, the main challenges facing the Health Sector in Jordan as a result of the treatment of the Syrian refugees can be summarised as follows [23]:

- The demand for health services increased dramatically at a rate that exceeds the capacity of the Public Health Sector.
- Increased workload pressure on hospitals staff, hospital infrastructures and health facilities.
- Lack of pharmaceutical and health staff.
- The need for more financial resources as the MoH has increased expenses due to the displacement of the Syrians which is estimated to be 53 million dinars in 2013, including 20 million dinars for the vaccination campaigns.
- A negative effect on Jordanian patients as they are competing with Syrian refugees for the available but scarce health resources.
- More vaccination campaigns are needed because of the risks of diseases spreading among Jordanians.

12.2.4 Health Indicators in Jordan After the Syrian Crisis

Table 12.2 below shows some health indicators in Jordan before and after Syrian crisis.

12.3 Pharmaceutical Situation of Jordan's Pharmaceutical Industry(Key Statistics, Pharmaceutical Industry, Trade Import Export)

There are currently 20 pharmaceutical companies in Jordan, exporting approximately 75% of their production to foreign markets. The relative success of this industry is due to the good reputation and quality of Jordanian manufactured medicines, which conform to international standards. Jordanian medicines are

Table 12.2 Some health indicators in Jordan before and after the Syrian Crisis

Indicator	Before Syrian refugees (population number = 6.4 million	After Syrian refugees (population number = 8 million)
Physicians/10,000 citizens	28.6	23.4
Dentist/10,000	10.4	8.5
Nurse/10,000	44.8	36.6
Pharmacist/10,000	17.8	14.5
Bed/10,000 citizens	18	15.1
Bed/10,000 citizen in Mafraq	8	6
Proportion of population covered by health services	98	90

Source: Ajlouni [5]

available in approximately 70 countries around the world, and the largest portion is exported to Arab countries [23].

The Jordanian pharmaceutical industry's role in achieving drug availability and increasing its contribution to the national economy has grown significantly. The Jordanian pharmaceutical companies have moved towards developing the required technological expertise to ensure that Jordan is the centre for pharmaceutical technology in the region. Some companies have started to manufacture oncology pharmaceuticals and are involved in the manufacture of biotechnology and biological drugs, through strategic alliances with major multinational originators companies in the drugs industry [23]. The positive contribution to the trade balance and the medicine availability achieved by the Jordanian pharmaceutical industry contributes to the advancement of the national economy. In 2012, exports of pharmaceutical products accounted for approximately 9% of the total Jordanian exports and the pharmaceutical industry is the second largest export-oriented sector in Jordan. Exports in 2013 had a growth of 14.6%, which was an increase from to 382 million dinars in 2012–438 million Jordanian dinars (JD) in 2013 [23].

The pharmaceutical industry provides more than 6000 jobs in Jordan, in addition to thousands of workers in the supporting sectors, such as shipping, transportation, distribution, advertising, printing and packaging. Moreover, this sector exports hundreds of skilled professionals to work in the various branches of Jordanian companies operating outside Jordan. Jordanian medicine also contributes positively by reducing the therapeutic bill by competing with global companies in the official bidding, as well as in the private sector [23].

12.4 Jordan's Regulatory Environment

12.4.1 Pharmaceutical Regulation in Jordan

Jordan is a member of the World Trade Organization (WTO) [54], a signatory to the Trade-Related Aspects of the Intellectual Property Rights Agreement (TRIPs), and it strictly adheres to Intellectual Property Rights. The Jordanian pharmaceutical industry was greatly affected by the implementation of WTO agreements. Like other WTO member states, Jordan was required to introduce TRIPS-plus provisions in its National Patent law [51, 52]. As such, Jordan amended its law to require prior consent of a Patent holder. The new Patent Law grants 20 years of protection for both products and processes and enshrines the right to act against infringement. Before TRIPS, copies of medicines protected by a patent in major industrialised countries were widely available, usually at a lower price than the original patented drug. The copies were either manufactured by local companies in Jordan or imported without having to ask the patent holders' permission. This practice is now coming to an end. Jordan's agreement with the World Trade Organization (WTO) poses major challenges for the local pharmaceutical industries in Jordan. Compliance

with TRIPS provisions has naturally resulted in adverse outcomes, such as increased medicine prices, and a dwindling local pharmaceutical industry, in part, as a consequence of its inability to access advanced, patented technology on reasonable commercial terms. However, the TRIPS Agreement does not prevent members from taking measures to protect public health and to enhance access to medicines. According to this agreement, each member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted [53].

Article 31 of the Agreement sets forth a number of conditions for the granting of compulsory licenses. These include a case-by-case determination of compulsory license applications, the need to demonstrate prior (unsuccessful) negotiations with the patent owner for a voluntary license and the payment of adequate remuneration to the patent holder. The US–Jordan Free Trade Agreement (FTA) in 2001 limits the grounds under which a compulsory license can be issued far beyond those in Article 31 of the TRIPS Agreement. It only permits compulsory licenses to remedy anti-competitive practices, for public non-commercial use, for a 'national emergency', or in case of 'extreme urgency'. Furthermore, compulsory licenses can only be granted to government entities or legal entities operating under the government. The pharmaceutical sector is highly regulated in Jordan, which still requires proof of safety and efficiency before permitting a medicine to be sold in the market. In the context of Jordanian law, the most important initiative of the pharmaceutical sector is the Medicine and Pharmacy Act No. 80 of 2001.

This of course does not mean that all Jordanian laws affecting the pharmaceutical industry are found within this particular legislation. There are other laws and regulations that play a vital role in this field, such as the Jordan Food and Drug Administration (JFDA) Act No. 41 of 2008, the Public Health Act No. 47 of 2008 [18] and the Clinical Trials law of 2001, which were amended by the permanent law that were issued in January 2011. It can also be said that the JFDA actively regulates the pharmaceutical sector by monitoring the market, the licensing of individuals and entities conducting pharmaceutical activities and the issuing of regulations that enhance transparency and trust in the pharmaceutical industry. The JFDA is an independent public sector institution that is considered to be the main pharmaceutical regulatory body for ensuring drug safety and efficacy in addition to food safety and quality. Such an institution is empowered by law to conduct investigations as it considers necessary, and it takes the required steps to ensure that there is adequate consumer protection and to reinforce fairness, efficiency and transparency in the pharmaceutical industry. It can also be said that JFDA is responsible for product registration, such as the assessment of clinical trials, bioequivalence studies, pricing, accreditation of pharmaceutical manufacturers, the promotion of rational drug use and postmarketing surveillance.

The JFDA conducts its activities through a number of committees that operate within the registration department. One committee is dedicated to new chemical entities (NCEs), while another committee is responsible for generic medications, and a third has the responsibility of pricing.

Jordanian legislation states that it is prohibited to circulate any drugs, serums and vaccines until the item in question is registered, and there is a penalty if this law or any of its provisions are breached. It should be noted that the JFDA may give special permission for the import of medicines that are not registered in Jordan but are already registered by the U.S. FDA or EMA, if there is a proof of an urgent need based on the full details of the case, including a clear prescription from a specialised physician. Patients then would directly pay the drug's international price, as fixed by the pharmaceutical company in the country of origin.

Pharmaceutical registration in Jordan covers drugs, vaccines, serums, intravenous solutions, vitamins, surgical equipment, baby food, herbal products and cosmetics. Drugs are always registered by their INN (international non-proprietary names) or Brand name + INN.(JFDA registration criteria, JFDA). It should be noted at this point that the JFDA usually takes into account registration status by well-recognised authorities, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

In order to register any drug in Jordan, certain conditions must be fulfilled. First, the pharmaceutical company must submit documentation that includes the chemical structure, pharmacologic and chemical properties, and an Anatomical Therapeutic Chemical classification [27], which relates to the drug's therapeutic value, as well as the active ingredients of the drug according to the organs or systems on which they act [28]. Registration of any drug usually requires the drug to be marketed at least for 1 year in its country of origin or in any JFDA reference country. The drug application should also provide the JFDA with all the information regarding the manufacturing facility, a drug plant profile, the origin of the material, a Good Manufacturing Practice (GMP) certificate, and a Technical File related to the properties of the product, the methods of drug preparation, analysis, stability data, storage conditions, studies of the drug's bioequivalence and non-clinical and clinical studies, and suggested price [29].

Once the drug registration is validated, the new product will be subjected to analysis at a JFDA Quality Control Laboratory. Quality control inspectors examine the products and materials for defects or deviations from the specifications. This implies that samples are collected by specialist inspectors for undertaking postmarketing surveillance testing [34].

After the laboratory analysis and manufacturing site approvals are complete, the documentation will be transferred to a JFDA Technical Committee for studying, verification and approval.

The approval process for new products takes approximately 12 months. The primary purpose of the above process is to ensure that all marketed pharmaceutical products meet the criteria of safety, efficacy and quality. In addition to registration, the JFDA has the responsibility of accrediting producers and pricing [34]. According to the legal provisions in Jordan, manufacturers (both domestic and international) must comply with GMP (Arab Union of the Manufacturers of Pharmaceuticals and Medical Appliances Arab Guidelines on Current Good Manufacturing Practices) [8].

Importers, wholesalers and distributors should also be licensed and comply with Good Distributing Practices. Jordanian Law allows JFDA inspectors to inspect premises where pharmaceutical activities are performed. Such inspections are required by law and are a prerequisite for the licensing of facilities [33]. Legal provisions exist, which require the marketing authorisation holder to continuously monitor the safety of their products and report to the JFDA. This allows a continuous relationship between the marketing authorisation holder and the JFDA and also provides the necessary requirement for the monitoring and reporting of potential risk. This allows the JFDA to comply with the provisions of the law [30]. Although Jordan has proceeded with upgrading its legislation to regulate the pharmaceutical industry, prohibit common forms of misconduct and protect the rights of all parties involved in the pharmaceutical market, it needs to do more in order to secure a suitable climate for such industry and enhance Patients' access to medicines.

12.4.2 Pharmacovigilance

12.4.2.1 Role of Pharmacovigilance in Jordan

In most cases, the preclinical and clinical testing stages do not guarantee absolute safety of a medicine. When a medicine is marketed and prescribed to large and varied population, adverse drug reactions can occur, which were not seen in clinical trials. It is essential to have an effective system to continuously monitor the effects of a drug throughout its lifecycle. Pharmacovigilance (PV) plays a vital role in improving public health and safety in relation to the use of medicines, by detecting problems related to the use of medicines, monitoring drug risks and their effects on humans, and thus balancing the medicine's benefit against its potential harm and communicating the findings in a timely manner [49].

Jordan has recognised the importance of having a well-established pharmacovigilance system in order to ensure the ongoing safety of pharmaceutical products from preclinical trials to postmarketing. Jordan established the Jordan Pharmacovigilance Centre (JPC) in 2001, within the Ministry of Health, to gather and evaluate all the information on pharmaceutical products marketed in Jordan, with particular emphasis on adverse reactions. One of the main duties of the JPC is to monitor, analyse and evaluate drug safety information and then to supply the Uppsala Monitoring Centre with all the drug safety data from Jordan and the organisational procedures conducted by the JFDA in regard to drug safety. Jordan has a stable pharmaceutical industry with skilled human resources. It is vital to have these two factors in order to operate an effective pharacovigilance system. However, the low availability of funds for JFDA will represent a serious challenge in this regard [38].

In the context of Jordanian law, pharmacovigilance has been regulated by the Directives of Pharmacovigilance, issued by the High Commission of Drug and Pharmacy (Article 5/A of the Law of Drug and Pharmacy) (JFDA [28, 29]). According

to Article (2) of the Directives of Pharmacovigilance, the pharmacovigilance system is defined as a system that is concerned in collecting, analysing and evaluating any adverse drug reactions and the problems related in using postmarketed drugs, with the aim of reducing or eliminating any such reactions. Pharmacovigilance should be a continuous improvable process rather than a one-off activity. It is necessary that such a process must involve a combination of the pharmaceutical companies, regulatory authorities, health professionals and patients [31, 32].

Hence Article (5) of the Pharmacovigilance Directives requires a qualified medical practitioner, pharmacist, drug manufacturing company or the marketing authorisation holder should continuously monitor the safety of their products and inform the administration of any serious adverse reactions, no later than 15 days from the date of receiving the minimum information that needs to be reported [31, 32].

12.4.2.2 Counterfeit Medicines

A recent study found that there is no indication of a drug counterfeiting problem in Jordan [7].

This is thought to be due to two contributing factors: first, the effective legislative campaigns conducted by the health authorities' in Jordan against counterfeit trade through the new public health and pharmacy law which has been launched in 2008. Second, the rigorous tough enforcement measures are conducted by health and law enforcement agencies in the country [7].

Moreover, according to two recent interviews with the general director of JFDA, there is almost no counterfeit medicine in Jordan [41, 42].

12.5 Medicines Supply System (Procurement and Distribution)

12.5.1 The Supply and Distribution of Essential Medicines in Jordan

Like other countries, Jordan aims to ensure an uninterrupted availability of essential medicines in sufficient quantities, procured at the lowest prices to secure the maximum therapeutic value to the largest number of beneficiaries. To meet this goal, the Joint Procurement Department (JPD) was created in 2005, with the objective of enhancing the efficiency of the procurement process in the public sector and to provide quality pharmaceutical products to all Jordanians on a regular basis. By doing so, JPD serves as the Procurement agency for its five partners: MoH, RMS, official Jordanian University Hospitals (Jordan University Hospital and King Abdullah University Hospital) and The King Hussein Cancer Centre (KHCC) [15]. The JPD is responsible for organising procurement procedures and concluding procurement

contracts and also responsible for the preparation, verification and approval of the bidding document as well as the determination of the necessary securities required for the bids. Moreover, the JPD maintains and stores supplies in central warehouses to enable distribution to regional areas [15, 25].

The procurement is organised yearly, and it starts with the issuance of a purchase order from each of its five partners that are sent to the JPD specifying the items needed and are accompanied by an approved financial document confirming the availability of funds. The JPD then consolidates the orders and checks that the partners have sufficient funds available to cover their submitted orders. A tender is subsequently sent out with a bidding window of 4 weeks. It is only open to companies registered by the JFDA, and a 3% bid bond is required [25].

The bids received are examined by the Tender Committee that is composed of experienced pharmacists and procurement specialists. The companies of which bids are selected are published on the JPD's web page, and contracts are signed within 4 days of the award announcement. At the time of contract signing, the 3% bid bond is released and is substituted by a 10% performance bond. The delivery of the first (of two) batches occurs 3 months after the bid award in Jun/Jul. The second is expected 7 months after the bid award. Ideally, three bids are required. If there are no bidders, an additional request for a quotation or direct purchasing is carried out. In the event of an order being out of stock, there is a small budget of 20.000 JD (below 30.000 USD) for the urgent procurement of out-of-stock drug [25]. Also, the district and provincial hospitals are allowed to purchase directly, but only when the usual supply channel is out of stock. In other cases of out of stock items, physicians are instructed to provide alternative drugs, if available. If not, patients may be given a Government stamped prescription in order to receive prescribed drugs from the private sector and the MOH, through the Health Insurance Directorate, will then repay them back. However, many pharmacies ask these drugs to be purchased out-of-pocket by the patient due to the very complex and slow repayment system by the Ministry of Health [25].

Healthcare delivery in the public sector is mainly provided by two services in Jordan. One is the MoH, and the second is the Jordanian Royal Medical Services (RMS), each has its own delivery system. Although legal provisions exist for licensing wholesalers and distributors in the private sector, there is little coordination among government and private sector entities. Jordan is divided into 14 health districts which are required to place their orders (hand delivered or by phone/fax) before a preset date each month. While the Department of Procurement and Distribution manages the storage and distribution of drugs for the MoH, each of the five JPD partners is responsible for the storage and distribution of their procured drugs. The MOH has three main warehouses: one in Amman and two smaller ones located in the north and in the south of the country. Upon receiving the order from the districts, each warehouse prepares and ships the orders, usually within a working week if in stock. Unfortunately, Jordan has no national guidelines on Good Distribution Practices (GDP) [15].

The procurement system in Jordan has systematic procedures based on local tendering, appropriate evaluation and award processes. Furthermore, such procedures

involve the main healthcare providers in the country and therefore, encompass almost all locations in Jordan. However, this system can also be subjected to much criticism. First, this system lacks the attitude, vision and experiences to enable it to conduct long-term forecasting properly [15]. Forecasting within such a system is mainly based on demand and consumption. In addition, the limited financial resources and lengthy bureaucratic procedures may lead to certain essential drugs becoming out of stock. An additional complicating factor is that Jordan provides asylum for a large numbers of refugees, including many from Syria and Iraq.

In view of the limited financial resources in Jordan, it is uncertain whether the Jordanian pharmaceutical system will be capable of adjusting to the new demands being placed by its high rate of population growth over the medium and long term. If maximising the efficiency of the procurement process is our goal, then more work is needed to review several aspects of the current method of procurement. It may now be time to implement strategies that could increase competition in supply sources [15]. In 2006, the government officially adopted the Jordan Essential Drug List. The essential drug list was developed to select and buy cost effective medicines to meet the majority health needs of the population. The selection in this list is based on internationally recognised criteria obtained from several World Health Organisation published sources. Several factors contribute to the selection of the medicines, such as the relevance to the disease area in question, the drug formulation, quality control standards and the efficacy and safety based on sufficient pharmacological studies. The selection process is conducted by a special committee, comprising of physicians and pharmacists, who provide technical support and advice on the revision and update of the JRDL. This process has been widely criticised as it does not provide any sufficient guidance in relation to the selection criteria for appointing committee members [50].

12.6 Medicines Financing

12.6.1 Spending on Medicine

The spending on medicines in Jordan in 2012 is about 445 million dinars, 1 dinars equal to 0.71 dollar [14], which form 26.75% of total health budget. Spending was divided between the public (202.6 million dinars [12.17%]) and private sectors (242.8 million [14.58%]). As seen in the table below (Table 12.3), the proportion of spending on medication as a percentage of total health expenditure has fallen between 2008 and 2012.

No recent data were available; however, spending on medicines in Jordan formed 2.03% of GDP in 2012, compared with a ratio of 1.6 of GDP in the European Union countries. This ratio is high for a country such as Jordan which is classified as middle-income country. Therefore, a strategy to rationalise spending on medicine in Jordan should be developed [23].

Table 12.3 Spending on medicine in Jordan Indicators

Indicator	2008	2009	2010	2011	2012
Total spending on drugs in dinars	496,453,222	449,395,115	423,658,862	427,835,670	445,408,952
Per capita share of spending on drugs	84.86	75.15	69.30	68.46	69.73
Spending on drugs/GDP	3.08%	2.66%	2.26%	2.09%	2.03%
Spending on drugs/spending on health	35.94%	27.91%	27.56%	27.07%	26.75%
Distribution of spending on drugs					
Public sector	13.81%	14.14%	13.01%	12.22%	12.17%
Private sector	22.12%	13.77%	14.55%	14.85%	14.58%
Distribution of spending on drugs/spending on health by sector					
Public sector	38.44%	50.67%	47.19%	45.12%	45.49%
Private sector	61.56%	49.33%	52.81%	54.88%	54.51%

Source: The Higher Health Council [23]

12.6.2 Pharmaceutical Pricing Policy in Jordan

The JFDA has responsibility for setting the price of medicines for sale in community pharmacies (private sector). Article 11 of the Drug and Pharmacy Law determines the membership of the pricing committee that includes the director of the drug directorate in the JFDA, the director of supply and purchasing, the head of the pricing department, an internist, a pharmacist specialist in pharmacology or clinical pharmacy and two experts (one being an expert in cost accounting). While the pricing committee is involved in the determination of the price of medicines distributed through community and hospital pharmacies, it is not involved in the pricing of medicines obtained through tenders [28, 29].

12.6.3 Originator Brand Pricing in Jordan

In Jordan, according to the pricing instructions approved by the Prime Minister, the price of a NCE (originator brand) is allocated based on the lowest price resulting from one of the following five different methodologies [35].

- If the goods are on a Cost, Insurance and Freight (CIF) basis, the drug price to the Jordanian public is computed from the cost price. This is on the basis of the factory-listed price from the invoice issued (from the party designated to issue invoices) plus the addition of customs duties, bank's charges, insurance, clearing and inland transportation (plus the profits of the wholesaler, pharmacy and their administrative costs). If the basis of shipment is Free On Board (FOB), the shipping costs will be added to the above [35].
- The drug price to the Jordanian public is computed from the cost of the imported drug on the basis of the public price in the country of origin after deducting the value added tax (VAT) there, if applicable, and after deducting the profits of wholesalers and retailers there and adding the shipping costs, bank's expenses and charges, insurance clearing and inland transportation (plus the profits of the drug store and pharmacy and their administrative costs) [35].
- The median price resulting from the prices of the public in the following countries: UK, France, Spain, Italy, Belgium, Greece, Netherlands, Australia, Cyprus, Hungary, Ireland, New Zealand, Portugal, Czech republic, Croatia and Austria. In the event that it is not priced in all of those countries, the median price where available in not less than four countries is used [35].
- The price computed from the export price to the Saudi market. As for any unregistered drug in Saudi Arabia, its price in Jordan will be reviewed upon its registration there. The agent is committed to provide the JFDA with the export price to Saudi Arabia within a period not exceeding 4 months from the date of pricing it there [35].
- If the drug is registered and priced in the country of origin only and the average median public prices from the countries above become impracticable, then it is priced on the basis of drug prices having close chemical composition and/or therapeutic effect [35].

12.6.4 Locally Manufactured Generic Medicines Pricing

The pricing policy stated that the requested price for the locally manufactured generic medicines should not exceed 80% of the price of the originator drug when first registered and priced or upon repricing or 80% of its current price whichever is less [35].

12.6.5 Imported Generic Medicines Pricing

Regarding imported generic medicines, the Jordanian price is determined as the lowest price resulting from the application of the following methods [35].

- If the goods are on a CIF basis, the drug price to the Jordanian public is computed from the cost price. This is on the basis of the factory-listed price in the

invoice issued from the party designated to issue invoices by adding to its customs duties, bank's charges, insurance, clearing and inland transportation (plus the profits of the wholesaler, pharmacy and their administrative costs). If the basis of shipment is FOB, the shipping costs need to be added to the above [35].

- The drug price to the Jordanian public is computed from the cost of the imported drug on the basis of the public price in the Country of Origin after deducting the VAT there, if applicable, and the profits of wholesalers and retailers there and adding the shipping costs, bank's expenses and charges, insurance clearing and inland transportation (plus the profits of the drug store and pharmacy and their administrative costs) [35].
- The export price to the Saudi market, and if it is not registered there, its pricing shall be reviewed upon its registration and the agent is committed to provide the JFDA with the price within a period not exceeding 4 months [35].

12.6.6 Pricing Decision Making

The applicant has 30 days in which to appeal a pricing decision to the Director General of the JFDA. Such an appeal will be registered to the Drug Pricing Committee who has 30 days to make its recommendation. A price is considered inoperative if the applicant has not accepted it within 6 months of notification [35].

The Director General, by a recommendation from the pricing committee, is entitled to cancel the registration of a drug or prohibit its reregistration, except after 1 year from its cancellation, in the event of the following breaches [35].

- If it becomes apparent that the drug pricing was done on the basis of false information submitted by the manufacturing company or the agent.
- If the price to the public in the country of origin is reduced and such reduction was not reflected on the selling price to the Jordanian public, and the manufacturing company or its agent did not notify the committee within a period not exceeding 4 months from the date of the reduction.
- If the manufacturing company or its agents did not submit the export price to Saudi Arabia within 4 months from its pricing there, unless a document from the manufacturing company or its agent is submitted proving that the drug is not being marketed there.

The Director General of the JFDA issues a schedule of exchange rates in July each year, and these are determined from the average rate for June using exchange rates published by the Central Bank of Jordan. Prices of products can be revised if the variation in the exchange rates exceeds 5% for three consecutive months [35].

The pricing committee revises the prices of new products after 2 years of registration, and the price of all products is reviewed upon renewal of registration which is every 5 years. When there is a price reduction in the originator drug, all generics

must reduce their price, except where the price is due to an exchange rate movement or at the request of the originator country of origin's company [35].

12.6.7 Calculation of the Public Price for Drugs

In Jordan, all pharmaceutical prices include the same margin for all products. Drug stores (wholesaler) receive 15% on the landed cost plus 4% for expenses while pharmacy receives 20% on the wholesale price plus 6% expenses. These percentages are cumulative. As a result, there are strong incentives for both wholesalers and retailers to promote and sell the highest priced drugs or brands as these attract the highest return in money terms [35].

The public price (final selling price) of pharmaceuticals is calculated as follows (the amount of ex-factory price is illustrative):

Ex-factory price (excluding bank charges, customs duties, insurance, clearing and inland transport and R&D costings)	*JD100 (Jordanian Dinar)*
Add drug store (wholesaler) profit (15%)	*JD115*
Add drug store expenses (4%)	*JD119.60 (cost for pharmacy)*
Add pharmacy profit (20%)	*JD143.52*
Add pharmacy expenses (6%)	*JD152.13*
Add Value Added Tax (VAT) (4%)	*JD158.22 (public price)*

These percentages are cumulative. Thus, out of the total price of JD158.22, the government receives JD6.09 or 3.8% of the public price as a value added tax (VAT); pharmacy receives JD32.53 or 20.6% of the public price; drug stores get JD19.60 or 12.4% of the public price and suppliers (manufacturers) get JD100 or 63.2% of the public price (Fig. 12.2). Please note that as the ex-factory price excluded the bank charges, customs duties, insurance, clearing and inland transport and R&D castings, the percentage gain, therefore, for each sector excluding the manufacturer will be even higher.

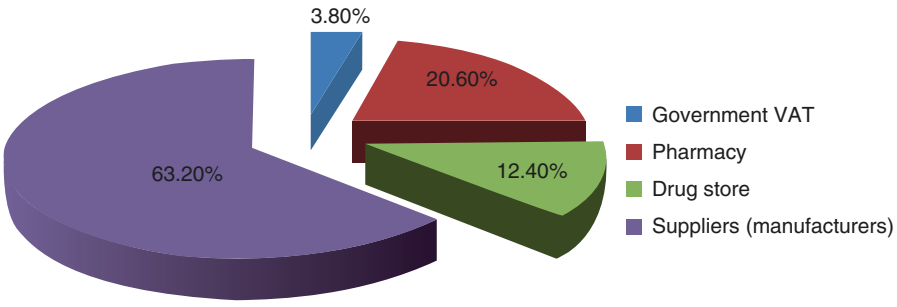

Fig. 12.2 Cumulative percentage of public drug price in Jordan

12.6.8 Jordan Medicine Prices Problem

According to the research conducted by El-Dahiyat [16] where the prices of medicines were compared in Jordan to the UK, it was reported that the prices of medicines in Jordan were the same or higher than a relatively rich country, 70.79% of originators were priced higher in Jordan compared with the UK. Jordanian originator prices were on average more than 1.5-fold greater than their prices in UK (+51.47%). The price differences ranged from −96.40% to +1804.14%. Moreover, 86% of the generic drugs sample studied were priced higher in Jordan compared with the UK. Jordanian generic prices were on average around triple the prices in UK (+290.4%). However, the prices differences ranged from −80.66% to + 997.06%.

These results emphasised that the prices are relatively high in Jordan, especially considering the difference in income per capita between the two countries, almost seven times lower in Jordan [47]. These high prices results were consistent with the previous pricing survey conducted by Health Action International in 2004 [20].

12.6.9 Reasons for Unaffordable Medicine Prices in Jordan

The reasons for unaffordable medicine prices in Jordan, reported by El-Dahiyat [16], included the pharmaceutical pricing policy and its application. It allows for local manufacturers to price their products up to 80% from originator price. Moreover, the low demand in the small Jordanian market makes local manufacturers request the highest prices possible, as they depend on the exportation market that tends to request the country of origin price at price negotiation. The current policy encourages competition between generics and originators only, but not between generics. The pharmaceutical industry in Jordan is private and profit seeking. The reason behind the weak pricing policy in Jordan may be due to the local generic industry and originator wholesalers influencing the policy [16].

12.6.10 Drug Store (Wholesaler) Margin

The current markup (15 + 4%) for drug stores (wholesalers) in Jordan is very high compared with other countries, such as Australia where the wholesalers receive only 7.5% markup [9]. Croatia is a developing country with similar demography to Jordan, and reports show that their markup margin is 8.5% [44].In the UK, the nominal margin is 12.5%. However, discounts may be negotiated between manufacturers and wholesalers and between wholesalers and pharmacists. The NHS list price includes wholesalers' distribution margin [48]. In addition, originator brands were found to cost 1.5 times higher than in the UK. International originator manufacturers usually give large discounts to developing countries (price discrimination

or differential pricing); however, this is not the case in Jordan. A study by Lichtenberg [37] found that patients in the lowest income bracket usually pay 25% less prices for pharmaceuticals compared with patients in the high-income bracket [37]. However, this was not shown in the originator prices in Jordan, as the reference countries used for the pricing of generics are those from European high income countries.

Therefore, the current level of the markup provided for drug stores for their profits; 15% and operational expenses 4%; (19% cumulative) should be reviewed.

12.6.11 Bonus Practices in the Jordanian Pharmaceutical Market

According to the JFDA website, some local manufacturers and wholesalers in Jordan provide incentives to pharmacies to stock their products. These incentives are in the form of bonuses. Bonuses range between 120% and 200% and even more are used for both the local domestic Jordanian market and the export markets. Pharmaceutical wholesalers and local manufacturer sometimes give ten free packs of medicines for every five packs purchased by a pharmacy; as the pharmacy purchases more stock as these bonuses increase. In 2006, the JFDA tried to put an end to this unethical practice. However, all companies opposed the proposal, and the practice is still continued in the Jordanian market to date [32].

12.7 Medicines Use (Issues Impacting on Rationale Medicines Use in Jordan)

12.7.1 Essential Medicine List, Selection of Essential Medicines and Treatment Guidelines

In Jordan, the objective of Jordan's Essential Drug List is to ensure the availability of appropriate medicines according to patients' clinical needs at affordable prices to them and their community [6]. The Essential Drug List is periodically updated by considering the safety of the drugs and using different pharmacoeconomic evaluation methods to meet the health needs of the population. The inclusion criteria for new medicines and for the removal of existing medicines from the list are based on both the cost and health needs of the population.

The essential drugs are selected based on internationally recognised criteria obtained from several World Health Organization selection criteria. The Selection and Use of Essential Medicines, 2002; Promoting Rational Use of Medicines, 2002; and WHO Model List of Essential Medicines, 2002

A selection committee comprising physicians and pharmacists provides technical support and advice on the revision and update of the JRDL. However, a limitation of the process relates to the fact that there is no written guidance in relation to the conflict of interest of those serving on the committee [50].

The rational drug use department at JFDA issues and updates both the JRDL and the Jordan National Drug Formulary (NDF). Moreover, the department is responsible for the development of treatment guidelines and protocols, support and monitor the Pharmacy and Therapeutic committees in hospitals. In addition to arranging Rational use of medicines's awareness campaigns [36].

12.7.2 Prescribing Behaviour (Factors Affecting Prescribing Behaviour)

According to many studies, the prescribing behaviour of physicians is considered to be crucial for generic utilisation, as they determine whether their patients are prescribed originator branded medications or generics [1]. A generic medicine may not always be suitable for the patient [10].

Several factors play a significant role in influencing the physicians' prescribing behaviour, such as the 'trust' and the 'quality image' of the pharmaceutical company [40]. Physicians' prescribing behaviour can also be influenced by pharmaceutical companies through a variety of incentives such as high-end education programmes or even some cash payment for prescriptions [45]. In addition, free samples and gifts can also influence prescribing. This can indirectly influence prescribing habits as prescribers remember these companies' brands [12, 46]. Subsequently, this can affect the cost of medicines and adherence of patients by prescribing higher priced originator-branded products instead of equally effective, lower -cost generics [43].

Few studies have investigated the prescribing behaviour in Jordan. The reason for the high level of drug consumption, according to the Jordan National Health accounts published by the High Health Council in Jordan, could be due to the prescribing behaviour of prescribers and dispensing practices of pharmacists. It has been concluded that changing the prescribing behaviour and dispensing practices is a necessary condition to achieve overall cost containment objectives [21].

A recent study assessing how factors affect prescribing behaviour in Jordan ranked the contributing factors. The study reported that the clinical effectiveness and safety of a medicine prescribed were the first factor. The second factor was the dosage form and regimen, the cost of medicine was the third factor. Patient preference and availability as a generic and country of origin were fourth, fifth and sixth factors, respectively. The majority of the prescribers in Jordan (86.7%) use international treatment guidelines to justify their prescribing decisions. Local protocols and medical journal publications and online databases were used by 57.4% and 54.5%, respectively. Conferences and pharmaceutical sales representatives were used by 37.2% and 12% of the physicians, respectively, in order to justify their prescribing decision. However, only a few responders (2.7%) justify their decision by other reasons such as their own experience and patient clinical history. According to the same study, the majority of Jordanian physicians sampled (77.4%) often prescribe generic medicines and (80.1%) use International Non-proprietary Name (INN) while prescribing [17].

More than two thirds of the physicians (69.4%) accepted generic substitution by pharmacists. The study also found a significant association between their opinion and their employment sector. Physicians who work in the private sector tended to oppose generic substitution, compared with physicians who work in the public sector. In general, Jordanian physicians have a positive attitude towards generic medicines and are very willing to accept strategies that encourage generic utilisation, INN prescribing and generic substitution [17].

12.7.3 Barriers for Generic Medicine Use in Jordan

As concluded by El-Dahiyat [16] that the barriers to prescribing/dispensing generic medicines in Jordan are believed to include reasons such as legal barriers, that is where the substitution is not allowed, and financial disincentives. This remuneration method provides incentives for pharmacists to sell high-priced originators to the public rather than the cheaper equivalent generics in order to achieve high net profit. The effect of this fixed profit margin could be seen clearly in the following example (Table 12.4).

Professional responsibility of the pharmacists should include medicines dispensing, patient counseling and advice on how to use medicines correctly, in addition to maintenance of patients' record. This could be reflected by introducing a remuneration fee.

Other barriers to the prescribing and dispensing of generic drugs could be due to advertising campaigns by originator companies in Jordan which may result in their high market share. The studies have shown that the amount of advertising and length of time in the market are positively correlated with market share after patent expiry [24].

12.7.4 The Role of the Pharmacist

The main role of Pharmacists in Jordan is the traditional dispensing medicines only. At present, there are no available studies about the community pharmacy services in Jordan or the role of the pharmacist in hospitals or community pharmacies. Furthermore, under the current Jordanian legislation, pharmacists are not permitted

Table 12.4 Famotidine products' differences in the pharmacy profit margin

Famotidine	Brand name	Strength and pack size	Pharmacy cost	Public price no VAT	Net pharmacy profit
Originator brand	PEPCIDIN®	20 mg 30 tablets	16.10	20.29	4.19
Generic brand	AMODINE®	20 mg 30 tablets	3.37	4.25	0.88

Source: El-Dahiyat [16]

to make any change or substitution to prescriptions, unless the pharmacist first contacts the prescriber and requests permission to substitute the originator with a generic [52].

12.8 Conclusions: Summary and Way Forward

Jordanian pharmaceutical policy tries to improve availability, affordability and utilisation of essential medicines through endorsement of good governance and management practices in the pharmaceutical sector.

Like other countries, Jordan aims to ensure an uninterrupted availability of essential medicines especially in view of a significant burden on the Jordanian pharmaceutical sector, which part is also a result of the Syrian refugee crisis.

Jordan has also proceeded with upgrading its legislation to govern the conduct of pharmaceutical market, prohibit common forms of misconduct and protect the rights of all parties involved in the pharmaceutical industry, especially after joining the world trade organisation.

However; as seen in this chapter, the pricing policy needs to be revised to keep medicines prices affordable in private sector. Moreover, educational programmes for public, physicians and pharmacists should be developed and conducted in order to encourage the use of generics as it considered a cost containment tool. These programmes should be supported by legislation, to address brand substitution and also to revise current generic pricing policy. Educational programmes should target the public in general and the elderly and patients getting their first chronic disease repeated prescription in particular.

The role of the pharmacists in Jordan needs to be broadened to ensure that the role complies with international standards, which includes dispensing medicines, monitoring patient health, educating patients on the proper use of medicines and prescribing for minor ailments conditions.

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Chapter 13
Pharmaceutical Policy in Russia

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Abstract Pricing and reimbursement policies have changed significantly in Russia during the last 20 years, largely due to ongoing reform processes within the healthcare system. The current structure of the Russian healthcare system includes federal and regional levels with different requirements and funding allocations due to diversity in the population (average and population density), overall and per capita income, and other factors. The federal level is governed by the Federal Ministry of Health, which is responsible for the pricing and reimbursement policies in the country. Federal budgeting covers the majority of healthcare programs, while the regional budget provides additional financing for regional needs. Reimbursement of drugs is incorporated in these programs, along with other expenses (hospitalization, laboratory testing, and so forth).

In terms of pharmaceutical policy, inclusion of medicines into reimbursement lists includes two staged steps in Russia. In the first step, the drug must be included in the Essential Drug List (EDL) and a pricing cap is then applied. The upper margin of the drug price is determined as a referral price for imported medicines (based on a basket of 21 countries). It can also be based on drug development and manufacturing expenses and include regional markups specified for each region. Cost-effectiveness analysis is part of the requirement for submission of an EDL dossier in Russia. The second step in the process is the inclusion of EDL-listed drugs into federal healthcare disease specific programs (oncology, HIV, and so forth). Regions can establish healthcare programs in addition to the federal activity based on regional requirements and their own regional funding allocations and budgets. There are different needs within the healthcare system at federal and regional levels; including hospital and industrial corporations who have their own healthcare

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services. This can contribute to challenges in implementation of uniform approaches to Health Technology Assessment (HTA) at different levels and in the different regions.

13.1 Overview of the Russian Federation

The *Russian Federation* (РоссúйскаяФедерáция, *Rossiyskaya Federatsiya*), commonly known as *Russia (Rossiya)*, is a transcontinental country extending over much of northern Eurasia (Asia and Europe). Russia has a fascinating history and recent changes in the health care system and demographics of the population have had a significant impact on pharmaceutical policy and practice. These are addressed in this chapter.

In Russia in 2014, demographic analyses highlight that the birth rate exceeded the death rate, resulting in a net population growth. The State Statistical Agency reports that the population of Russia is 146 million people, with an average life expectancy of 65 years for males and 76.4 for females. The most significant causes of mortality include diseases of the circulatory system (653.9 per 100,000), cancer (201.9 per 100,000), and injuries (129.9 per 100,000) [1].

13.2 The Health System of the Russian Federation

The current healthcare system of Russia is a fusion of features from the former Union of Soviet Socialist Republics (Soviet Union) with changes made by the Russian Federation in the time since the dissolution of the former Soviet Union in December 1991. Under the guidance of the Soviet Union the system was created as a centralized structure to ensure maximum efficiency of managerial decisions supported by tight administrative control. The objectives of the system at that time were to ensure uniform principles of healthcare organization and access to healthcare for the entire population of the country at the expense of a state-funded budget [2–4]. Nowadays, the centralized system of healthcare is put in place by the Federal Ministry of Health and is supported by the Ministries of Health in 85 regions, with their own budgets and regional development programs. Expenditure on healthcare delivery and patient treatment is provided by Federal and Regional Target Programs supervised by the Federal and Regional Ministries and a budget is provided by either regional or federal state insurance funds. Reimbursement of pharmaceuticals is included in these programs alongside other expenditures [4, 5].

Under this current system, some expenses are covered by patients themselves or by other sources including additional voluntary insurance (private insurance) and corporate finance allocations for employees. Currently, the healthcare system in Russia has three dimensions that are continually changing and include financial

sources, institutions, and management. The following sources contribute to the healthcare budget:

1. State-funded programs using federal and regional budgets. These programs have specific target populations dependent on disease state or patient status or disability (oncology, AIDS, disabled, pediatric, etc.).
2. Insurance funds (obligatory and voluntary).
3. Patient self-funded ("out-of-pocket" expenses).
4. Corporate funded programs (national air company "Aeroflot", Russian Railways, etc.) with their own budgets and structures and provide in and outpatient services.

All of the above is managed by Federal and Regional Ministries of Health, corporate healthcare management (for the corporations), and municipal authorities. Additionally, there are insurance funds: voluntary schemes, which are flexible in decision making, and obligatory schemes, which need to distribute resources according to policies and procedures.

Some interactions between these healthcare components are very formal (such as the distribution of budgets from obligatory insurance funds to state-budgeted hospitals), while others are flexible (the same hospitals can also accept money from voluntary insurance funds, patients or in accordance with contracts with corporations) and can be changed within a relatively short period of time.

Drugs are distributed via networks of community pharmacies or hospital pharmacies for inpatient clinics. The State Program for Healthcare Development prioritizes prevention of diseases with special attention on the health of mothers and children [6]. There is also a focus on the implementation of innovative medical technologies into practice: target therapy using biologics, noninvasive methods of breast cancer diagnostics, etc. In 2015, the main healthcare objective was the prevention and decrease of cardiovascular disease burden, with nearly half of deaths caused by this (49.9%) in Russia [1].The strategies declared by the Federal Ministry of Health include a comprehensive set of activities, including population awareness regarding the adoption of healthy lifestyles, additional education in this area for healthcare practitioners, and general improvement of healthcare management [1]. This involves adaptation of the whole system to new conditions, which include the economic situation, budgeting, recent changes in healthcare technologies, and management structure and methods.

13.2.1 Federal Level

The Ministry of Health is the Supreme Health Authority in the Russian Federation [5]. It is headed by the Minister appointed by the Prime Minister upon approval of candidacy by the State Duma.

The Ministry of Health sets policy in Russia and officially retains the right to monitor the regional health and enforcement of decisions in healthcare entities of the Russian Federation. However, the extension of the powers of local authorities,

and primarily their right to form their own budget, means that the Ministry can no longer count on the fulfillment of its central instructions.

The budget of the Ministry of Health is established by the Ministry of Finance. This budget also supports scientific research institutes, scientific centers, and medical educational institutions working under the supervision of the Ministry of Health. The federal healthcare budget is established and approved by the government as part of the general federal budget. The Ministry of Finance distributes funds to the appropriate ministries and these ministries (Federal Ministry of Health as well) supervise and manage proper distribution of the budget according to the healthcare programs. The Federal Ministry of Health is, therefore, responsible for these activities at the federal level. Regional Ministries of Health have the same responsibilities and communication lines at a regional level and supervise regional programs in addition to the federal ones. Thus, in each region there are federal programs and additional regional programs with attached federal and regional sources of funding and subsequent budgeting.

The public healthcare system includes the Ministry of Health of the Russian Federation, the Regional Ministries (Departments) of Health of the republics of the Russian Federation, the bodies of health administration of the autonomous region, edges, areas, cities of Moscow and St. Petersburg, and the State Committee for sanitary and epidemiological supervision of the Russian Federation. This system also includes state-owned hospitals and outpatients clinics, research institutions, educational institutions, pharmaceutical companies and organizations, pharmacies, institutions of forensic medical examination, and enterprises for the production of medicines and medical equipment.

13.2.2 Regional Health Care

The regions of the Russian Federation are obliged to ensure the fulfillment of Federal Targeted Programs, primarily aimed at monitoring the epidemiological situation and the fight against infectious diseases, but they do not report to the Federal Ministry of Health. The regions have their Ministries of Health reporting to regional authorities and are capable of developing regional healthcare programs according to regional needs and opportunities in addition to those at the federal level.

13.2.3 Municipal Health Care System

The municipal healthcare system includes municipal governments and municipally owned clinical and research institutions, pharmaceutical companies and organizations, pharmaceutical institutions, institutions of forensic medical examination, and

educational institutions which are legal entities and operate in accordance with the legislation of the Russian Federation and the local legislation.

13.2.4 Private Health Care

Private healthcare is available in the Russian Federation which includes provision by private clinical institutions and community pharmacies with staff engaged in private medical practice and pharmaceutical practice. The System of Voluntary Health Insurance (VHI) includes several private insurance companies. Funding of VHI is provided partially by the employer, and partly by the patient. The patient also contributes the full amount of the premium if the employer does not pay into the scheme. The list of medical services that are covered under the policy varies in the different VHI programs and includes: medical care only in emergency cases and certain types of inpatient and/or outpatient treatment. Certain services in dental care may also be included in the VHI program.

13.2.5 Federal and Regional Insurance Funds

Insurance funds were a significant component of healthcare system reform in the Russian Federation in the 1990s [4, 5]. Government policymakers had to improve the national healthcare financing arrangements and to move the healthcare system into an open market style of management, which was expected to increase economic efficiency, quality, and improve access of medical care for all Russians. Under the new scheme of financing, key resources were the funds of mandatory medical insurance including the Federal Fund of Compulsory Medical Insurance and Regional funds, one in each region ("subject of state"), of the Russian Federation.

Insurance funds collect premiums and distribute resource for the provision of healthcare in their territories. Working citizens pay about 3.6% (3.4% to regional funds and 0.2% to the Federal Fund) of their wages, while the contribution for non-working individuals (children, pensioners, unemployed, and so on) is paid for by local authorities. Regional funds transfer the received budgets to the insurance companies (also referred to as health insurance organizations) or branches of the regional funds and on behalf of the insured, enter into contracts for medical services with clinical institutions. Federal and territorial funds are public nonprofit organizations. The Federal MHI Fund is a legally independent organization and is not under the Ministry of Health, but it monitors its activities through their representatives on the Board.

The Federal Insurance Fund oversees the activities of territorial funds; the situation of the compulsory health insurance system corresponds to the position of the Regional Health Authorities. Federal funds are primarily required to manage the entire system and to monitor the financial equality within the regions.

13.2.6 Insurance Companies

The next key element established by Russian Federation law on health insurance is an independent organization carrying out payment for medical services on behalf of the insured population. Based on analysis of the Federal Insurance Fund [7] there are two types of organizations: independent insurance companies and branches of regional insurance funds, who take on the role of insurance companies in their absence in the area. Insurance companies receive funds for each insured person and select preferred medical institutions to provide medical services to the insured population. Insurance companies are able to promote competition between those medical institutions to encourage them to reduce costs and improve the quality of medical services. Insurance companies monitor the volume and quality of medical services and in accordance with their findings, issue medical institution funds.

There are insurance funds for compulsory medical insurance and the objective of these is to distribute and deliver federal and regional funds. The flow of remuneration is "one-way" from federal or regional budgets to the patients. These insurance companies are expected to follow federal and/or regional healthcare programs and do not have the right to make fund-related decisions at their own discretion. Another type of insurance company (Voluntary Health Insurance) operates through patient payment of levies/premiums, or any other entities. These pay for those patients associated with corporations, etc., and not related with state (federal or regional) healthcare programs. These Voluntary Health Insurance companies are privately owned and are more flexible in their decision making around the programs they provide to their patients. A few years ago, there was a considerable gap between these two types of insurance companies in terms of what they offered but now these differences are reducing and these days compulsory insurance funds can provide programs for voluntary health insurance premium holders.

Insurance companies can organize their activities in a variety of ways. This includes providing paid medical services to a defined population on pre-agreed rates, or to establish general practice funding per capita, etc. The number of insurance companies peaked at the end of the 1990s when there were approximately 1350 insurance companies in operation, while now there are less than 300, and their numbers continue to decline.

13.3 The Pharmaceutical Situation in the Russian Federation

Official statistical data supported by independent research by private consulting company "DSM Group" indicates that the Russian pharmaceutical market is still growing in national currency terms, averaging 14% growth year on year. Based on 2014 data, in 2015 the market growth in national currency was expected to be 12% (1.3 trillion Russian Rubles). In foreign currency terms (US dollars, USD) a decrease of market

volumes of 18% was seen, down to a figure of 24.8 billion USD [1, 8]. This situation is due to the difference in exchange rates between the local currency being the Russian Ruble and the US dollar (USD). The market in terms of number of packs is growing, and the price for the average pack is also growing in local currency. At the same time, the exchange rate between local currency and the USD has been decreasing due to economic crises and inflation. As a result, the market growth in terms of USD is seen to decrease. The low value of local currency relative to the exchange rate provides advantages for local manufacturers (less to pay) and disadvantages for imported products including pharmaceuticals – they sell in local currency, they pay more in USD. This situation makes local (domestic) manufacturing beneficial and provides an opportunity for the Russian government to decrease prices for medicines as locally produced products cost less due to reduced manufacturing and transportation costs, among other factors.

The share of public procurement market was in the range of 28–30%, or approximately 309 billion Rubles [9, 10]. The commercial sector procurement amounts to 776 billion Rubles. The authors use the term "public" for state-budgeted programs of healthcare (including compulsory health insurance) and "commercial" for any other (out-of-the-pocket or corporative purchases, voluntary health insurance.)

The share of domestically produced medicines in 2014 amounted to 24.3% in monetary terms and 55.3% in terms of the quantities of packs sold. Over two-thirds (68%) of drugs listed on the Russian Essential Drugs List (EDL) are produced in Russia. According to IMS Health data, Russia ranks 11th of 15 countries for high per capita consumption of pharmaceuticals (in USD). According to the forecast of the Economist Intelligence Unit (EIU) by 2018, Russia will drop to occupy the 17th place ranking. A portion of medicines manufactured in Russia are exported to Uzbekistan, Ukraine, Kyrgyzstan, Azerbaijan, and other countries, but the quantities are less than the amount of drugs imported into Russia – i.e., imports are greater than exports [11, 12]

From the end of 2014, the pharmaceutical market has been under the influence of the general economic situation in the country, which has included devaluation of the national currency and a slowdown in the economy. The geopolitical situation and sanctions against Russia have resulted in changes in the law regarding prices of medicines on the EDL. The new regulations were also aimed to support local manufacturing of medicines [13]. In accordance with this decree, tenders are required to be provided according to the International Non-proprietary Name (INN) and the customer is expected to reject any medication manufactured in countries other than the member states of the Eurasian Economic Union in the case that there are at least two medicines produced in those countries.

According to experts surveyed by private consulting company DSM Group, professionals in the pharmaceutical industry are particularly concerned about:

- The economic situation in the country
- The necessity of improving the legislation that regulates the pharmaceutical industry
- Necessity to increase funding of healthcare programs and to support local business in the pharmaceutical industry
- The international political situation and its associated economic risks [8]

13.4 The Regulatory Environment in Russia

The Russian laws, which influence State affairs and the development of the health sector and the pharmaceutical industry, include:

- Federal law dated 21 November 2011 No. 323-FZ "About bases of health protection of citizens of the Russian Federation" [5]
- Federal law dated 12 April 2010 N 61-FZ "On circulation of medicines" (with amendments and additions) [14]
- Russian Federation Government resolution from February 17, 2011 N 91 "About the Federal target program Development of pharmaceutical and medical industry of the Russian Federation for the period till 2020 and the further prospect" [11]

The principles laid down in these laws and recent changes prioritize quantitative and qualitative development of the domestic pharmaceutical industry and are expected to reduce the dependence on imported medicines and to increase the share of Russian medicines in the domestic market. This provides an opportunity to reduce the risk of political bans and the high cost of imported pharmaceuticals compared to those manufactured in the Russian Federation. Measures include:

- Restriction in the participation of products from foreign producers in budget tenders, when medicines produced in the countries of the Eurasian Economic Union are available.
- Encouraging foreign manufacturers to establish a full production cycle in Russia and invest in Russian companies through the provision of benefit such as the opportunity to secure investments or obtain funding for transferring of manufacturing in the country.
- Separate pricing methodology for medicines in different price segments, including imported medicines compared to those manufactured locally.
- Transition to the GMP standards effective from 1 January 2016 in the Eurasian Economic Union. In order to create a unified market among the Eurasian Economic Union on 29 May 2014, member states signed an agreement outlining common principles and rules of engagement for circulation of medicinal products and drugs including registration of medicines and medical devices, thus they unified the standards of production and clinical trials.

Financial support for Russian manufacturers – for example, a Russian pharmaceutical company, which develops medicines is entitled to receive subsidies or partial compensation for the cost of debt loan payments, according to the Decree of the Government # 214 [15].

13.4.1 Medicines Regulatory Authority

The Ministry of Health is the medicines regulatory authority in the Russian Federation along with Regional Ministries of Health, in each of the 85 regions [8].

The Federal Ministry of Health is responsible for registration (market access) and pricing processes associated with pharmaceuticals. This function is performed by the Department of State Regulations for Medicine's Circulations in the Federal Ministry of Health.

There are the following Divisions in this Department:

- Division of Registration
- Division of Clinical Research
- Division of Regulation of Restricted Medicines
- Division of Pricing for Medicines from the EDL

The responsibility for registration of medical devices is still held by *Roszdravnadzor. This* agency is also responsible for control of the safety and quality of registered medicines and medical devices in Russia.

There are three institutions within *Roszdravnadzor*:

- Center of monitoring and clinico-economical expertise, which is responsible for the evaluation of the quality of healthcare, development, and use of medical devices and the storage and wholesaling of pharmaceuticals).
- Information and methodical center on expertise, analysis, and counting of medical products [16].
- Russian Research and Test Institute for Medical Devices [17]. This organization conducts testing for the purpose of registration and certification on request of the Department of Registration from the Federal Ministry of Health [18].

Quality control of medical products at all stages of the supply chain including transportation to the pharmacy, storage, and delivery to patients is the responsibility of the Roszdravnadzor. The main responsibilities of this organization include the state quality control of medical care, licensing of medical activity, and verifying the correctness and effectiveness of the use of budgetary funds.

13.4.2 Quality control

Medical Devices Roszdravnadzor carries out registration of medical devices, amendments to registration documents, and registration certificates for medical products and provides permission to import medicinal products. Roszdravnadzor also coordinates and issues permits for clinical trials of medicinal products, carries out control over the circulation of medical products, monitors the safety of medical devices, and issues licenses for the production and maintenance of medical equipment.

Pharmaceutical Products Roszdravnadzor supervises clinical and preclinical research, monitors drug safety, drug quality control, detection of inappropriate medicines (rejected or counterfeit), and issues permits for import and export, and licensing of medicinal products [19]. The agency also supports and evaluates the database for drug safety reports.

13.4.3 Pharmacovigilance

Roszdravnadzor carries out the statewide function of conducting safety monitoring for medicinal products in circulation within the territory of the Russian Federation. The stakeholders involved with the circulation of medicines include doctors, pharmaceutical companies, and patients and they are obliged to inform Roszdravnadzor about any cases of unlisted side effects, unexpected or serious interactions for registered medicines and those that are undergoing clinical trials. In the framework of monitoring the safety of medicines, Roszdravnadzor carries out an analysis of periodic reports on the safety of medicines received from manufacturers and developers of medicinal products. Roszdravnadzor carries out analyses under the framework of monitoring drug safety information. The results of these analyses are sent to the Ministry of Health for decision making about amendments to the instructions on the use of drugs, the suspension of their circulation or re-introducing the circulation of drugs [14]. It is interesting to note that in the Russian Federation, community pharmacies do not usually have two-way communication with patients. Patients receive or buy drugs in these outlets but in case of adverse events or any other reaction they refer to doctors (not pharmacies) and thus pharmacies cannot be considered as a reliable source of information for pharmacovigilance reporting. Pharmacies are expected to report adverse reactions if they have patient information about them; however, the probability of pharmacies doing so is very low.

13.4.4 The Presence of Counterfeit Medicines in the Russian Federation

Roszdravnadzor carries out regular inspections and identifies rejected and counterfeit drugs. Defective drugs are produced legally but are inconsistent in terms of presence of active ingredients in the medicine or the inclusion of impurities, or either noncompliance with labeling requirements. Roszdravnadzor prepares a list of defective and adulterated products, which it publishes and distributes to pharmacies. According to Roszdravnadzor expert opinion, spot checks revealed that only a part of the substandard and counterfeit products are available in the Russian Federation. It is estimated by experts that 7–8% of Russian pharmaceuticals are substandard and that 0.5–0.6% are counterfeit. Most often counterfeit drugs lie in the middle price segment with a value from 150 to 500 Rubles (2 – USD 10 per pack). In this regard, the establishment of a monitoring system of defective products is relevant and important [18].

13.5 The Medicines Supply System in the Russian Federation

There are two ways for funding the distribution and access of pharmaceuticals in the Russian Federation. These include out-of-pocket where the patient pays the full amount (via municipal and private pharmacies) and in accordance with the

programs of budget financing through the State. The surveys performed by the DSM Group of companies indicate that the share of publicly funded procurement is in the range of 28–30% of the total pharmaceutical expenditure across all funding mechanisms [8].

There are three main levels of procurement which are usually undertaken in the format of tenders including federal, regional, and at the level of individual medical institutions. The main criterion for selection is the lowest price compared to competitors [11]. Tenders are drawn on the basis of the International Nonproprietary Names (INN). If INN presents two or more manufacturers from the Eurasian region, then parties with drugs manufactured in other countries are not permitted to participate in the tender process [11].

Once procured, the drugs are delivered to clinics and pharmacies, both municipal and private. Municipal and private pharmacies have different ownership structures. Historically, all pharmacies where patients could source medicines were municipal and patients also received medicines in hospital pharmacies (as departments within hospitals) according to state-budgeted healthcare programs. Any pharmacy must hold a supply of medicine according to the list (the minimal register of drugs, which must be in any pharmacy) and they may stock supplies beyond this list. In the 1990s, privately owned pharmacies began to emerge and were more flexible compared to government-owned municipal pharmacies. These pharmacies generally have more medicines available but medicines are often highly priced as compared to municipal pharmacies. Nowadays, the difference between the two types of pharmacies is not so obvious (ownership is different but the legal requirements are the same) and in some cases they attract the same group of patients.

In Russian hospitals, medicines for inpatients are stored in the pharmacy and are issued at the request of attending physicians. For patients with disabilities and for vulnerable populations there is a program called "Additional Medicinal Maintenance". In this scenario, drugs are dispensed from a municipal pharmacy, free of charge.

Corporations and agencies that are supported by federal funding also need to perform tenders for drug procurement. Private healthcare institutions are not required to comply with this law and they can purchase medicines according to their corporate procedures. However, this segment of the market is relatively small, the exact figure is unknown and this is an interesting area for future research.

13.6 The Financing of Medicines

The financing of medicines in the Russian Federation is based on federal, regional, and municipality budget funds, as well as insurance funds and budgets of corporations and other private agencies. In terms of financing, the "Corporations" are private or at least are run in a fashion that is most like a private corporation. At the same time, one of the owners can be the Russian Federation government or the company can be a monopolist. The biggest examples are "Gasprom", "Russian Railways", and "Aeroflot." These corporations

have a huge workforce, which requires healthcare services, including the provision of medicines and they can make decisions regarding medical services at their own discretion. These companies can also allocate healthcare budgets based on their income and profits and also decide the kind of healthcare strategy they wish to use. For example, a few years ago "Gasprom" and "Russian Railways" decided to unite their medical services and now there is one combined healthcare system that provides services for both organizations, and this was affordable due to economies of scale.

According to official statistical data and the DSM Group of companies analyses, healthcare costs amount to 3.3–3.5% of gross domestic product (GDP) per capita [20, 8]. The cost of consolidated federal and regional budgets amounted to 1024 billion (35.9 per cent) in 2013, while the budgets of the federal insurance fund amounted to 1521 billion rubles (53.3%). The remaining 10.2% was "out-pocket payment". Of these funds about 309 billion rubles was spent on medicines procurement. Federally targeted programs include the national project "Health", vaccination, prevention, and treatment of AIDS, tuberculosis, cancer, psychiatry, diabetes, pediatrics, and orphan diseases program ("7 nozologies").

Regional budgets are utilized for regional target programs in addition to federal ones. Regional programs are not simply localized replications of the federal program. In fact, regional programs cover those aspects that are not covered by the federal ones. For example, if a patient has cancer then the federal oncology program will cover that. If the patient needs additional procedures or medicines (some more MRI tests, new and expensive target therapies, etc.) these expensive interventions will be covered by regional programs if there is one in place, or by the patient in the case these funded programs do not exist.

Corporations and other private agencies finance their hospitals and procure drugs at their own cost in accordance with their needs.

13.6.1 Pharmacoeconomics, Medicines Pricing, and Access

13.6.1.1 Market Access: The Registration Process

All new medicines, including generics, combination medicines, new forms, and doses of medicines should be registered with the Federal Ministry of Health. There are stated time limits for approvals within the registrations process, which is expected to be no longer than 210 working days. Data from clinical research conducted in Russia are now a compulsory requirement for registration within the Federation. The exception to this rule is whereby data is available from a multicenter study where there was a Russian study center within an international program. Expertise to assess the registration portfolios is found within the expert center under the Roszdravnadzor. There is a fixed tax fee for the registration process to be paid to the appropriate agency [16].

13.6.1.2 The Pricing Process in Russia

The power of price setting for medicines paid "out of pocket" by the consumer is held by the manufacturer and typically the price depends on the market situation. The wholesale and pharmacy remuneration for these medicines is linear and they vary by region with the largest variance with prices being higher in the remote Northern part of Russia; for example, in the Yamal region where other consumer goods are also more expensive than in urban Russia [20].

Medicines are divided into two groups in the Russian Federation: locally manufactured (the price depends on prices for this drug in the country before inclusion into the EDL) and those drugs manufactured abroad [21, 22]. For drugs manufactured abroad, the price can be established based on the prices overseas. The price regulation is applied to medicines from the List of Vital and Essential Medicines (there are multiple names for this list and it is also called EDL). The upper price margin for EDL drugs on this list is fixed and this is based on referral pricing of the 21-country basket. This is in the context of this drug having been marketed abroad before. For locally manufactured medicines or those that had not been marketed abroad before, the procedure is based on the actual price of a medicinal product for a certain period of time and the actual production costs of drugs from the EDL.

The executive authority of the Russian Federation also fixes medicines prices to maximum wholesale and retail levels and also set a ceiling on profit margins. Thus, the pricing process is transparent and monitored at both federal and regional levels. The use of this method of regulation of prices for medicines in the Russian Federation prevented the uncontrolled growth of prices during the global financial crisis of 2008.

Final prices for medicines are stipulated and determined during the tendering process. Remuneration for the medicines from the List of Vital and Essential Medicines is available for those that have market authorization and for which the price was registered.

The level of value-added tax (VAT) for medicines in the Russian Federation is approximately 18%. The exception to the VAT is for medicines, which are manufactured in a pharmacy and some medical devices, such as bandages, devices for disabled patients, and so on.

13.6.1.3 The Reimbursement Process

There is a formal requirement for Health Economic Assessment (HEA) for the inclusion of medicines in the EDL. The decision to include a medicine is made on the basis of a dossier and a formal questionnaire, in which product features are valued by the number of points. Since 2014, there has been a requirement in the questionnaire to provide results of analyses of "cost-effectiveness". This allows the addition or subtraction of 1 point from the integral evaluation of the product. For comparison, the criterion of "cost reduction" allows the addition or subtraction from

1 to 9 points depending on the size of the effect. The final decision to include a medicine in the reimbursement list is made by the Cross-disciplinary Commission. Composition of the Cross-disciplinary Commission is constituted and approved by the order of the Ministry of Health. It formulates a potential list of drugs, which becomes the actual final list after approval by the government. This list is valid for a period of 1 year until the next revision is undertaken in the same manner. There are more than 600 medicines (international nonpatent names) in the Russian List of Vital and Essential medicines, but there are only half of the listed medicines available in most regions.

The inclusion of drugs in EDL makes possible further inclusion in the programs of budgetary financing, but it also means that there is a restriction on the price.

It is fair to assume that most readers may not have heard about a medicine reimbursement process. It may not be in common with other countries, but there is a list of the State Programs that allow patients to receive medicines for free. In other words, the reimbursement level is 100% for state-budgeted programs. The federal list includes seven most expensive diseases to treat, which include hemophilia, organ transplantation, onco-hematology, tuberculosis, human immunodeficiency virus (HIV), and vaccines, as per the national immunization calendar.

Regional State Programs include oncology and 24 rare diseases such as pulmonary arterial hypertension and juvenile rheumatoid arthritis. Also there is 100% reimbursement for all medicines from the hospital's formularies for the inpatient sector. In the Russian Federation, there is also a form of subsidy through copayment: *50%* for some vulnerable groups (unemployed adults with disability of II and III groups) on the regional level and *13%* – for all employed citizens paying for their children or other direct relatives. EDL is the base for all lists mentioned above.

13.6.2 The Role of HTA in the Decision-Making Process

Now at the federal level, for inclusion in the Russian EDL, there is a formal requirement to provide the results of a cost-effective analysis as one of the elements of the Health Technology Assessment (HTA). HTA is conducted by independent experts or expert organizations, and it is a compulsory part of a dossier for inclusion in the EDL. Currently, there are no common standards and quality criteria for the procedure of conducting an HTA. In fact, there is no authorized HTA agency in Russia. Different participants in the healthcare market (doctors, HTA experts, decision makers and payers, patients) have different views on the issue. The creation of Federal HTA as an institution requires good relations with all parties involved in this process, as well as making it transparent. One of the main objectives, therefore, must be to develop good communication with all healthcare market participants. And this is indeed an important step to make HTA a reality.

13.6.3 The Perception of HTA by Health Care Market Participants

A survey of experts has been undertaken to assess the current perception of HTA by participants with different roles in the Russian healthcare market in 2015. The survey involved Russian experts in HTA, members of Regional Ministries of Health, representatives of industry (representing market access), specialists from medical schools and representatives of Patients' Advocacy Groups and State Insurance Funds.

Fifty-one surveys were returned from 78 (response rate = 65.39%) and nonrespondents were largely specialists from insurance funds and patient advocacy groups (see Table 13.1). The percentage of experts who gave an explanation of the term "HTA" according to the WHO definition was high in the group of HTA experts (83%), and industry representatives (foreign companies) (75%) and moderate for employees of Regional Ministries of Health and Healthcare Practitioners (both 60%). HTA is the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies. It is ideal that the HTA be conducted by interdisciplinary groups that use explicit analytical frameworks drawing on a variety of methods. The survey also indicated the necessity to implement HTA educational programs into medical schools and programs of continuing education for healthcare specialists. The responses provided by insurance funds and patient advocacy groups were expected due to their recent emergence in the Russian healthcare sector. High rates of engagement for industry representatives (foreign companies) can be explained by their participation in the process of data generation for the global value packs for their products.

The survey also indicated that the main decision maker on the inclusion of medicines within the EDL and budgeted healthcare programs (federal and regional) were the staff of the Ministries of Health (4.7–4.8 points of 5 max) along with the "Cross-disciplinary commission" (3.2–3.5 points of max 5). These two categories

Table 13.1 Percentage of completed surveys and answers compliant with the WHO term "HTA"

Role in the market	Compliant to WHO	Not compliant to WHO	Completed surveys (%)
HTA experts	83	17	100
Industry (market access)	75	25	100
Regional Ministries of Health	60	40	100
Healthcare Practitioners (GCPs)	60	40	60
The staff of the research institutes/ universities	18	82	100
Insurance funds	n/a	n/a	0[a]
Patients' advocacy groups	n/a	100	9

[a]Twenty-one sent out 0 returned

Table 13.2 Influence of various stakeholder groups on the budgeting of pharmaceuticals in the Russian Federation

Experts and institutions	EDL	Federal programs	Regional programs	Hospital lists
Federal Ministry of Health (FMoH)	4.8	4.8	1.8	2.0
FMoH external consultants ("Cross-disciplinary commission")	3.2	3.0	1.7	1.8
Regional Ministry of Health (RMoH)	1.4	1.0	4.7	3.2
RMoH external consultants ("Cross-disciplinary commission")	1.6	0.7	3.5	2.7
Industry	2.2	2.2	2.3	2.5
Universities (high medical schools)	1.7	1.5	1.3	1.4
HTA experts	1.9	1.5	1.4	1.3

were followed by the industry (2.2–2.5 from 5 max), in third place and experts on HTA (1.3–1.9 points). The least influential were the employees of medical schools who were indeed not involved in the decision-making process (1.4–1.7 out of 5 points max – see Table 13.2).

13.6.4 Multiple Levels of HTA Use

HTA should follow finance flows and decision making to distribute budgets effectively. The healthcare structure in Russia now includes several levels of decision making: federal, regional (in each region according to local conditions), hospital level (like HTA in Italy), and corporate level (something new but close to different HTAs in the United States). At the federal level, the decision should be related to EDL and federal healthcare programs. Moreover, there is a formal requirement for "cost-effectiveness" analyses for EDL inclusion. The next step is the regional HTA level for creation of regional programs. Below this is the hospital level.

HTA can be used to compile lists of medicines for federal and regional programs. It is difficult to use it for purchasing of drugs according to state budget purchasing [23]. Under this scenario, the INN must be used for tenders, with the exception of orphan drugs. In this case, the generic product would have price advantages and would probably be seen as more beneficial than the originator branded drug. This tendering process helps to decrease direct medical costs (expenses for drugs) but does not take into consideration "cost-effectiveness" or any other types of clinical-economic analyses. Only privately funded hospitals (or "commercial" departments of hospitals) can purchase medicines at their discretion and based on HTA data, because they are not government funded (i.e., they are not state budgeted). Based on this it is expected that private hospitals (or their "commercial" departments) will also be the first ones to implement HTA at the hospital level.

Opportunities for HTA implementation at the regional level are under consideration, but the need for the rational use of healthcare resources according to regional characteristics obviously exists.

13.6.5 Hospital Level

Currently, the possibility of using HTA at the hospital level is being discussed, but not to a great extent. Some medical institutions have the opportunity to use part of the funding for drug procurement in accordance with their own needs. Those hospitals which receive state budgets (federal, regional, or municipal) must follow tendering procedures in order to purchase drugs. As a result they will obtain medicines according to the INN (international nonproprietary name) at a minimal price. In the case when there is competition between brand name and generic drugs, it is most likely that the generic will be successful. This algorithm makes it possible to decrease expenditures and manage within budgets. On the other hand, it does not take into consideration parameters such as efficacy, efficiency, or cost-effectiveness. Only those medical institutions (private or corporate with independent (not state) funding), which do not receive non-state-budgeted funds (and thus they are not the subject of this legislation) can take these parameters into consideration and purchase drugs based on cost-effectiveness. Based on this, it is likely that private hospitals would be the first to implement HTA as soon as they have their own budgets and have flexibility to implement their version of rational use of medicines into their own practices.

13.6.6 Agency Level

Large corporations usually have individual employees with specific needs requiring healthcare and the assessment of medicines use. In the Russian Federation such organizations include medical services for the Russian Railways, civil aviation, and Ministry of Internal Affairs, among others. The number of employees in these agencies is large enough to sustain health programs and so these agencies have an opportunity to fund health programs relevant to occupational and professional activities of their employees.

The Federal Agency for Research Organizations (FANO) is responsible for the funding of subordinated research institutions, which are involved in the development of innovative medical technologies according to the federal program of pharmaceutical industry development [13, 24]. The focus is on developing technologies and the HTA methodology is used to assess the feasibility of developing drugs, devices, diagnostic methods, prevention and treatment as well as the evaluation of clinical and economic effectiveness of drugs in phase IV clinical under the direction of FANO. There is also a focus on venture assessment and development and FANO has budgetary discretion regarding which technological development is to be supported.

In 2015, an Expert Council for the assessment of new medicines, devices, diagnostic methods, prevention and treatment of the FANO was established. Expert and technical support expertise for this Council provides the “National Public Health Research Institute named after Semashko” [16]. The objectives are to develop

expertise to conduct health economic evaluations for medical technologies before and after market authorization, as well as market scanning and estimating effectiveness in future markets. The establishment of an institutional structure, which depends neither on industry nor on the Ministry of Health, creates the potential for its use as part of developing the HTA system in Russia.

13.6.7 Generic Medicines

The use of generic medicines in clinical practice provides an opportunity for effective drug supply to a wider Russian population at a lesser expense to the individual and/or to the State. The Russian Federation legislates and gives priority to generic drugs in competitive bidding. Another advantage of utilizing generic medicines is the constraint of participation in tenders by foreign companies, if the tenders involve at least two companies representing the countries of the Eurasian Union (which produce mainly generic drugs) [23, 25]. Empirical data on the ratio of the use of generics and originator branded medicines is not available in the Russian Federation.

13.7 Rational Medicines Use

Currently, a comprehensive system, which evaluates the rational use of medicines in Russia, is under establishment with different elements of the system being under the responsibility of various authorities. The following indicators are used for that purpose: clinical efficacy and safety including risk of appropriate use (GPs); reduction of expenses (payers); limiting the spread of antibiotic use including resistance and sensitivity (GPs). The meaning of rational use of medicines differs and varies by stakeholder group and this also presents challenges as funders having a focus on financial aspects and practitioners on clinical effectiveness.

13.7.1 Medicines Use in General

Medicines are provided free of charge for treatment received by individual patients in hospitals. In this case, the doctor prescribes the drugs that are available in a hospital pharmacy, procured in accordance with the federal and regional programs budget financing or formulary. There are clinical pharmacists working in the hospitals and they are making recommendations. More recently they have started to collect and assess other information available relating to economic effectiveness. At the same time, there is restriction in the clinical choices available to them based on the tendering system. Patients receive free medicines at the municipal stores in accordance with the Federal program of Additional Medicinal Maintenance (DLO).

Medicines are also available in municipal and private pharmacies, but in this case, patients have to reimburse the costs themselves and no clinical activity occurs through these medicines outlets.

13.7.2 Essential Medicines List, Selection of Essential Medicines, and Standard Treatment Guidelines

Currently, there are three main types of formal documents, which are approved by the Ministry of Health:

Only medicines from EDL can be included in federal and regional programs of drug supply. The upper limits rates are estimated for the medicines from EDL. It is the pricing policy in Russia.

- Standards of care (indicate the frequency of use of drugs for the treatment of diseases).
- Orders of providing medical aid (a list and sequence of actions of the physicians in the diagnosis and treatment of diseases).
- Clinical guidelines are only recommendations and are taken into account when creating the standards and orders of providing medical aid.

There is no one single association responsible for overseeing evidence-based medicine in the Russian Federation. In terms of clinical guidelines, the situation is the same as in many other countries. Guidelines are usually published on web pages of General Practitioner (GPs) associations [1, 9, 20, 26]. Sometimes international guidelines are used as it is, or adapted within the Russian context.

13.7.3 Prescribing Behavior and Factors Affecting Prescribing Behavior

Prescribing behavior has been widely discussed within professional associations and on internet forums in Russia. However, not many peer-reviewed publications on the matter are available. Review of forums and personal communications with Russian doctors indicates that their preferences significantly influence the list of prescribed medications that a patient may receive. In practice, many GPs prescribe those medicines which they use in daily practice. They also receive information from representatives of pharmaceutical companies but this information can be biased. Information from literature and scientific events is more reliable but considerable effort is needed to change the prescribing behavior of Russian doctors. It is thought that only a relatively small proportion of GPs actively look for information across a range of sources. The large majority of GPs accept information from the pharmaceutical industry through communication with medical representatives who are interested in their product being used as first line therapy. As such there is the

potential for representatives to be biased in the way that they present information about their products.

Patients may obtain information about drugs from internet forums and specialized web-sites or from patient advocacy groups.

Review of information available about prescribing behavior indicates that the activities of the pharmaceutical industry as well as perception of efficacy and safety criteria by GPs and patients can influence the market share that individual medicines have. This is anecdotal and a systematic approach needs to be taken in the Russian context to better understand this phenomenon.

13.7.4 Medicines Promotional Practices

In Russia, this includes medical conferences around specific themes, and interaction between company representatives and doctors. There is specialization among employees of pharmaceutical companies depending on their target population. As a general rule, GPs from outpatient departments of hospitals interact with the medical representatives, key opinion leaders communicate with the medical specialists of the pharmaceutical companies while decision makers with financial responsibilities are approached by market access staff. As outlined previously, the pharmaceutical industry can have considerable influence on what is selected to be prescribed from the approved list of pharmaceuticals. This is largely through the provision of information about their products and interactions between pharmaceutical company representatives and medical staff.

13.7.5 The Role of the Pharmacist in Russia

There are two main groups of specialists with different backgrounds and roles pertaining to medicines in the Russian healthcare system. The pharmacist is responsible for drug storage and distribution at any pharmacy or hospital. Routinely if they work at community pharmacies they advise their clients regarding medicines and they are also capable of performing such procedures as measuring blood pressure and blood glucose levels. At hospitals, pharmacists do not need to advise patients or perform clinical procedures but their focus lies not only with storage and distribution of medicines but also with their preparation (mainly infusion solutions).

Pharmacists are responsible for storage, preparation, and distribution of medicines in pharmacy (hospital, municipal, or private) and clinical consultations. In the case of "out-of-pocket" medicines, they can recommend the treatment. Self-treatment is still wide spread among Russian citizens, so the role of pharmacists for recommendation of nonprescription drugs is substantive. There is a list of medicines which cannot be sold in the pharmacy without a prescription including drugs used in psychiatry, opioid drugs, and some others.

Clinical pharmacologists advise physicians on the clinical efficacy and safety of drugs. These medical specialists have graduated from High Medical School with

appropriate specialization. Clinical pharmacologists are part of the representative team of the "Cross-disciplinary Commission" of Federal or Regional Ministry of Health and are responsible for the creation of reimbursement lists for medicines. Mostly these specialists are present in Federal Medical institutions or some hospitals in the larger cities such as Moscow and St. Petersburg

In the case of Moscow, which is divided into 12 regions, there is a position of a clinical pharmacologist in each region which suggests a lack of these professionals.

13.7.6 Pharmaceutical Care Interventions (PCI) and Assessment of Community Pharmacy Practice

Compliance with procedures that apply to the use of medicines and assessment of community pharmacy practice is conducted by Roszdravnadzor during regular and "for case" checks. Pharmaceutical care interventions (PCI) are not the main responsibility of pharmacies in the Russian Federation. The majority of such activities are being undertaken in medical institutions. Pharmacy staff can also perform some simple medical evaluations such as blood pressure readings or blood glucose tests. In the Russian Federation, these activities are not the main tasks of pharmacies and patients generally go to medical institutions for these purposes. The geographical network of outpatient polyclinics provides an opportunity to do this quite easily.

13.7.7 Medicines Use Research (Including Drug Utilization Evaluation [DUE] Research)

Formal accountability for the monitoring of compliance with procedures of disposal of drugs occurs and is the responsibility of the healthcare service. These are conducted regularly with "case for" verification. As previously described, optimal utilization of medicines is done through according to standards and procedures listed by Roszdravnadzor. At the same time, a number of hospitals (mainly large hospitals owned and sponsored by corporations) have "clinical pharmacists" responsible for advising GPs about the most effective use of medicines. It is also the case that sometimes a single clinical pharmacy specialist serves a number of medical institutions.

13.8 Conclusions: Summary and Way Forward

This chapter has outlined the current status of pharmaceutical policy and practice within the context of the Russian Federation. There has been significant change over recent years in Russia and this chapter highlights the progress that has been made. An effective system of assessment and use of medicines, which aims to reduce cost

and support local manufacturers, has been established in the Russian Federation. At the same time, there are limitations and areas to work on. The system does not take cost-effectiveness factors into consideration when selecting medicines due to the inability to increase the healthcare budget. Inclusion of new medications into federal and regional healthcare programs results in the need to withdraw or reduce the share of other medicines and other healthcare expenses as well (due to the joint healthcare programs budgets). Discrepancy between the fixed budget and cost-effectiveness models of HTA has probably caused delays in the creation of a comprehensive HTA system. Current elements of HTA exist in the format of legal requirements. For example, cost-effectiveness and budget impact data need to be presented in a submission dossier for EDL inclusion. There is also a dearth of information which evaluates the service provision within pharmacy and the optimal use of medicines through Drug Utilization Evaluation (DUE) research. As such medicines use evaluation is a significant area of future research in the Russian Federation.

The heterogeneous market of medical services in Russia and the complex levels of decision making require a multilevel HTA based system capable of providing expertise at the federal and regional levels and at the agencies, depending on funding and specific challenges. The important elements of HTA relevant to the market have not been assembled within the system, ensuring the satisfaction of these needs. There is a legislative requirement for "cost-effectiveness analyses" in the dossier for inclusion of drugs in Essential Drug List (EDL) but this requirement does not impact on the final decision. Health economic analyses are a part of the responsibilities of the expert Council at The Federal Agency for Research Organizations (FANO) along with horizon scanning and market access for locally developed innovative medicines. There are a number of other institutions which have not been involved in the health-economic arena before but can take part in those activities in the future. In the near future, we can expect the structuring of the HTA system as well as defining of formal structures responsible for clinical-economic analysis, assessment of the quality of this analysis, identification of needs, and development of an effective and transparent procedure of decision making.

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Chapter 14
Pharmaceutical Policy in South Africa

Fatima Suleman and Andy Gray

Abstract South Africa has implemented a number of important medicine policies in the post-apartheid era, informed by the 1996 National Drug Policy. Despite considerable resistance, firstly from the transnational pharmaceutical industry but later from a wider range of stakeholders, a number of legal reforms have been successfully implemented. In the public sector, medicine use is governed by standard treatment guidelines and essential medicines lists. However, these do not apply in the more fragmented private sector. Nonetheless, generic utilisation in the private health sector has increased over time. Maximum dispensing fees have also been introduced in the private sector but may need to be complemented by more sophisticated professional remuneration models that more effectively advance the responsible use of medicines. Greater use of pharmacoeconomics will help to inform rational selection and reimbursement policies, especially as the country moves towards universal health coverage in the form of National Health Insurance. The state tender system will also need to be reconsidered, as the separation between public and private healthcare financing and delivery becomes blurred. Major changes are in progress at the national medicines regulatory authority, which faces a considerable backlog in applications for marketing authorisation.

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14.1 Introduction

This chapter provides an overview of the pharmaceutical policy environment in South Africa, an upper-middle-income country located at the southern tip of Africa. South Africa provides a rather unique case study, not only as an example of a post-colonial health system, but because of the consequences for health and healthcare delivery of decades of racial segregation under the *apartheid*[1] regime. Since the country's transition to democracy in 1994, and the finalisation of a new Constitution in 1996 [1], there has been an almost continuous period of health policy reform. This has included the implementation of a National Drug Policy (NDP), published in 1996 [2]. Policy changes continue to be proposed and implemented, as the country progresses towards the implementation of universal health coverage (UHC). A 14-year process of implementing a system of National Health Insurance has been announced in the form of a policy White Paper [3]. Once implemented, National Health Insurance will not only fundamentally alter the way in which healthcare in South Africa is financed, but also how services, including pharmaceuticals, are provided.

14.2 The South African Health System

South Africa is a large (1219 100km^2), upper-middle-income country (gross national income PPP$12530 in 2013), with a population of approximately 55 million [4, 5]. In 2001, 57.5% of the population were already living in urban settings [6], and this had grown to 67.3% in 2011 [7]. In 2012, the total health expenditure was 8.3% of gross domestic product (GDP), of which government contributed 48.4% [8]. In the same year, government health expenditure was 14.0% of total government expenditure, just short of the 15% target set by the African Union in the Abuja Declaration of 2001 [9]. By 2011, only one African country had met this target [9]. The country has a deficit of health personnel, with 7.8 medical practitioners, 51.1 nurses and 4.1 pharmaceutical personnel per 10,000 population [8]. Although some health statistics are indicative of good coverage (e.g., 97% of pregnant women attend at least one antenatal visit), others are less satisfactory (only 66% of children have been vaccinated against measles at 1 year of age). A selection of key health indicators is provided in Table 14.1, as reported in the World Health Statistics 2015 [8]. These figures reflect not only the persistent sequelae of the neglect which characterised the colonial and *apartheid* years, but also the growing non-communicable disease

[1] 'Apartheid' is an Afrikaans term meaning 'separateness', which refers to the legislated system of racial segregation which was applied in South Africa between 1948 and 1994. However, racially inspired laws and practices were also applied before 1948 and were a prominent feature of the colonial era (1652–1961).

Table 14.1 Selected South African health statistics

Health statistic (unit; year of reporting)	Value
Life expectancy at birth (years; 2013)	Male: 57 Female: 64
Infant mortality rate (per 1000 live births; 2013)	32.8
Under-5 mortality rate (per 1000 live births; 2013)	43.9
Age-standardised mortality rate by cause (per 100,000 population; 2012)	Communicable disease: 612 Non-communicable disease: 71 Injury: 104
Maternal mortality rate (per 100,000 live births; 2013)	140
Prevalence of HIV (per 100,000 population; 2013)	11,888
Prevalence of tuberculosis (per 100,000 population; 2013)	715

Source: World Health Statistics 2015 [6]

burden which co-exists with a high communicable disease burden, in particular some of the highest prevalence of HIV and tuberculosis [10].

A consistent feature of South Africa's colonial era health system, as described by van Rensburg, was the repeated call for fundamental change, followed by small adjustments or changes [11]. At the core of the problem was the deeply rooted fragmentation of the health system, 'both within the public health sector and between the public and private sectors' [12]. Health services in the public sector in the apartheid era were provided separately to different ethnic groups: the majority black Africans, and the minority White, mixed race (so-called Coloured) and those descended from South Asian (Indian) immigrants. Such health facilities were funded differentially, with a higher per capita expenditure on those designated for the White minority. Prior to 1994, South Africa was divided into four provinces, the Cape Province, Orange Free State, Transvaal and Natal. Health services were divided between predominately curative services managed and provided by provincial authorities and preventive and promotive services managed and provided by the National Department of Health (called the National Department of Health and Population Development prior to 1994). A further division was the result of the creation of a series of tribal '*bantustans'* (also referred to as 'homelands') for black African ethnic groups. By 1994, the supposedly independent *bantustans* of the Transkei, Bophuthatswana, Venda and Ciskei operated their own Departments of Health. The situation varied in the remaining *bantustans*, with various services separated from or integrated with those offered by the surrounding provinces. The net result was that '[b]y the end of the apartheid era, there were 14 separate health departments in South Africa, health services were focused on the hospital sector, and primary level services were underdeveloped' [11].

The challenges facing the South African health system were described by Chopra et al. as due to the country having 'undergone a protracted and polarised health transition, which is shown by the persistence of infectious diseases, high maternal and child mortality, and the rise of non-communicable diseases' [13]. Chopra et al. also emphasised that 'South Africa has been substantially shaped by its colonial and apartheid past that divided society by race, class, and sex'.

Since 1994, the fragmentation of the public sector has been addressed through the creation of a unitary health system, constructed as spheres of government (national, provincial, local) in accordance with the Constitution [1]. The basic orientation of the post-apartheid health system was outlined in the White Paper on the Transformation of the Health System in South Africa in 1997 [14]. The White Paper stated: 'We have set ourselves the task of developing a unified health system capable of delivering quality health care to all our citizens efficiently and in a caring environment'. The White Paper outlined the concept of Primary Health Care, delivered through a District Health System. In accordance with South Africa's quasi-federal system, health is the responsibility of the National Department of Health (NDOH), nine provincial Departments of Health co-ordinated through a National Health Council, as well as local authorities. The relationship between the three spheres of government (national, provincial and local) is defined in the Constitution and, specifically, in the National Health Act [15]. In parallel, a large and well-resourced private sector provides healthcare services predominantly to approximately 8.8 million beneficiaries of medical schemes (private health insurance) [16].

In December 2014, there were 87 medical schemes registered in South Africa. In total, medical schemes paid out ZAR[2]124.1 billion in2014, which equaled an average spend per beneficiary per year of ZAR14 185.50. In contrast, the total public sector health expenditure in the 2013/14 fiscal year was ZAR153.703 billion, with an average per capita public sector health spend of ZAR3011 [17]. However, this arrangement will be altered with the introduction of National Health Insurance, a centralised health-financing scheme and the introduction of a purchaser-provider split (which refers to the separation of the components that are responsible for the purchasing of health services from those responsible for the provision of health services) [3]. The National Health Insurance system will therefore pool financial resources but is also expected to make greater use of accredited public and private providers to meet the healthcare needs of the majority of the population. This division between the purchaser's role and the provider's is markedly different from the current situation, where the funding provided from the Treasury is mostly used within the public sector, whereas funding provided through private insurance (by medical scheme members and their employers) is largely used in the private sector.

14.3 South Africa's Pharmaceutical Situation

Fragmentation was a prominent feature of the pharmaceutical supply system in the *apartheid* era. In the public sector, the selection of medicines was decided separately by each of the provincial Departments of Health, predominantly for curative services. However, for preventive and promotive services, selection was done by the

[2] In December 2015, ZAR 16 was equivalent to approximately US$1.

National Department of Health and Population Development. Each of the *bantustans* operated its own medicines selection process. Overall, these selection processes were weak and reflected the biases of individual prescribers and academics. The procurement lists were thus illogical, duplicative and inefficient. Each of the four pre-democracy provinces operated at least one pharmaceutical depot (central stores), with the Cape Province maintaining two such facilities. From the end of World War II until 1988, medicines for the National Department of Health and Population Development and the *bantustans* were procured by the Medical Base Depot operated by the South African Defence Force. Currently, all public sector medicines are procured in terms of a national competitive bid (tender) and delivered either to provincial stores in the nine provinces or directly to public health facilities. A National Essential Medicines List (NEML), which is derived from detailed, evidence-based Standard Treatment Guidelines (STGs), informs all public sector procurement [18].

14.3.1 Infrastructure and Human Resources

South Africa has a large and highly developed private pharmaceutical manufacturing system. Although local production is almost entirely dependent on imported active pharmaceutical ingredients (APIs), all steps of the pharmaceutical value chain are represented. This includes limited local production of (APIs), extensive facilities for producing finished pharmaceutical products (FPPs) and a highly developed distribution and wholesaling sector. As of August 2014, the South African Medicines Control Council (MCC) had licensed 266 entities as manufacturers, importers and/or exporters of medicines, secondary packers or testing laboratories (or in at least one of these categories) [19]. Of these, 78 entities were listed as manufacturers of medicines, meaning that some element of local production was involved. The list included locally registered subsidiaries or offices of both transnational pharmaceutical concerns and international generic pharmaceutical manufacturers.

As of August 2014, the MCC listed 186 pharmaceutical wholesalers and one pharmaceutical bond store (a building or other secured area in which pharmaceutical goods may be stored, manipulated or undergo manufacturing processes without payment of duty) [19].

As of December 2015, the South African Pharmacy Council website states 3095 private sector community pharmacies, 647 public sector institutional (hospital and community health centre) pharmacies and 276 private sector institutional (mostly hospital) pharmacies [20].

Of 13,479 pharmacists on the Pharmacy Council register in 2015, 4655 (34.5) were based in the Gauteng province, where only 24.0% of the population lived [21]. Only 4970 pharmacists (36.9% of those on the register) were employed in the public sector, which caters for more than 80% of the population. However, this had increased from 1853 in 2008 (then 15.6% of registered pharmacists).

14.3.2 Pharmaceutical Market in South Africa

The South African pharmaceuticals market was worth ZAR30 billion in 2011 [22]. Although the public sector accounted for 75% of volume, this constituted only 35% of the market by value. Accordingly, the private market was estimated to account for 25% of the volume but 65% of the market by value.

Generic penetration was expected to be far higher in the public sector but has not been measured in any systematic way. Citing data from IMS Health, generic medicines were estimated to account for about 65% of all items dispensed in the private sector and 40% of expenditure [23]. Data on generic utilisation in the private sector is only reported publicly by Mediscor, a pharmaceutical benefit management organisation, which provides services to medical schemes with a total of about 1 million beneficiaries. In 2015, Mediscor reported that generic medicines accounted for 56.2% of items claimed on behalf of these beneficiaries [24]. Mediscor is serving a number of medical schemes with over a million beneficiaries, also reported that in 76.5% of instances where a generic equivalent was available, the generic was actually dispensed.

The World Health Statistics 2015 reported that out-of-pocket expenditure accounted for 13.8% of private sector expenditure on health in 2012 in South Africa [8]. Some of this expenditure is due to public sector–dependent (uninsured) persons, accessing health care, including medicines, in the private sector. In 2011, the over-the-counter (OTC) products market in South Africa was worth ZAR10.3 billion, with the majority of sales by value (65%) being made in community pharmacies [20].

Imports of finished pharmaceutical products increased from ZAR8.25 billion in 2007 to ZAR17.5 billion in 2013 [25]. In the same year, South Africa exported pharmaceuticals worth ZAR1274 million. In terms of the global pharmaceutical market, South Africa contributed just 0.4% of this market by value and less than 1% by volume at global level [23]. Imports of innovator and branded products are mainly from Europe and the USA. India topped the list of countries from which finished pharmaceutical products, mostly generics, were imported. South African medicines are exported to other African countries, but also to the USA, Australia and France. Within Africa, the major export markets are Kenya, Zambia and Zimbabwe [23].

14.3.3 The Policy Environment: The National Drug Policy 1996

One of the earliest post-apartheid health policy instruments issued by the first democratic government in South Africa was the National Drug Policy, issued in 1996 [2] and then appended to the White Paper on the Transformation of the Health System in South Africa in 1997 [3]. Implementation of the national medicines policy was

assisted by the creation of an externally funded South African Drug Action Programme (SADAP), within the National Department of Health [26].

The objectives of the NDP 1996 were expressed in three broad groups. The policy set the following health objectives: to ensure the availability and accessibility of essential drugs to all citizens; to ensure the safety, efficacy and quality of drugs and to ensure good dispensing and prescribing practices. To promote the rational use of drugs by prescribers, dispensers and patients through provision of the necessary training, education and information and to promote the concept of individual responsibility for health, preventive care and informed decision making were some other objectives. The economic objectives were to lower the cost of drugs in both the private and public sectors; to promote the cost-effective and rational use of drugs and to establish a complementary partnership between Government bodies and private providers in the pharmaceutical sector. In addition, a number of national development objectives were also set. These were to improve the knowledge, efficiency and management skills of pharmaceutical personnel; to re-orientate medical, paramedical and pharmaceutical education towards the principles underlying the National Drug Policy and also to support the development of the local pharmaceutical industry and the local production of essential drugs. Another national development objective was to promote the acquisition, documentation and sharing of knowledge and experience through the establishment of advisory groups in rational drug use, pharmacoeconomics and other areas of the pharmaceutical sector.

Although the NDP 1996 has been instrumental in guiding a number of important reforms in the pharmaceutical sector, the policy document has not been revised since 1996. Areas in which the policy was somewhat vague, such as in relation to medicine pricing, have evolved considerably but without a clear policy prescription. Other areas, such as the measures to stimulate local production, have never been well developed or implemented as part of health policy. The pro-generic stance and the commitment to an essential medicines approach have been more successfully implemented, although monitoring and evaluation of their impact has been weak. In particular, the extent to which rational medicines use interventions have been successful has received less attention than might have been desired.

14.4 The South African Medicines Regulatory Environment

All medicines sold in South Africa have to be registered by the Medicines Control Council (MCC), a statutory medicines regulatory authority created by an Act of Parliament [27]. The MCC consists of 23 ministerially appointed members. The Council is supported by a series of nine expert committees, with a total of 146 members (including members of Council) [28]. In addition to the enabling Act, the operations of the MCC are governed by extensive regulations issued by the Minister of Health and by a detailed set of guidelines. The secretariat of the MCC is currently located within the National Department of Health. The MCC is required to only consider issues of quality, efficacy and safety, and there is no linkage between

patent status and regulatory approval. The MCC is in the process of transitioning to a new structure, the South African Health Products Regulatory Authority. Under the new system, which will be co-funded from increased user fees, decision making will be done by the staff of the Authority, rather than the appointed members of the Council. The number of technically qualified staff is therefore expected to rise considerably, even though access to advice from external expert committees will still be possible. The legislation to give effect to these changes was passed by Parliament in late 2015 but has yet to be brought into effect [29].

Although accurate and updated data are difficult to access, it is known that there are considerable delays in the regulatory approval of medicines in South Africa. Delays ranging from 18 months to 3 years have been reported, affecting both new chemical entities and generic applications [23]. Although provision is made for an expedited approval process, it is unclear whether this has resulted in any faster approvals. The uncritical application of this procedure to all medicines that appear on the Essential Medicines List, regardless of how many equivalents are already registered, has been blamed by Leng et al. for exacerbating the backlog of applications at the MCC [30]. Leng et al. cited reports of a back-log of more than 3000 applications in 2010. They also provided data showing that, between 2007 and 2012, the MCC issued 149 marketing authorisations for new chemical entities, 18 for biological medicines, 2626 for generic medicines (of which 513 were 'multiples', where two or more dossiers for the same product were submitted, under different proprietary names). In this period, 14 new chemical entities and 158 generic medicines were registered via the expedited approval process. Critically, there is no publicly accessible register of medicines, showing all products for which a marketing authorisation has been issued by the MCC. It is also not possible to determine the basis for registration of generic medicines. A new Electronic Data Management System (EDMS) is under development but has yet to be fully implemented. Use of the electronic Common Technical Document (eCTD) format for dossier submissions is also being piloted.

Nonetheless, South Africa's medicines regulatory system is considered to be of adequate quality, as shown by its membership of the Pharmaceutical Inspection Co-operation Scheme (PIC/S), of which the South African Registrar of Medicines is the current chairperson [31]. As the PIC/S web site explains: 'Before a regulatory authority can become a member of the PIC Scheme, a detailed assessment is undertaken to determine whether the authority has the arrangements and competence necessary to apply an inspection system comparable to that of current PIC/S members. This assessment involves an examination of the authority's inspection and licensing system, quality system, legislative requirements, inspector training, etc., and is followed by a visit by a PIC/S delegation to observe inspectors carrying out actual GMP inspections.'

The MCC does not operate its own quality control laboratories but out-sources such services to the WHO-accredited Centre for Quality Assurance of Medicines (CENQAM), located at the North-West University [32]. The Centre is also a designated as the WHO Collaborating Centre for the Quality Assurance of Medicines. No data are available on the extent to which substandard, spurious, falsely labelled,

falsified and counterfeit (SSFFC) medical products have been detected or reported in South Africa.

14.4.1 Pharmacovigilance in South Africa

The Medicines Control Council's obligations in terms of pharmacovigilance are delegated to the National Adverse Drug Event Monitoring Centre (NADEMC), located at the University of Cape Town [33]. This Centre is responsible for collating data on adverse drug event reports and performing assessments of causality. The Centre provides inputs to the Pharmacovigilance Expert Committee of the MCC and also submits reports to the Uppsala Monitoring Centre (UMC), for inclusion in VigiBase®, the global database of Individual Case Safety Reports (ICSRs). The NADEMC has recently implemented VigiFlow™, a web-based management system for ICSRs. The level of reporting has been low but has increased more recently, as emphasis has been placed on reporting antiretroviral-related adverse events in the public sector [34]. The authors cited data from UMC that showed an increase from 2902 reports in 2010 (58/million population) to 4088 (77/million population) in 2011. The authors also noted that '[t]here were other institutions following up on signals from spontaneous ADRs but they are working independently and information is not being fed into the national system. Other parallel systems exist for public health programs and NGOs but data are not being fed centrally' [34]. Obligatory reporting of adverse events brought to the notice of the holders of marketing authorisations (manufacturers and importers) is in place. However, if providers also report directly to the NADEMC, this may result in duplication of efforts [35].

14.5 Medicines Supply System

The current medicines supply system, in both the public and private sectors in South Africa, is described, together with some explanation of its history and the impact of the NDP 1996 [2].

14.5.1 Medicine Selection

As described earlier, the selection of medicines for the public sector was highly fragmented during the *apartheid* era. As can be expected from a system that was largely dependent on expert opinion, the list of medicines procured in the various national, provincial and *Bantustan* departments of health increased over time. By 1994, a total of about 2600 medicines were being procured in the public sector [36]. The list included a large number of medicines from the same

pharmacological classes, reflecting the personal preferences of those responsible for selection, rather than a deliberate choice between interchangeable options. Attention to rational medicines selection was therefore a key component of the NDP 1996. The creation of the first National Essential Drugs List Committee (later renamed as the National Essential Medicines List Committee or NEMLC) actually preceded the publication of the national medicines policy. By 1998, a far more restricted list of 337 medicines (in 422 dosage forms) had been compiled, which compared well with the WHO Model List Essential Medicines. In 1999, the WHO Model List contained 307 items, in 547 dosage forms. The NEDLC was among the first such national structures to approach the development of a national list through the process of developing comprehensive standard treatment guidelines [37]. Since the initial Primary Health Care (PHC) volume published in 1996, further ten editions have been published; three for PHC (2003, 2008, 2014), four for Adult Hospital care (1998, 2006, 2012, 2015) and three for Paediatric Hospital care (1998, 2006, 2013) [18]. A further volume for Paediatric Hospital care is in process, and the revision of the PHC volumes has been initiated, with calls for nominations for the responsible Expert Review Committees. In addition, there is an ongoing process of selection of medicines for use at the tertiary/quaternary or academic level health facilities, although this is not accompanied by treatment guidelines [38]. Between 1996 and 2008, the number of medicines for PHC increased from 156 to 198, while the number of medicines in the standard treatment guidelines for adult hospital care decreased from 372 to 366 [39].

The situation in the private sector is very different, and still reflects the significant fragmentation in that sector. Each medical scheme is responsible for its own selection of medicines and, while it may lean on the selection made in the public sector, it is under no obligations to do so. The prevailing legislation in this sector makes provision for the practice of managed health care. Regulations therefore allow medical schemes to use a formulary or restricted list of medicines, provided that it is evidence-based and explicit. In addition, where a medicine on that list is shown to be ineffective or could result in an adverse reaction in a beneficiary, access to an alternative has to be provided, without penalty [40]. Medical schemes are regulated by the Council of Medical Schemes to whom complaints can be submitted by scheme members. A major change in policy, signaled in the NDP 1996, but not brought into effect until 2003, is the mandatory offer of generic substitution. This enabled private sector medical schemes to strengthen pro-generic policies, using co-payments for instance, which had been in effect for some years [41]. Medical schemes are required to provide funding for a basic minimum package of care known as the Prescribed Minimum Benefits, which includes certain emergency conditions, treatment of approximately 270 Diagnostic and Treatment Paired (DTP) conditions as well as medicines specified in the minimum treatment algorithms for a range of 25 chronic conditions [42]. However, these algorithms have rarely been updated. The private health care sector in South Africa faces considerable challenges, including an ageing insured population and the high cost of healthcare [16, 43].

14.5.2 Medicines Procurement and Distribution

Currently the process of medicines procurement and distribution in the public sector is highly dependent on the ten central medical stores, located in each of the provinces (with the Eastern Cape province operating two such stores). Increasingly, provinces are arranging for direct delivery of medicines from manufacturers to health facilities, by passing the depot. While this means less work for the depots, which have limited capacity, it does require effective supply chain management practice at the facility level. While larger public sector hospital pharmacies may have the necessary physical and personnel capacity, the same is less likely to be true of smaller facilities. The centralised limited competitive bid (tender) system has been in place since 1985 and has been considerably strengthened by the efforts of the NEMLC. However, accurate quantification of demand remains a challenge, with poor quality and non-interoperable information systems complicating the use of prior consumption data and preventing greater use of morbidity-based estimates. Nonetheless, the use of indicative prices, based on global data, has been credited with considerable savings. South Africa is able to use the monopsony power of the public health sector to achieve very advantageous prices, especially for antiretrovirals [44].

In the private sector, medicine supply from manufactures to end dispensers is done by wholesalers or distributors. Medicine supply to the public is through community and private hospital pharmacies with a large number of prescribers also licensed to dispense medicines to their own patients. Although the NDP 1996 signalled an intention to restrict dispensing by prescribers, this has proven difficult to implement and has been successfully challenged in court and progressively weakened over time [45].

14.6 Medicines Financing and Pricing

Although accurate figures on the per capita expenditure on medicines are difficult to obtain, an indication of the very different scale of health care financing in the public and private sectors in South Africa can be obtained from the overall per capita expenditure. In 2014, per capita spending on health in the public sector was ZAR3183 and in the private sector, excluding out-of-pocket expenditure, it was ZAR14 186 [46]. The public sector is largely funded from the Treasury and caters to the needs of the uninsured. The private sector is funded largely from insurance premiums (paid by individuals and employers) but also from out-of-pocket payments. It caters mostly, but not exclusively, to the needs of the members of registered medical schemes.

Since the MCC does not make available a publicly accessible medicines register, it is difficult to provide accurate data on the growth of the generic medicines market since 2003, when a mandatory offer of generic substitution was implemented.

However, it appears from the data presented by Leng et al. that the vast majority of new products registered by the MCC are generic medicines and not new chemical entities [30]. These authors also pointed out that many registered medicines are not being actively marketed. Generic substitution, together with the wide application of internal reference pricing mechanisms, have resulted in increasing generic utilisation. Only one pharmaceutical benefit manager (Mediscor) has regularly reported on the degree to which generic medicines are being dispensed [24]. This degree of generic penetration can be compared with global figures reported by IMS Health in 2015 [47]. In value terms, the contribution of generic medicines reported by Mediscor broadly matches that projected by IMS Health for the global market but is considerably projected lower than typical emerging markets. This is perhaps an indication that the South African private sector market more closely resembles developed country markets, but it also points to the potential for considerable shifts in utilisation patterns under the proposed National Health Insurance [3].

14.6.1 Medicines Pricing

Informed by the NDP 1996, the 1997 amendment to the Medicines and Related Substances Amendment Act created the Pricing Committee as an advisory body to the Minister of Health [48]. The subsequent reforms have included far-reaching changes to the medicines pricing system, including the introduction in 2005 of a single exit price (SEP) for all prescription medicines, in the form of a fixed ex-factory price with a logistics fee component (and value added tax) for medicines sold to all purchasers other than the State. This is complemented with a provision for a regulated maximum increase in the single exit price, determined annually by the Minister of Health, on the advice of the Pricing Committee [48].

The annual maximum increases since the intervention was first launched in 2005 have varied from a minimum of 0% in 2011 to a maximum of 13.2% in 2009. The most recent increase for 2016 was set at 4.8% [49]. In order to ban offering discounts on the single exit price effective, a ban has also been imposed on the supply of free samples of medicines. No additional mark-ups for logistics services can be charged to pharmacies, hospitals or dispensing practitioners, and wholesalers and distributors are reimbursed from the single exit price. The law has also been used to regulate the maximum dispensing fee charged by pharmacists and licensed dispensing practitioners and to provide for annual reviews of these fees as well.

A number of elements of the pricing system are still evolving. The logistics fee is presently not disclosed by manufacturers and the extent of the logistics fee is not regulated in any way [50]. Proposals in that regard have been made, but as yet not implemented. The ban on off-invoice bonuses, rebates and various other marketing incentives has been difficult to enforce, and a draft set of definitions of such practices in regulations has been published for comment, but not yet finalised [51]. Since 2013, although guidelines for the submission of pharmacoeconomic evaluations of new medicines, justifying their initial single exit prices, have been available,

such submissions have remained voluntary [52]. The planned introduction of external reference pricing referred to locally as international benchmarking has also not been finalised [53]. The initial basket of comparator countries includes Australia, Canada, New Zealand and Spain.

Before the pricing interventions came into effect, A WHO/HAI pricing survey of medicines in public and private sector facilities in Gauteng Province revealed that proprietary brand products sold in private sector pharmacies and private hospitals were 25–26 times more expensive than the median price quoted by the International Drug Price Indicator Guide produced by Management Sciences for Health [54]. These median prices are called international reference prices (IRPs). The lowest priced generics in the private sector were about 6.5 times more expensive than the IRP. Based on the prices quoted in tender documents, the public sector was shown to have paid on average 1.6 times the median international price.

Some indication of the impact of the medicine pricing policies over time can be indirectly assessed in terms of the contribution of the cost of medicines to total medical scheme expenditures as reported in the annual reports of the Council for Medical Schemes [16]. In contrast to the increases in expenditure on private hospitals and medical specialists, expenditures on all other health professionals (general practitioners, dental specialists, dentists and other supplementary and allied health professionals) and providers (such as provincial hospitals) have remained relatively constant. Expenditures on medicines declined after 2003 reaching a low in 2005, after adjustment for inflation [16]. This could be related to the introduction of mandatory offer of generic substitution in 2003 and the introduction of SEP in 2005. However, by 2009, expenditures in constant Rands had rebounded to the same level as 2001 and have continued to increase [16]. The largest of the medical scheme administrators has estimated that the introduction of the single exit price mechanism resulted in an approximately 22% reduction in medicine prices and saved the scheme about ZAR319 million per year in medicine expenditure since 2004 [55].

14.7 Medicines Use

Standard treatment guidelines and essential medicines lists should also guide the rational use of medicines. However, evidence on the extent to which rational medicines use has improved as proposed by the NDP 1996 is scant. The provinces conducted baseline surveys in 1998, in relation to medicines use in public sector primary care facilities, and then a national survey was conducted in 2003, using the WHO/INRUD indicator approach [56]. The mean number of items per prescription decreased from 2.5 in 1998 to 2.2 in 2003, and the percentage of medicines prescribed from the EML increased from 65% to 90%. A positive change in the percentage of encounters in which an injection was prescribed was also detected, with a decrease from 11 to 5% (implying more rational use of injections and safe medicine use). The appropriate PHC EML/STG was available in 97% of facilities in 2003, compared with only 59% in 1998. However, the percentage of encounters in

which an antibiotic was prescribed increased from 36% to 47% between the same two time periods. On a smaller scale, a cross-sectional study of 100 prescriptions for hypertension in each of 21 health facilities in the eThekwini district in 2007 showed that the mean compliance with the guidelines was only 22% [57]. The low mean compliance with standard treatment guidelines was mainly due to the absence of a diagnosis recorded on the prescription and the widespread use of poly-pharmacy.

South Africa lacks a clear monitoring and evaluation system that is able to track what medicines are available and how these are being used across the country, even in the public sector. Based on telephone interviews with staff of 2463 public sector facilities, the Stop Stockouts report showed that 25% of facilities had experienced a stock-out of HIV or tuberculosis medicines in the 3 months prior to the survey in 2015 [58]. South Africa has also experienced shortages of medicines due to manufacturers' failures to meet demand or decisions to withdraw products from the market [59, 60].

Comprehensive data on medicines use in the private sector is even more scant, though some indications are provided in the annual Mediscor Medicines Review [24]. Medicines utilisation studies have also been conducted using the claims data from various medical schemes [61–63]. Recently, a network of medicines utilisation researchers in Africa has been created, to which South African researchers are contributing [64]. Also, in March 2009, the South African Pharmacy Council made a submission to the National Department of Health's ministerial task team. In this proposal, the SAPC outlined three categories of specialist pharmacists: clinical pharmacists, public health pharmacists and industrial pharmacists [65]. In the clinical pharmacist category, a number of sub-specialities were identified: oncology, pharmacokinetics, paediatrics, radiopharmacy, veterinary pharmacy and antiretroviral therapy. Details of the educational path to registration have been published for comment but not finalised as yet [66]. Some academics argue for a more flexible approach to demonstrate the development of competencies rather than a single route to registration [59].

14.8 Conclusions: Summary and Way Forward

As is the case with many developing countries that are embarking on the realisation of universal health coverage (UHC), South Africa is having to contend with the consequences of many decades of fragmentation in relation to health. At present, healthcare services, including pharmaceutical services, are provided separately by an over-burdened public sector catering for the majority of the population and, by an increasingly unaffordable but lavishly resourced private sector, catering for the insured minority. A variety of pharmaceutical policy interventions have been implemented since South Africa's democratic transition in 1994, as informed by the National Drug Policy (NDP) issued in 1996. However, it is felt that the policy document is inadequate to deal with the demands of the proposed National Health Insurance system.

Pricing policies will also have to be reviewed based on the fluctuations in South African currency, which could impact on the supply of essential medicines. The regulated maximum single exit price increases need to consider exceptional circumstances that may arise as the result of extreme currency fluctuations within a given calendar year. In addition, the publication of the White Paper on National Health Insurance in South Africa has presented scenarios where private sector resources could be tapped to deliver health care services under the NHI umbrella. There is a potential future role for wholesalers and distributors to exist under NHI by directly supplying medicines to health care facilities. This will markedly reduce the role of the current Medicine Depot model used by the provinces. It is also important to ensure that a supply chain is sustained in the private sector as only then can such systems be in a position to contribute under NHI.

A revised national medicines policy, which confronts the demands of a purchaser-provider split and a completely reformed health financing system are needed to guide pharmaceutical practice in the future. Such a policy will need to build on the gains achieved, in particular with regard to the selection of essential medicines, the promotion of generic utilisation and the various medicines pricing interventions. However, it will also need to focus far greater attention on the question of the responsible use of medicines.

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Part III
High Income Countries

Chapter 15
Pharmaceutical Policy in Poland

Irmina Wlodarczyk and Shane L. Scahill

Abstract The Polish healthcare system has undergone a number of changes in recent years related to the reimbursement of pharmaceuticals. The public healthcare system is primarily supported through government-funded public health insurance. The reimbursement system in Poland is one of the most restrictive systems in Europe. In addition, as a member of the European Union (EU), Polish legislation must frequently adapt to the changing requirements within this environment. The pharmaceutical market in Poland has been steadily growing over the last two decades. Pharmaceutical companies are important players in the national economy and are valuable employers that contribute significantly to the economy. As a nation, Poland is also known throughout the pharmaceutical industry as a country with sound outsourcing potential, there being interest from numerous multinational pharmaceutical companies. One of the most important characteristics of the pharmaceutical market in Poland is the high market share enjoyed by generic medicines, as well as the growing popularity in use of over the counter (OTC) medicines. Over recent years, there has been an increase in the number of pharmacies and a corresponding increase in the average patient's expenditure on medicines and dietary supplements. In line with this positive growth, Poland has had to struggle with a number of obstacles associated with pharmaceutical use, including the illegal export of cheap drugs from Poland and an undersupply of physicians that can prescribe these agents. There are also several major health reforms on the horizon that are likely to significantly change the landscape of the pharmaceutical sector in Poland.

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Abbreviations

AHTAPol	The Agency for Health Technology Assessment in Poland
CVS	Cardiovascular
EMA	European Medicines Agency
EU	European Union
GDP	Gross Domestic Product
GIF	Main Pharmaceutical Inspectorate (*Główny Inspektorat Farmaceutyczny*)
GP	Gross Profit
INN	International Nonproprietary Names
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MoH	Ministry of Health
MS	Member State
NFZ	National Health Fund (*Narodowy Fundusz Zdrowia*)
OECD	Organisation for Economic Co-operation and Development
OTC	Over the Counter
PF	Pharmaceutical Law (*Prawo Farmaceutyczne*)
PPA	Polish Public Procurement Act
R&D	Research and Development
RA	Reimbursement Act
URPLWMiPB	Office for Registration of Medicinal Products Medical Devices and Biocidal Products (*Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych I Produktów Biobójczych*)
WHO	World Health Organization
WIF	Voivodeship Pharmaceutical Inspectorates (*Wojewódzkie Inspektoraty Farmaceutyczne*)

15.1 Health System of the Country

15.1.1 Health System in Poland

The healthcare system in Poland went through a degree of transformation in 2003 with the introduction of public insurance and the National Health Fund (*Narodowy Fundusz Zdrowia*, NFZ). The NFZ is currently the executor of the public health insurance scheme and its main principles are social solidarity (the amount of health insurance premium contributed does not affect quantity, quality, and types of services received), equal treatment of citizens, as well as the free choice of healthcare service providers [1, 2]. The Ministry of Health (MoH) and NFZ are committed to fund the provision of healthcare services through government funding [3]. In brief,

public expenditure on healthcare (pharmaceuticals and medical services) in Poland is covered to some degree by the NFZ, with a significant contribution through patient copayments, with a lesser contribution coming from the country's health funding envelope [1, 4].

In 2011, healthcare-related spending in Poland amounted to PLN 105 billion, which was 6.9% of the Polish Gross Domestic Product (GDP). A large portion of the expenditure in 2011 was consumed by the provision of health services (approximately 93% of the total amount). Investment and development expenses amounted to 7% of the total expenditure. A major part (55%) of the total expenditure was related to patient treatment and rehabilitation [4].

Those who are employed, the self-employed, children, students, pensioners, and registered unemployed persons are all covered by the public health insurance scheme [5]. Patients must confirm their right to medical care through registering with a healthcare entity either via an online electronic system, known in Poland as eWUS, or by presenting a hard copy of the document that proves the right to publicly funded healthcare services [6]. Patients' rights are regulated by the Act of 6 November 2008 on Patient Rights and the Patient Rights Ombudsman, which lists among others, the right to free healthcare benefits and the right to dignity, privacy, and confidentiality about health [7, 8].

15.1.2 National Health Status

The outcomes for the basic health indicators in Poland are mostly on the lower side as compared to other OECD (Organization for Economic Co-operation and Development) countries [9]. According to OECD data, mean life expectancy in Poland is 77 years, which is 3 years less than the average in OECD countries [4]. Nonetheless, the average life expectancy in Poland has increased by 7 years from 70.7 years in the early 1990s (70.7 years) [10].

Another health indicator reported by the World Health Organization (WHO), is the age-standardized mortality rate (per 100,000 population). In 2012 in Poland, the rate amounted to 565.9 for both genders combined. Diseases of affluence are a significant cause of death in Poland. Morbidity rate due to cardiovascular (CVS) diseases was 253.4 (almost a half of these deaths are the consequence of ischemic heart disease) and for diabetes mellitus it was 9.4 [11]. The estimated mortality rate for malignant neoplasm combined for male and female was 149.7, which closely follows CVS diseases. Infectious and parasitic diseases had a lower rate of 3.2, and for tuberculosis, even lower at 1.2 [11].

With regard to access to healthcare in Poland, in 2011 the statistics show that 14.2% of Polish citizens reported they had unmet medical care needs. There may be several reasons for this situation; the main one being financial constraint and another being waiting times for visits due to the low number of healthcare professionals available per patient [10].

15.2 Pharmaceutical Situation in Poland

15.2.1 Overview

The value of the pharmaceutical market in 2015 reached PLN 30 billion (which is equal to around USD 7.8 billion) [12] and this number has been growing consistently over the last two decades [13]. In October 2015, the value of sales of the pharmaceutical market was nearly PLN 2698 million representing over 5% (+ 5.7%) growth compared to October 2014. Sales of reimbursed drugs in October 2015 amounted to PLN 1000 million (+ 5.4% compared to October 2014). Mean turnover of a regular community pharmacy in October 2015 amounted to PLN 185.5 thousand (gross retail prices), and was 3.1% higher than in October 2014. The average retail price of a drug sold in a pharmacy was PLN 17.07[1] [14].

Poland is in the Tier 3 group of "pharmerging" countries; those are the countries where the use of and expenditure on pharmaceuticals is growing rapidly and where GDP is less than $25,000 per individual [15, 16]. Countries from the Tier 3 category are expected to spend $96 on drugs per capita in 2016 [15]. In Poland, products distributed in the pharmaceutical market belong to one of three main segments: reimbursed medicines, nonreimbursed prescription drugs, and over the counter (OTC) medicines [17].

The number of community pharmacies in Poland has been steadily growing in past years. In 1997 the total number of pharmacies 8000 approximately, whereas in 2011 the number had grown to 13,500 [18]. In 2013, around 50 new pharmacy chains opened into the Polish pharmaceutical market. In 2014, more than 29% of pharmacies were members of pharmacy chains and nearly half (44%) of sales of community pharmacies were generated by chain pharmacies [19]. The consequence of this situation is an increase in the level of competition between pharmacies and a lower number of patients per pharmacy. In 2002, there were 4000 patients per pharmacy; in 2011, this number had decreased to 3600. This has pressured pharmacy owners to join large pharmacy chains, group purchasing organizations or franchises [18].

15.2.2 The Pharmaceutical Industry in Poland

According to a report by the Independent Center for Economic Studies (*Niezalezny Osrodek Badan Ekonomicznych*, NOBE) in 2010, the development of the pharmaceutical industry in Poland was occurring at a much higher rate than observed by overall Polish economy. Despite this, Poland's share of the overall European pharmaceutical market was still relatively low [20].

The Polish market contains more than 300 companies that market drugs, dietary supplements, and medical devices [13]. Pharmaceutical companies play a signifi-

[1] For a drug from the reimbursement list the average retail price was PLN 27.73.

cant role in the national economy. In 2010, the pharmaceutical industry's contribution to the total industrial output of Poland amounted to 1.5%. The other key advantage that large pharmaceutical corporations bring to the Polish economic environment is the creation of relatively stable employment conditions. In 2010, three leading pharmaceutical companies (GlaxoSmithKline®, Novartis®, Sanofi-Aventis®) with affiliate offices in Poland hired more than 4000 people [20]. Additionally, some pharmaceutical companies (e.g., Polpharma®, Johnson & Johnson®) demonstrated and emphasized Corporate Social Responsibility (CSR) activities and have a general positive impact on Polish society [21].

A decrease in financial performance was seen in the Polish pharmaceutical market for the 2011–2012 period. Gross profit across the entire market in 2010 amounted to PLN 1.81 billion, whereas in 2012 it fell to PLN 0.99 million. However, rebound in the industry was observed in 2013. In 2010, the gross margin in the pharma sector was 11.35%, which in 2012 decreased to 7.17%, but in the third quarter of 2013 increased again to 11.82% [22]. The reasons for that decline could be the "patent cliff" in 2012[2] as well as the implementation of Reimbursement Act (RA) [23, 24].

A specific feature of the Polish pharmaceutical market is the high share of generic medicine sales, which amounted to 66% of the market in 2012, being one of the highest rates in Europe. The reason for this high market share in Poland is the fact that generic prices are much lower when as compared to originators and there is active promotion of generics in the market [22]. It has been observed that Poland is among those countries where companies outsource research and development (R&D), for example, clinical trials. This is due to the lower costs of clinical trials implementation and maintenance, when compared to the United States or Western Europe [25]. Poland has also been recognized as an attractive place to establish pharmaceutical manufacturing sites [26].

The pharmaceutical sector in Poland is a national industry leader in terms of expenditure on research and development (R&D) and technological innovations. In 2013, expenditure on these activities amounted to 60% of the total expenditure, while the average in all types of industries is around 23%. The pharmaceutical sector launches the greatest number of innovative products in Poland every year, relative to other industries. This is supported by the fact that during the period from 2012 to 2014, 42.5% of companies in the pharmaceutical industry launched new products, and as a consequence this sector has moved ahead of the refined petroleum products industries, which were previously the leading industry sector [27].

15.2.3 Pharmaceutical Trade in Poland

There are significant supply side issues with pharmaceutical availability in Poland with one report suggesting local production was only able to meet one third of the societal demand for medicines [20]. Drugs that do not have a Marketing Authorization

[2] It was the culmination of the expiry of many drug patents.

(MA) in Poland can be imported via direct import, which is regulated by the MoH [28]. Drugs imported in this way do not need an additional authorization to be sold, as long as they meet the following conditions: they must be necessary to save the life or improve the health of a patient and they cannot be registered in Poland as an equivalent drug with the same active ingredient [29]. An example of not meeting these requirements was the attempt to launch Kalydeco®—an orphan drug, in the Polish market. It did not meet the direct import rules, due to the fact that it was registered through the EU centralized procedure and in this way it was registered in the Poland [28].

Poland had the third largest increase in the level of export of medicines for the first decade of the twenty first century in Europe (+ 30%). However, this increase could be due to the small share of the international drug market that Poland had in the beginning of the century [25]. It has been reported that drugs from Poland, which have much lower prices than those sold in the Western European markets, are illegally exported to Western European countries. The easiest and most popular way of illegal export is designated as "resale", which involves the selling of a drug from a pharmacy back into a pharmaceutical warehouse. This can be undertaken by sending back to a warehouse those medicines for which allegedly there is no demand and making a relevant correction of the invoice. The illegal export creates a "double chain of distribution" and allows medicines to be purchased for higher prices in Western Europe [30, 31].

There is a new Act regulating drug exports which came into force in Poland on 12 July 2015. The amendment of the law means that wholesalers are obliged to report to the Main Pharmaceutical Inspectorate (*Główny Inspektorat Farmaceutyczny*, GIF) an intention to export medications from the country. The obligation covers products for which there is an identified risk of unavailability in Poland [32].

15.3 Polish Regulatory Environment

15.3.1 Medicines Regulatory Authority

In Poland, as in other EU Member States, after completion of phase III clinical trials, it is possible to apply for registration and Marketing Authorization for a medicinal product. The authority that deals with registration of pharmaceutical products is the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products (*Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych I Produktów Biobójczych*, URPLWMiPB). The process of drug registration is aligned with the European Commission Directive 2001/83/EC (the directive on the Community code relating to medicinal products for human use). The registration can be carried out in accordance with one of four procedures: purely national, centralized, mutual recognition or decentralized. The registration procedure should be completed within 210 days (it can be extended, when it is necessary to complete gaps in documentation or clarify explanations with the applicant). Each of the

different registration pathways has benefits and drawbacks, and the choice between them depends primarily on the characteristics of a product. However, there are restrictions and some kinds of medicinal products such as orphan drugs which must be registered via centralized procedures [33–36].

The process of registration of medicines in the Polish Republic requires the applicant to go through several stages, during which collected documentation is analyzed both from a scientific and technical point of view. The registration dossier is also assessed as to whether it meets administrative requirements. The dossier that is submitted to the regulatory authority must be in the form of a Common Technical Document, which consists of five specific modules. The result of the procedure might be either granting or denial of a Marketing Authorization. The Marketing Authorization for the medicinal product is issued for a period of 5 years with the possibility of shortening or extension. As a result, a new entry in the register of medicinal products authorized in Poland is created [33].

The process of drug registration is considered to be expensive, complicated and time-consuming. Nonetheless, it is much easier in the case of the registration procedure for generic medicines. The potential Marketing Authorization Holder (MAH) for a generic product is not obliged to show the results of clinical and preclinical trials. Other documentation requirements are the same as in the case of innovative products, including summary of product characteristics, information about the experts, and the manufacturing process details. In addition, it is necessary to prove the bioequivalence of a generic and an original product with the appropriate studies [36].

15.3.2 Quality Control of Medicines

For every pharmaceutical product that is granted Marketing Authorization in Poland, the sponsoring company is obligated to abide by Good Manufacturing Practices (GMP) that helps to ensure the high quality and safety of drugs. The document that describes methods of drug and raw materials testing and packaging is the Polish Pharmacopeia, which is aligned to the European Pharmacopeia [37].

The majority of raw materials used in Poland are imported from abroad, largely China or India, which may be of varying quality. However, the efforts of large pharmaceutical companies to maintain a high level of quality through their careful monitoring and planning of the production processes and detail risk management is often impacted by this [38]. The authorities designated by Polish Pharmaceutical Law (*Prawo Farmaceutyczne*, PF) to supervise the quality of drugs are the GIF and 16 Voivodeship Pharmaceutical Inspectorates (*Wojewódzkie Inspektoraty Farmaceutyczne*, WIF) [37, 39]. WIF and the GIF are able to suspend marketing of a certain batch or series of a medicinal product. If issues arise, the sale of the identified series or batch of a particular drug product is stopped by WIF or GIF at the level of wholesalers and pharmacies, until the laboratory testing results confirm or exclude a quality issue. If an issue relating to the quality of a product is confirmed

and is deemed serious enough, then GIF might decide to action the drug's withdrawal [39].

At the European level, the quality of medicines is controlled by the Official Medicines Control Laboratory Networks, which is in-turn controlled by the European Directorate for the Quality of Medicines. The Polish entity that belongs to this network is the National Medicines Institute (National Control Laboratory of Medicinal Products, Medical Devices, and Biocides). This performs laboratory tests on drug samples to confirm compliance with their specifications [40].

15.3.3 Pharmacovigilance

Pharmacovigilance-related activities in Poland are regulated by two legislative Acts that were implemented by the European Medicines Agency (EMA): Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 and Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010. The new EU legislation contributed to enact a relevant Polish law on 13 September 2013. It was expected that this law would reduce any potential medicines-induced harm [41, 42].

According to Pharmaceutical Law any patient can report an adverse event to a medicine. Adverse events may be reported to a healthcare professional, to the President of the Regulatory Authority or to the MAH of a suspected drug [43]. In the case of a justified signal that a product may indeed cause serious side effects, Pharmaceutical Law gives mandate to the Main Pharmaceutical Inspectorate to decide upon temporary suspension of the product's marketing, or its full withdrawal [37, 43]. One of the innovations in adverse event reporting in Poland is the option of transmitting information to the Regulatory Authority via a special mobile application [44].

15.3.4 Counterfeit Medicines

As far as the authors are aware, at the time of writing, the global problem of the availability of counterfeit drugs does not seem to be a concern for Polish community pharmacies. National research laboratories conduct tests on samples of medicines taken from pharmacies and pharmaceutical warehouses and to date there has been no evidence to suggest the availability of counterfeit medicines in the Polish market [45].

The most common sources of counterfeit medicinal products as well as drugs not having a Marketing Authorization in Poland are via illegal online stores. These products can also be found in commercial establishments including sex shops, stores with nutritional supplements for athletes, service providers (e.g., fitness clubs, massage parlors), bazaars, and marketplaces. The punishment for selling counterfeit drugs in Poland is up to 8 years of imprisonment [46].

15.4 Medicines Supply System

15.4.1 Procurement

Currently, drugs in the EU that are subject to public contracts are regulated by national legislation on public procurement. Nevertheless, they must comply with the European directives on procurement procedures: Directive 2004/17/EC and Directive 2004/18/EC [47, 48].

Entities that procure medicines for the healthcare sector in Poland are the Ministry of Health (major awarding entity), public healthcare entities, and nonpublic healthcare entities. Their activities regarding public procurement must comply with the regulations mentioned previously. The procurement process is supervised each step of the way by the GIF and Regulatory Authority. All "contracting authorities" (Ministry of Health and public entities as well as nonpublic entities under some conditions) must apply to the Polish Public Procurement Act (PPA) if a contract's worth is greater than EUR 14000. When a hospital selects a supplier, there are specific criteria for the award, from which at least 50% of the weighted average of the award criteria is the price of a supplied product. Hospital pharmacies in Poland are trying to coordinate this process through the implementation of drug management programs, which involve the opinion of clinicians. Nonpublic entities, when not forced by the PPA, tend to purchase medicines through tender processes [47].

15.4.2 Distribution

The market distribution of pharmaceuticals has undergone many changes in Poland over recent years, including privatization of warehouses, development of pharmacy chains and the growth of nonpharmacy drug trading. The distribution of medicines is strictly regulated by Pharmaceutical Law [49–53]. The wholesaling of medicinal products must be performed only by pharmaceutical wholesalers and/or bonded or consignment warehouses. The introduction of a medicinal product to the wholesale trade market requires prior notification to the Marketing Authorization Holder and to the President of the Regulatory Authority [49, 50].

In order to operate a pharmaceutical warehouse, an applicant is required to obtain a permit from the Main Pharmaceutical Inspectorate. An additional permit is required for the wholesale trade of narcotics, psychotropic substances, and precursors of the I-R group (this group consists of any substances that can be transformed into a narcotic drug or psychotropic substance, e.g., pseudoephedrine, lysergic acid). Wholesalers are required to work in accordance with the Good Distribution Practices guidelines, which describe the specific requirements for pharmaceutical premises, storage of drugs, receipt of consignments, loading and transport [24, 49, 51].

The total value of drugs in the pharmaceutical wholesale warehouses in Poland is around PLN 1.6 billion (including the value of reimbursed drugs that amounts to

PLN 500 million). However, due to the effect of PF changes the revenue of Polish warehouses has been decreasing since the RA was introduced in 2012. At present, the Polish wholesale pharmaceutical market is preparing to introduce new demands pertaining to the EU Directive 2011/62/EU on preventing the launch of counterfeit medicinal products into the legal supply chain [24].

More and more companies in Poland are interested in a novel way of drug supply denoted "Direct to Pharmacy" distribution. This method of delivery leads to the omission of wholesaler activity and products are purchased by pharmacies without intermediaries being involved. The first "big pharma" company that introduced this system in Poland was Astra Zeneca and despite the fact that it faced criticism from Polish pharmacists, the popularity of this form of distribution has been on the increase. There are a number of companies that specialize in providing the pharmaceutical industry with comprehensive support associated with this "Direct to Pharmacy" distribution mechanism [52]. Direct contact between a pharmaceutical company and a pharmacy is aimed to improve the process of production planning and supply chain management, which should lead to better access to key medicines in the market [53].

15.5 Medicines Financing

15.5.1 Medicine Expenditure in General

In the scale of the entire national economy of Poland expenditure on pharmaceuticals constitutes approximately 30% of the total healthcare spend [54]. Drug prices in Poland are much lower when compared to other European markets [49]. According to Pharma Experts, expenditure on drugs in 2015 grew by 5.1% compared with 2014 [13].

According to IMS data, Poland spent PLN 27.3 billion on drugs in 2014 (including PLN 11.4 billion on OTC drugs), which is PLN 3.3 billion more when compared to the previous year [55, 56]. The Central Statistical Office of Poland informs that the average per-capita expenditure on drugs for Polish citizens in 2015 was PLN 58 per month, which is approximately 10% more than in 2014. These costs increase under the scenario of patients suffering from chronic diseases and may even reach PLN 700 monthly in this case [57]. For around 40% of people in Poland, medicines are unaffordable to some extent, medicinal products are a burdensome expense, where affordability is low [58].

15.5.2 Pharmacoeconomics in Poland

Pharmacoeconomic analyses are used by the National Health Fund in cooperation with The Agency for Health Technology Assessment in Poland (AHTAPol). This is in order to determine the prices of individual medicines, amount of reimbursement, validity of registrations and cost-effectiveness of preventive actions [59].

AHTAPol issues recommendations inter alia on the merits of drug reimbursement. It also performs economic evaluations that include the cost-effectiveness of therapies and the impact they may have on the national pharmaceutical budget. Establishment of AHTA Pol has contributed to the popularization of pharmacoeconomics and its application within the Polish market. According to the guidelines of AHTA Pol, each Marketing Authorization Holder that applies for reimbursement of drugs must provide a cost-effectiveness analysis and a budget impact analysis [60].

15.5.3 Medicines Pricing and Access

The Reimbursement Act (RA) was implemented on 1 January 2012 and caused far-reaching changes in the reimbursement system in Poland. The Reimbursement Act introduced fixed reference prices of reimbursed drugs and the limitation of pharmaceutical product price adjustments (such as discounts). It also changed the access of drugs for patients, since review of the reimbursement list occurs every 2 months. However, the impact of frequent changes to the list has been disputed. The Reimbursement Act was intended to completely readjust Polish legislation to meet the requirements of Directive 89/105/EWG on transparency of pricing regulations for medicinal products and their inclusion in the scope of the public health insurance system [61]. Control of drug prices has a significant impact on the pharmaceutical market, which can be carried through individual negotiations with drug manufacturers. The reference price is determined on the basis of an application for the establishment of such a price, which is required to be submitted to the MoH, together with an application for the drug's reimbursement, which are then simultaneously evaluated. Review of an application for reimbursement and establishment of a reference price is required to be undertaken in 180 days or less. However, a deadline for the submission of applications is outlined on a quarterly basis and the average number of applications to the Ministry of Health is approximately 150–200 per quarter. The processing of this number of applications can result in delays. The price of drugs that are not reimbursed fall under the decision of companies that have the right to commercialize them (Marketing Authorization Holders) [62–64].

Drugs, foodstuffs, or medical devices can be reimbursed by NFZ if they are prescribed on a properly issued prescription, purchased in a pharmacy and if they are on the reimbursement list. In Poland, there is a relatively complex pricing schedule and the following levels of payment apply to reimbursed drugs: those that are free (up to the limit), lump sum, 50% (for a fee of 50% up to a limit of financing, which is the amount of reimbursement for a drug), and 30% (for a fee of 30% up to a limit of financing). If a retail price of a reimbursed drug exceeds a limit of publicly funded reimbursement, then a patient has to pay the difference between the actual price and the ceiling limit for reimbursement. There are also additional special reimbursement privileges for groups such as veterans, military invalids, or honorary donor transplants [65, 66].

Currently, the list of reimbursed drugs is kept well up to date with it being issued by the Ministry of Health every 2 months [67]. According to the Official Journal of

the Ministry of Health from 29 June 2016, there are 3875 different reimbursed drugs available in pharmacies on prescription. This includes the entire range of approved indications or in the indication for a specific clinical state, 67 foods for particular nutritional uses, 302 medications available within a drug program, and 545 medical devices [68]. When compared to the other EU countries, the level of reimbursement in Poland is much lower and the pharmaceuticals on reimbursement lists are indicated for a much narrower range of diseases [27].

15.5.4 The Generic Medicines Market in Poland

According to IMS data, the Polish pharmaceutical market has one of the largest shares of generics in Europe [69] and the generic market is considered to be mature [70] and is also of high-volume and of low-value products [71]. A generic drug may only be marketed in Poland provided once all patents and supplementary protection certificates covering the original drug have expired [72, 73].

Polish law guarantees the patient the opportunity to replace an original drug with a generic equivalent and pharmacists are required to present to their patients an original drug's substitutability to a cheaper generic. In Poland, most of the generic drugs on the market are branded generics, which means they have their own trade names [74]. The generic products in the market can be up to 90% cheaper than originator branded medicines [71]. According to the RA, in order for a generic drug to be placed on the reimbursement list, its price must be at least 25% lower than the price of the originator branded drug [75].

Biosimilars are not very common in Poland and pharmacists' knowledge about them is considered to be limited [76]. The most important advantage for a Polish patient in the case of biosimilar medicines is that they have much lower prices than original biological agents. It was estimated that biosimilars in 2009 generated savings of EUR 1.4 trillion within the EU. This perhaps shows that there will be room for growth in the Polish biosimilars marketplace [68].

15.6 Medicines Use

15.6.1 Issues Impacting on Rational Medicines Use in Poland

In Poland, a very large share of the market belongs to OTC drugs, which is linked to the fact that Polish patients have a strong tendency to self-medicate [77]. The most popular OTC drugs are those indicated for treating pain and the common cold, as well as vitamins [78]. Patients can ask for help from a pharmacist when choosing a product; however, OTC medicines are available in numerous places other than pharmacies, such as supermarkets and petrol stations. When patients are selecting medicines, they often make their decisions based on information presented in advertising, not by

recommendations from pharmacists or doctors [77, 78]. This happens despite the general opinion that medicines advertisements are not trustworthy and unreliable [79].

Constantly increasing access to OTC medicines escalates the risks arising from improper use and possible interactions. Patients also often do not read drug labels [77]. Despite the constantly rising prices of medicines (in 1997 the average price of a drug in a pharmacy was PLN 3.80, in 2011 it was PLN 16.20 [18]), the trend of the growth in medicines consumption initiated in the early 90s, remains today [80]. On the other hand, unfortunately, there are people in Poland who cannot afford to purchase all the medicines which are prescribed to them and the main reason for this is the cost of drugs which is too high compared to their earnings [81]. According to the data from Pentor Research International Agency, one in four chronically ill patients reported purchasing only part of their prescribed drug regimen [82].

15.6.2 Medicines Use in Community Pharmacies

It was reported in January 2015 that people in Poland still buy most of their drugs in pharmacies and nonpharmacy sales represent only 1.5% of the market. There has also been a steady increase in the range of products offered in pharmacies, since many new products are launched into the market every year [83].

In the last few years, it has been observed that there is a trend to purchase medicines online. Such sales are regulated by pharmaceutical laws along with the decree issued on 26 March 2015 by the MoH. These requirements ensure that the legal sale of prescription drugs can be undertaken through pharmacies and that the shipment of drugs does not harm the safety and quality of the products. All websites that have a legal permission to sell drugs have a common green logo with a link below, which signifies that the pharmacy is on the National Register of Permits to Operate the Pharmacies, Pharmaceutical Dispensaries and the Registry of Granted Approval for the Hospital and Workplace Pharmacies [84].

Since 1 July 2015, new regulations have been implemented that aim to reduce drug abuse. Medicines used for cold and cough that contain pseudoephedrine (which may be used in the synthesis of methamphetamine), dextromethorphan, or codeine, that could be purchased in any amount, are now limited to one pack per adult. Breaking this law could result in fines for a pharmacist amounting to PLN 500,000. Additionally, these drugs cannot be sold on the Internet [85].

15.6.3 Medicines Use in the Hospital Sector

Pharmaceutical expenditure in the hospital sector in 2013 amounted to PLN 3,091,235,244 (net wholesale prices), which equates to 67,948,318 units and 16% of the pharmaceutical market in Poland [86]. Hospitals have the option of creating purchasing groups, which are associations of hospitals carrying out joint purchases

and thus lowering their costs through volume and preferred supplier arrangements [87]. The downside of this approach is that it shifts the procurement focus to very standardized product orders and consequently there has been a significant reduction in the range of products available in Polish hospitals [86].

15.6.4 Standard Treatment Guidelines and Prescribing Behavior

Standard treatment guidelines in Poland are developed by medical associations, which consist of experts in relevant fields of medicine. Their decisions are made in compliance with current medical knowledge and the principles of evidence-based medicine [88].

It was observed during the project Happy Audit 2 (which was intended to describe the therapeutic decisions of family doctors with an emphasis on antibiotics) that the most commonly used antibiotic in Poland is amoxicillin, and the most common prescribed antibiotics groups are cephalosporins and macrolides [89].

It was estimated that in 2013 around 40% of Polish primary care physicians doubted that in terms of effectiveness generic medicines and original drugs are equal. Promotion of the Polish pharmaceutical industry, which is based on generic medicines, could therefore positively influence both the Polish domestic industry and doctors' prescribing behaviors associated with the generic drugs [90]. The use of cheaper equivalent drugs has been shown to enhance patient compliance [74]. Doctors are able to prescribe generic drugs either by writing the name of an originator (a pharmacist can still propose to a patient the generic equivalent if it is not clearly stated on the prescription that the doctor does not wish the drug to be substituted), the trade name of a generic or its INN (International Nonproprietary Name) [79]. Special precautions in the generic switching process are only required for drugs with a narrow therapeutic index (TI) or for modified release preparations [91].

Since 1 January 2016 in addition to doctors, registered nurses and midwives have been able to prescribe drugs in Poland as well. This legislation should reduce waiting time in clinics. The list of drugs that can be prescribed by a nurse consists of about 30 medicines [92]. Pharmacists are also able to issue pharmaceutical prescriptions in the case of emergency and danger to patients' lives. In such situations, the patient may purchase the smallest available package of a drug for 100% of the price regardless of whether the drug has reimbursement status [93].

15.6.5 Medicines Promotional Practices

The pharmaceutical industry is the second largest advertiser in Poland [55] with greater spend on advertising than banks or mobile network companies. In 2014, spending on advertising by Polish pharmaceutical companies amounted to PLN 871

million, which was 9% higher than in 2013. One of the leaders in this sector is Aflofarm® that mainly produces food supplements. Its expenditures on advertisements amounted to PLN 200 million in 2014 [56].

It is prohibited in Poland, pursuant to Pharmaceutical Law (PF), to advertise prescription only drugs. However, pharmaceutical company representatives provide doctors with gadgets that are labeled with their companies' logos. According to PF, the value of gifts that are handed to doctors cannot exceed PLN 100 (which is equal to around USD 26) [94, 95]. In order to reach the audience, pharmaceutical companies sponsor various conferences and promote these events through media [95].

An example of the effect of promotion on sales of drugs is the case of the OTC drug Metafen®. It is a medicine that contains two active ingredients: ibuprofen and paracetamol. The design of the drug's package was completely changed upon acquisition by Polpharma® and an intensive marketing campaign based mainly on television advertising was prepared. Until the launch of a promotional campaign, sales had been relatively low, but following intensive promotion sales growth of nearly 900% was achieved [96].

15.6.6 Role of the Pharmacist

In accordance with Article 90 of Pharmaceutical Law all activities in a pharmacy must be performed only by pharmacists (holders of Masters of Pharmacy degrees, trained for 5.5 years in medical universities) and pharmacy technicians within their professional capacity [49]. The professional role of the pharmacist[3] is to protect the health of the public, which includes provision of pharmaceutical care, collaboration with patients and doctors and taking care of pharmacotherapy in order to optimize treatment and to improve patients' quality of life [49, 97]. Pharmaceutical technicians perform similar tasks as qualified pharmacists; however, they are not allowed to sell very potent drugs or medications containing active ingredients considered to be poisons, or opioids [98].

Pursuant to Pharmaceutical Law, each pharmacy in Poland must have a manager who is responsible for the pharmacy. A pharmacist may transition to a pharmacy management role when they have 5 years of experience or 3 years of experience if they are specialized in retail pharmacy by training. Pharmacy managers in Poland must ensure the quality of medicinal products, as well as proper organization of work in a pharmacy, records of prescription medicine transactions, and reporting of adverse drug reactions [49].

There are also hospital pharmacists that according to Pharmaceutical Law are allowed to perform various tasks within a hospital pharmacy or a hospital ward, for example, rationalization of pharmacotherapy, monitoring of adverse reactions, and supporting of clinical trials are among some of these tasks [86, 99, 100]. The hospital pharmacist in Poland is usually a member of the pharmacy and therapeutic

[3] Regulated by the Act of 19 April 1991 On Pharmaceutical Chambers.

committee and contributes to selection and updating of hospital formularies [86, 101]. Nevertheless, pharmacists in Poland rarely take part in making decisions about treatment of individual patients or recommend alternative pharmacotherapeutic options. Additionally, in contrary to Western European countries, only a few Polish hospitals hire clinical pharmacists [99].

15.6.7 Pharmaceutical Care Interventions

During their studies, pharmacists in Poland are trained to provide pharmaceutical care [102]. Nevertheless, pharmaceutical care within the definition of the Western European countries (constructive intervention in the course of treatment) does not exist in Poland. Several organizations, such as the Polish Pharmaceutical Chamber, are working on development of pharmaceutical care programs [103, 104]. There is evidence that some pharmacies are organizing campaigns to promote health, diabetes care, or smoking cessation in Poland [103]. A pharmacist is often the first person that people make contact with about their health issues, due to the fact that contact with a doctor is difficult, more expensive, and time consuming. It is also stipulated that pharmacists in Poland make sure that a patient's self-diagnosis and the choice of a product when dispensing an OTC drug is correct [105].

Factors that hinder the implementation of pharmaceutical care in Poland are as follows [106, 107]:

- Due to the high level of competition in the pharmaceutical market, a pharmacist must be focused on activities directed to increase the pharmacy's profitability (e.g., looking for discounts and low-cost warehouses).
- Pharmacists are often reluctant to take responsibility for a patient's pharmacotherapy regime.
- Patients are often not aware that pharmacists can have the oversight of their drug therapy.

15.7 The Way Forward

The Polish government is required to align with numerous stipulations of EU law as well as society's demands to meet their health needs. This will require some adjustment and the EU requirements often exceed what can be done within the available healthcare budget in Poland. With Poland's ageing population and escalating levels of chronic disease (as with the rest of the world) demand continues to increase. In 2020, Member States of the EU are expected to spend 16% of their GDP on the healthcare sector [108].

Polish law regarding pharmaceutical industry market development and drug reimbursement is complex and could benefit from simplification. The obstacles that

investors face due to unfriendly regulations (e.g., regarding reimbursement of drugs) may inhibit interest in investment and development of the Polish pharmaceutical market [20]. According to experts from the Polish Association of Pharmaceutical Companies INFARMA, legislation in Poland should be more predictable, should better achieve the objectives of Pharmaceutical Law and should reduce negative impacts on healthcare entities and pharmaceutical companies. It would also be desirable if the Ministry of Health were to engage more with patients, healthcare specialists, and representatives of the pharmaceutical industry [109].

The pharmaceutical and general healthcare sector requires support to educate more healthcare professionals to have the required training to bolster the Polish health system [10, 20]. Polish people perceive their health system to be getting worse each year, which may be a consequence of Polish peoples growing expenditures on health services and drugs, as well as insufficient numbers of doctors available to service their medical needs (there are about 2.2 physicians for 1000 citizens) [58, 110].

According to the announcement in November 2015, there will be a number of reforms pertaining to the Polish healthcare system and medicines expenditures. This is due to the change in the governmental party in October 2015 (the party that had a majority in parliament for the last few years, Civic Platform, was replaced in the last election by the national-conservative Law and Justice party). Law and Justice considers returning to a healthcare system based on public budget funding, instead of the current national public healthcare insurance system The party also claims that drugs would be available for free to underprivileged people over the age of 75 years, which would cause substantial expense to the tax-payers in the population [111]. The initiative was launched in June 2016; however, not all the drugs are free as it was promised; the list of free drugs contains 84 active substances and the cost of the project is estimated to reach PLN 125 million [112].

15.8 Summary

The healthcare system in Poland is based on the public health insurance scheme, which is coordinated by the National Health Fund, in cooperation with the Ministry of Health. Most of the policies controlling the pharmaceutical market in Poland are pursuant to the Pharmaceutical Act; established in 2001 in Poland. Another source of medicines controlling legislation is European Union law, since Poland joined the EU in 2004. Moreover, reimbursement of medicinal products regulations is featured in the controversial Reimbursement Act, which was implemented in 2012.

Since the beginning of the Polish political transformation in the late 80s, the pharmaceutical market has developed rapidly and its value in market terms has doubled. In the last two decades, the wealth in Polish society has increased and the government has implemented a number of constructive reforms. There has been significant progress in privatization of the healthcare sector and an improvement in the quality of health service provision as well as increased access to drugs. Poland

is recognized as a low-cost country, which makes it an attractive place for outsourcing of expensive stages of clinical research into drug treatment, for example, conducting of clinical trials. Nonetheless, there are numerous difficulties for potential investors, such as low prices of reimbursed medicines and restrictive regulations on drug reimbursement.

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Chapter 16
Pharmaceutical Policy in Saudi Arabia

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Abstract Saudi Arabia has a well-developed national medicine policy as well as a well-established drug regulatory framework. Moreover, there is a well-defined pharmaceutical pricing policy, and the medicine prices are strictly controlled. The Saudi Pharmaceutical market is the largest market in the Middle East and African (MEA) region. Moreover, it is heavily dependent on imported medicines and dominated by patented and original medicines. Regarding rational use of medicines, there are several issues that need to be addressed. These include unrestricted access to medicines in the community pharmacies. Moreover, the involvement of community pharmacists in promoting rational use of medicines is currently limited. Additionally, generic medicines are still underutilized in the healthcare system. The way forward is the full implementation of these policies and the stricter enforcement of the laws governing medicines sales and dispensing.

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16.1 Healthcare System in Saudi Arabia

16.1.1 Saudi Healthcare System: A Brief Overview

The Kingdom of Saudi Arabia is located in the southwest corner of Asia and covers an area of approximately 2 million km^2. The total population is approximately 30.8 million in 2014 and women represent approximately 43.9% of the total population [1]. Saudi Arabia is administratively organized into 13 administrative regions, namely Riyadh, Makkah, Madinah, Qassim, Eastern Province, Asir, Tabuk, Hail, Northern Border Province, Jazan, Najran, Baha and Al-Jouf region [2]. Riyadh is the capital of Saudi Arabia and is located in the heart of the country. In 2014, its population was estimated to be 7.7 million. In Riyadh, 61% of the population is Saudi, while the rest (39%) are residents from different parts of the world, such as India, China, Bangladesh, Pakistan, Indonesia, Philippines, Yemen, Egypt, Sudan, Lebanon, Syria, Europe, USA, Canada, South Africa and Russia. Thus, Riyadh is considered to be one of the most cosmopolitan cities in the Arab world [1, 3].

The country has witnessed a huge improvement in socio-economic development during the past three decades. Tremendous efforts have been made to advance all sectors, including health, education, housing and the environment [4]. Currently, the country has excellent infrastructure, including an extensive network of modern roads, highways, airports, seaports, power, desalination plants and huge industrial complexes [4]. This, in turn, has transformed the country into one of the most urbanized countries in the Middle East [5].

Similarly, the Saudi healthcare system has gone through huge improvements in the last 50 years at all levels and aspects of healthcare services in terms of quality and quantity [4, 5, 6]. A large network of modern healthcare facilities, including hundreds of hospitals and thousands of primary care centres, are currently established in the country to provide healthcare to all citizens and residents in the country [5, 6]. Quality of care is also high; for instance, the King Faisal Specialist Hospital & Research Centre (KFSH & RC) was ranked in 2013 by the Spanish National Research Council (CSIC) as one of the top hospitals in the Middle East [7].

However, the healthcare system is currently facing several challenges. In addition to the major challenge of escalating costs in providing healthcare services, there are many other factors that challenge the efficiency of the system. These factors include a shortage of local healthcare professionals, as the majority of healthcare professionals are expatriates; a rapid population growth; the aging of the population; the high burden of chronic diseases (e.g., asthma 13%, hypertension 11%, diabetes 28%); and a growing demand for healthcare services. Some of the other challenges are poor referral systems between primary centres and hospitals; long waiting times, the unavailability of some medicines at some periods, underutilization of e-health and information systems and the maldistribution of healthcare services across geographical areas [6, 8].

In the public sector, for example, the waiting time for non-emergency surgery might be several months to a year [9]. Moreover, the general perception of consumers regarding the quality of care in Saudi Ministry of Health facilities is much lower than

the private sector and other government sectors [9]. Therefore, sustainability and maintaining the efficiency of the healthcare system is currently a major challenge [5]. However, to address these challenges and to improve the current healthcare system, the new Saudi health strategy was introduced in 2009. In this strategy, many issues were addressed, including health promotion and prevention of diseases, as well as non-communicable diseases (NCDs), which are highly burdensome and require costly treatment and high utilization of the system. Thus, the expansion of primary healthcare centres was recommended. Due to the tremendous increase in healthcare expenditure, alternative means of funding healthcare services were recommended. Thus, the cost-effective use of medicines was encouraged to lower the escalating trend in health expenditure in general and pharmaceutical expenditure in particular. Moreover, the private sector needed to expand involvement in the provision of health services to cover at least 50% of the total health expenditures. Furthermore, for government hospitals, in addition to annual allocations from government, other modes of financing (e.g., the privatization of some healthcare services) are needed [8].

16.1.2 Health System Organization and Provision of Healthcare

Healthcare in Saudi Arabia is provided by a three-level system (primary, secondary and tertiary healthcare). The concept of primary healthcare (PHC) started in the early 1980s by establishing PHC centres; secondary and tertiary healthcare are provided via general and specialist hospitals. The integrated healthcare services system, via referral with the feedback system, is the adopted approach in the provision of healthcare. In this approach, patients who need secondary or more specialized care are referred to the appropriate healthcare facility [10, 11].

Healthcare is provided via a dual system (i.e., public and private sector). The public sector is currently the main provider of healthcare and is mainly funded by the government budget. The Ministry of Health (MOH) and other government sectors are provided with financial appropriations on a yearly basis from the general government budget. Healthcare services provided by the private sector are financed by cooperative health insurance schemes and out-of-pocket payments [10, 11].

In the public sector, the Ministry of Health (MOH), established in 1951, is the major healthcare provider as it provides approximately 60% of all health services [10, 11]. In 2014, the MOH operated 270 hospitals and 2281 primary healthcare (PHC) centres. In terms of manpower, there were 38,458 physicians (29.9% were Saudi), 3357 dentists (62% were Saudi), 91,854 nurses (59.6% were Saudi), 2914 pharmacists (90.3% were Saudi) and 53,077 allied health personnel (92.9% were Saudi) [12].

Other government organizations also participate in the provision of healthcare. However, unlike the MOH, healthcare is provided mainly to these organizations' or ministries' employees and their families/dependents. These government sectors include the healthcare facilities of the Ministry of Defence and Aviation (MODA), the Ministry of Interior (MOI), the Saudi Arabian National Guard (SANG), Saudi Arabian Oil Company (ARAMCO) health services, health services in the Royal Commission

Table 16.1 Human resources for health in Saudi Arabia (as of 2014)

Indicator	Number	Rate per 10, 000 of the population
Physicians[a]	81,532	26.6
Pharmacists	22,241	7.23
Nurses	165,324	53.73
Allied health personnel	94,960	30.86
Hospital beds (All sectors)	67, 997	22.1
Primary healthcare centres-MOH	2281	0.74

Data source: Ministry of Health [12]
[a]This includes dentists

for Jubail & Yanbua, Ministry of Education health units and universities teaching hospitals [6, 11]. In 2014, the non-MOH government organization operated 42 hospitals. In terms of manpower, there were 14,328 physicians (47.67% were Saudi), 1099 dentists (69.7% were Saudi), 31,712 nurses (14.1% were Saudi), 2061 pharmacists (66.62% were Saudi) and 53,077 allied health personnel (92.9% were Saudi) [12].

The private sector has grown over the years and is now considered as an important component of the Saudi healthcare system [5, 9]. In 2014, there were 141 private hospitals and 2412 private polyclinics. In terms of manpower in the private sector, there were 28,871 physicians (2.5% were Saudi), 8329 dentists, 17,266 pharmacists (3.3% were Saudi), 41,768 nurses (5.2% were Saudi) and 18,476 allied healthcare professionals (25.7% were Saudi) [12]. Notably, most private sector premises are mainly located in urban cities, particularly in the following two regions: Riyadh and Jeddah. In fact, 24.1% of private hospitals ($n = 34$) are located in Riyadh and 23.4% ($n = 33$) are located in Jeddah. Similarly, for private polyclinics, 35.2% ($n = 848$) and 18.8% ($n = 454$) are located in Riyadh and Jeddah, respectively [12]. However, the growth of this sector is rapid, and the government is encouraging its expansion to cover all regions [13].

The community pharmacy private retail sector represents a major component of the primary healthcare system in Saudi Arabia in general. In 2014, there were 7322 community pharmacies, which were run by 12,506 pharmacists [12]. Table 16.1 summarizes the human resources for health in the country.

16.2 Healthcare Expenditure and Financing

Total health expenditure is steadily increasing, from approximately USD 7.981 billion in 2000 to USD 27.508 billion in 2015 (1 Saudi Riyal (SAR) = 3.75 US Dollar) [14, 15]. General government health expenditures represented approximately 64.77% of the total health expenditure in 2014 [14]. Moreover, financial appropriations from the government general budget to the MOH increased from approximately USD 6.082 billion in 2007 to reach USD 15.996 billion in 2014 [12, 16]. Regarding health funding, in the public sector, healthcare is mainly funded by the government general budget. The Ministry of Health (MOH) and other government

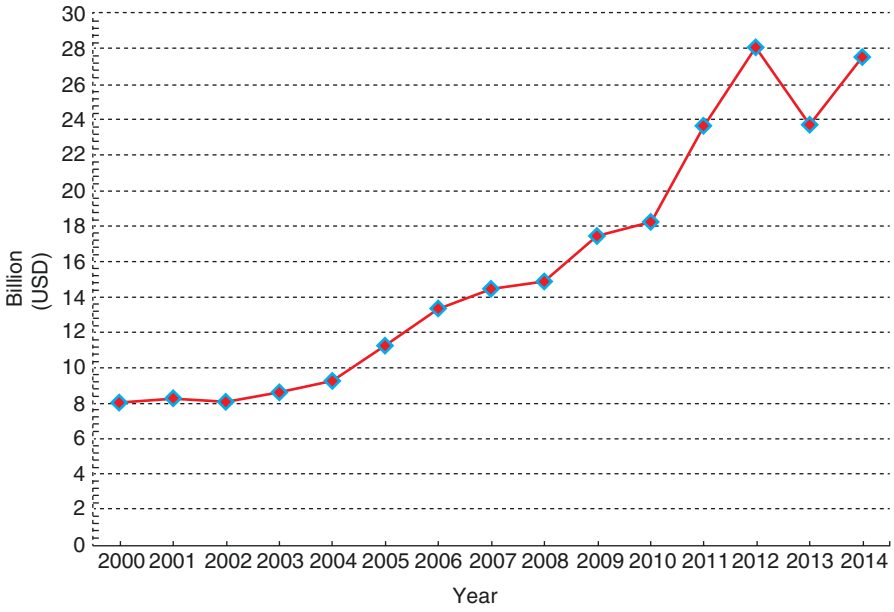

Fig. 16.1 The trend of total health expenditure in Saudi Arabia from 2000 to 2014 (Data source: WHO [15] from 2000–2011 and BMI [14] for 2012–2014)

sectors are provided with yearly financial appropriations from the government general budget. In 2014, the financial allocations to MOH represented 7% of the general government budget [12].

The total private health expenditure increased tremendously from USD 2.230 billion in 2000 to reach USD 9.692 billion in 2014 [14, 15]. In fact, it represents 35.23% of total health expenditure in 2014. Healthcare expenses in the private sector are financed by out-of-pocket payments and private health insurance (e.g., cooperative health insurance). In fact, health expenses in the private sector are currently mainly financed by out-of-pocket payments, as these represented 55.3% (USD 4.689 billion) of the total private health expenditure in 2013 [15]. Figure 16.1 shows the trend of total health expenditure in Saudi Arabia from 2000 to 2014.

16.3 Saudi Pharmaceutical Market

Similar to total health expenditure, pharmaceutical expenditure increased tremendously from USD 4.894 billion (SAR 18.354 billion) in 2011 to reach USD 7.562 billion (SAR 28.366 billion) in 2014. Thus, pharmaceutical expenditure represented approximately 27.5% of total health expenditure in 2014 [14] (Fig. 16.2). The trend of pharmaceutical expenditure in Saudi Arabia from 2011 to 2014 is presented in Fig. 16.3.

Moreover, as shown in Fig. 16.4, the Saudi pharmaceutical market represented approximately 60% of the total pharmaceutical sales of the Gulf Cooperative

Council (GCC) countries in 2014 (the GCC region includes Kingdom of Saudi Arabia (KSA), United Arab Emirates (UAE), Kuwait, Qatar, Oman and Bahrain). Additionally, the Saudi pharmaceutical market is currently the largest market in the Middle East and in the Africa (MEA) region [14, 17–21].

The Saudi market is heavily dominated by original and patented medicine brands. The patented medicines represented approximately 56.2% of the total medicine market and 64.5% of the prescription medicine market by value in 2014 [14]. On the other hand, generic medicines represented 30.9% of the total medicine market and only 35.5% of the prescription medicine market in 2014. Moreover, it is forecasted

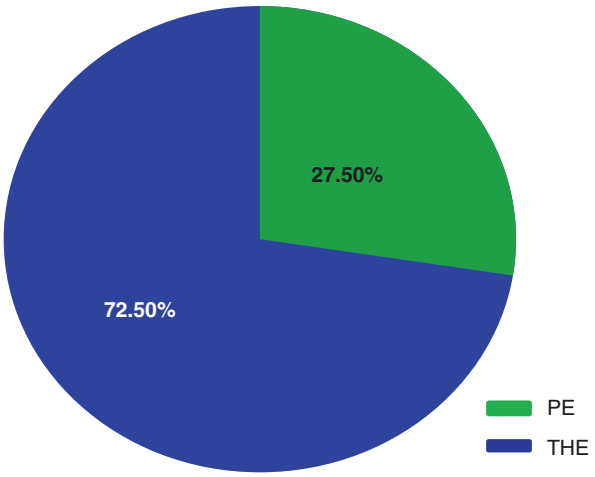

Fig. 16.2 The percentage of pharmaceutical expenditure (PE) in relation to total health expenditure (THE) in 2014

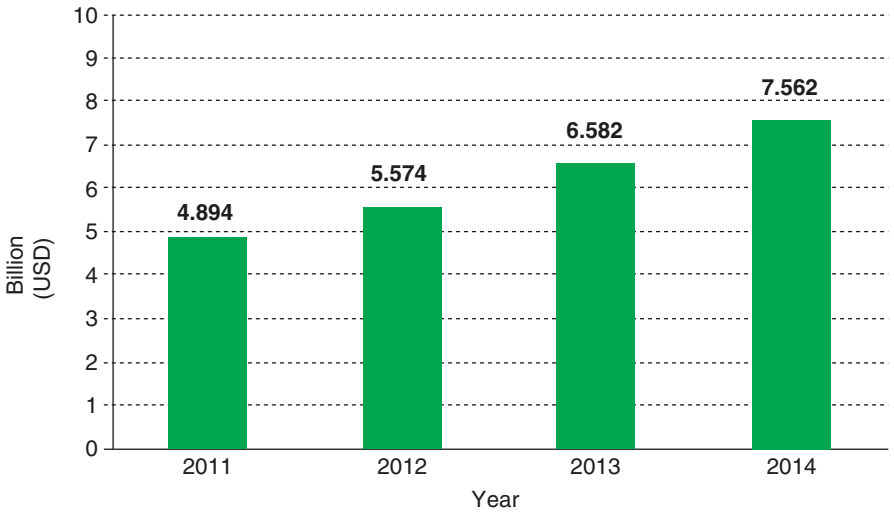

Fig. 16.3 The trend of pharmaceutical expenditure in Saudi Arabia from 2011 to 2014 (Data source: BMI [14])

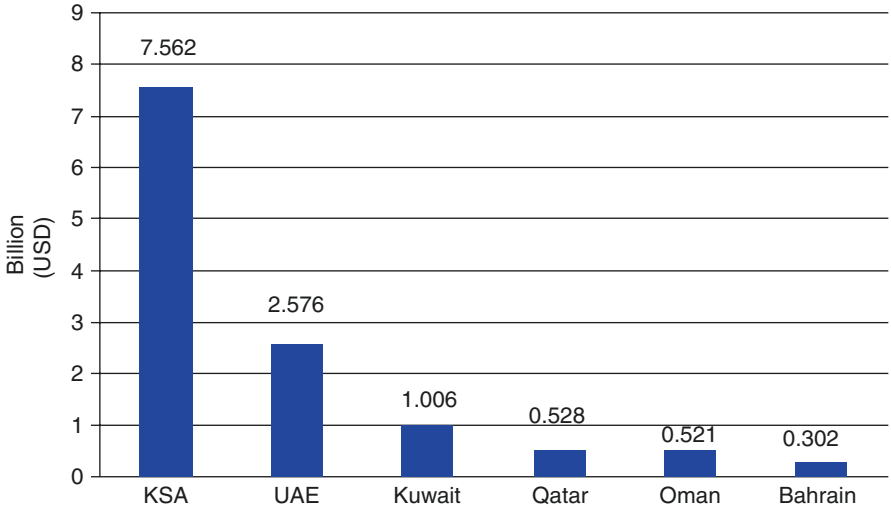

Fig. 16.4 Pharmaceutical expenditure in GCC countries in 2014 (Data source: BMI [14, 17–21])

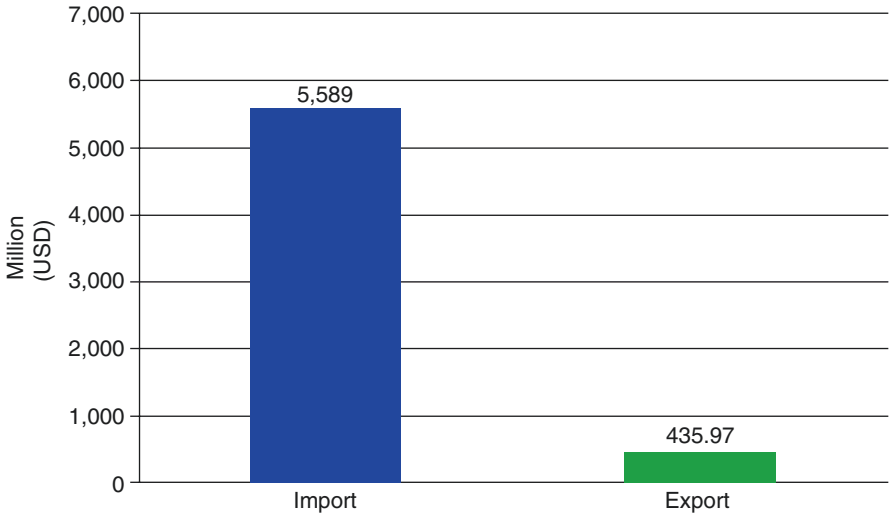

Fig. 16.5 Pharmaceutical trade-import and export (Data source: BMI [14])

that this would reach approximately 32.7 in 2019 [14]. The over-the-counter market represented approximately 13.0% of the market in 2014 [14].

The Saudi medicine market heavily depends on imported medicines (represented USD 5589 million in 2014). However, there is a plan to produce 40% of all medicines locally in the long term. To achieve this, large investments have been started [14]. Pharmaceutical exports currently represent a minor component of the local pharmaceutical industry [14] (Fig. 16.5). However, it is expected to increase from USD 435.97 million in 2014 to reached 981.00 in 2019 [14].

In Saudi Arabia, local pharmaceutical companies produce only approximately 17% of the domestic pharmaceuticals [14]. Moreover, some of the medicines produced by local companies are patented medicines. These medicines are produced through a license from multinational companies [22]. The presence of multinational drug companies is widespread in the Saudi market. The USA and European countries are the major suppliers of medicines to the market. Additionally, several drug companies from the Middle East, such as Egypt, Jordan, UAE and Oman, have a presence in the Saudi drug market [22].

16.4 Regulations and Registration of Medicines in Saudi Arabia

The Saudi Food and Drug Authority (SFDA), established in 2003, is the national regulatory body responsible for the regulation, registration and approval of medicines in Saudi Arabia. Hence, one of its main objectives is to ensure and observe the effectiveness, safety and quality of medicines [23]. In addition, it is responsible for developing and implementing policies and procedures related to medicines. In addition to its regulatory role, it is tasked with consumer awareness on all matters related to medicines [23]. Historically, the Ministry of Health (MOH) was the regulatory body responsible for the regulation, approval and registration of medicines in the country. In 2003, the SFDA was established as an independent body that directly reports to the President of the Council of Ministers. It stated its regulatory role in two phases. In the first phase that lasted 5 years, the SFDA developed and reviewed all policies, guidelines, regulations and standard specifications related to food, medicines and medical devices. In the second phase, the SFDA started its regulatory and supervisory tasks in 2008 and started receiving submissions for the approval and registration of medicines [23]. Now, the SFDA is responsible for all aspects related to medicines and pharmaceutical policies in the country. The functions of the SFDA include marketing authorization (registration), regulatory inspection, import control (i.e., authorization to import medicines), licensing (licensing of manufacturers, importers, wholesalers and distributors), market control and quality control (e.g., quality control testing of the products), medicine advertising and promotion, controlled medicines, clinical trials control and pharmacovigilance [24].

The SFDA applies strict requirements and a rigorous registration system to ensure the efficacy, safety and quality of medicines [25, 26]. In fact, the registration system in Saudi Arabia applies the most stringent policies in the Middle East [27]. In Saudi Arabia, manufacturers and drug companies must seek approval from the SFDA before marketing any medicine. Moreover, manufacturers and drug companies must first register with the SFDA to register their products in the country [28].

For example, regarding generic medicines' approval and registration, as shown in Fig. 16.6, according to the Regulatory Framework for Drug Approvals Version 5 [26],

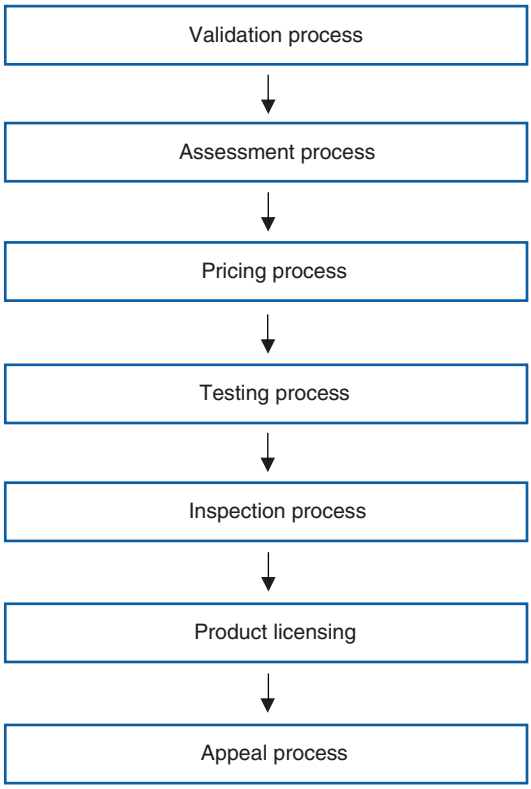

Fig. 16.6 The generic medicine approval process for granting market authorization (Data source: SFDA [26])

generic medicines will be assessed over a six-process procedure before being granted market authorization (MA) as follows:

- Validation process: in this process, the SFDA will validate and evaluate the drug file in terms of the completeness and accuracy of all information according to the SFDA generic medicine market authorization requirements and procedure. At this stage, the manufacturer must provide samples of the product for testing in a further step.
- Assessment process: in this process the product file will be assessed by two groups; quality and efficacy groups in the SFDA. The product file can proceed to the next step only after being recommended for approval and successfully passing the quality and efficacy assessment; otherwise it will be rejected.
- Pricing process: the pricing unit according to the SFDA pricing rules will determine the price of the product.
- Testing process: the drug samples received from the drug company will be sent to the laboratory for testing.
- Inspection process: in this process, the SFDA will check the product manufacturing line to ensure compliance with current good manufacturing practice (GMP).

It must hold a valid certificate from the Saudi MOH or SFDA; otherwise, an inspection team will be sent to check the line before granting the approval.
- Product licensing: This is the final stage in which the product will be granted marketing authorization (MA) based on reviewing all the reports (quality and efficacy assessment reports, pricing report, testing report, GMP inspection report and company registration) by the SFDA registration committee.
- Appeal process: the company has the right to appeal within 30 days of the final decision by the SFDA.

After marketing, the National Pharmacovigilance Centre (NPC), under the umbrella of the SFDA, is responsible for post-marketing drug surveillance.

In summary, Saudi Arabia has a well-established drug regulatory framework. Moreover, the drug regulatory authority (i.e., the SFDA) is an autonomous agency with established responsibilities and powers by the Law. There are regulations and policies for each aspect related to medicines. These are available publicly at the SFDA website: http://www.sfda.gov.sa/en/drug/drug_reg/Pages/default.aspx?news=Main [29]

16.5 Pricing Policy of Medicines

The medicine prices in Saudi Arabia are strictly controlled. Moreover, article no.14 of the Pharmacy, Pharmaceutical Institutions and Pharmaceuticals Law [30] stipulated that any drug product must be priced before marketing and the price should be written on the product package in a clear way [30]. Currently, the SFDA is the national regulatory body responsible for registering, approving and pricing medicines. In fact, pricing is one of the essential steps during the registration process [26].

To illustrate the pricing system, the pricing of generic medicines will be discussed in this chapter. The pricing of generic medicines is based on two guidelines, namely the common pricing criteria and the pricing rules of generic medicines. The common pricing criteria include considering the following factors when pricing any medicine [31]:

- Ex-factory price in the country of origin (COO)
- Wholesale price in the COO
- Public (retail) prices in the COO and other countries where the product is marketed
- Cost, insurance and freight (CIF) price to Saudi Arabia in the COO currency
- CIF prices to countries in which the product is marketed (currently there are 30 reference countries, namely Algeria, Argentina, Australia, Bahrain, Belgium, Canada, Cyprus, Denmark, Egypt, France, Germany, Greece, Holland, Hungary, Ireland, Italy, Japan, Jordan, Kuwait, Lebanon, New Zealand, Oman, Portugal, South Korea, Spain, Sweden, Switzerland, Turkey, UAE and the United Kingdom)
- The price in official pricing references (if available)
- Therapeutic significance of the product

- Pharmacoeconomic studies of the product (if available)
- Prices of similar medicines that are registered in Saudi (if available)
- The proposed price by the drug company in Saudi

Based on the common pricing criteria, the lowest price should be selected, and in all cases, the pricing rules for generic medicines should be considered. The SFDA pricing rules for generic medicines stated that the price of the first generic medicine to be marketed should be 35% lower than the price of the original brand medicine. After that, the price of the second generic medicine to be marketed should be 10% lower than the first generic medicine registered on the market. Then, when registering any generic medicine, it should be at least 10% lower than the price of the last generic medicine registered on the market. After the fourth generic medicine, the price will be fixed [31].

For original patented medicines, their prices are fixed based on common pricing criteria. Moreover, when the first equivalent generic medicine is registered, the price of the original medicine is reduced by 20% [31].

Thus, based on the common pricing criteria and pricing rule of generic medicines, the lowest price should be selected and fixed as the price of the generic medicine. This pricing system has led to significant differences in prices between the original brand medicines and generic medicines. Moreover, there is a significant difference in price among the generic medicines for the same original brand medicine as shown by the study conducted by Alnutafy [32]. Tables 16.2 and 16.3 illustrate the prices of simvastatin and ciprofloxacin as examples.

Table 16.2 The cost of simvastatin 40 mg (30s)

Trade name Price (SAR)	Price difference of brand to generic (SAR)	Price difference of generic to brand (%)
Zocor 215.45	–	–
Simvaten 89.40	126.05	140.99
Simvast 80.45	135.05	167.87
Vasta 72.40	143.05	197.58
Simva 65.15	150.3	230.70
Simvahexal 58.65	156.8	267.35

Data source: SFDA Official List of Registered Drugs and Herbal Products [33]

Table 16.3 The cost of ciprofloxacin 500 mg (10s)

Trade name Price (SAR)	Price difference of brand to generic (SAR)	Price difference of generic to brand (%)
Ciprobay 101.35	–	–
Cipromax 62.05	39.30	63.34
Ciproxen 50.25	51.10	101.69
Omacip 33.05	68.30	206.56
Ciproflacin 21.05	80.30	381.47
Ciprolet 9.70	91.65	944.85

Data source: SFDA Official List of Registered Drugs and Herbal Products [33]

16.6 Access to Healthcare and Medicines

In the public healthcare sector, healthcare services and medicines are provided free of charge to all citizens and expatriates working in the government sector [6, 9, 34]. However, for several reasons (e.g., quality of care, long waiting times), it is common for those who are entitled to free healthcare to seek treatment and medical care at private hospitals and polyclinics. In 2011, it was estimated that 61.6% (n = 26,327,464) of those who received care in the private sector were Saudis, even though they were entitled to free care in the public sector [16].

Because expatriates working in the private sector are not entitled to free healthcare in the public sector, the Cooperative Health Insurance Act was passed in 1999. The aim of this insurance was to provide health coverage for expatriates and their families or dependents who are working in the private sector in the kingdom. In this insurance scheme, it is compulsory for all employers to purchase health insurance for their employees and their families in the kingdom [35]. The insurance covers all medical examinations and consultations, medical treatments, medicines, vaccines, child and maternity care, laboratory investigations, X-rays and hospital admissions and hospitalizations, including those related to pregnancy, delivery and surgical operations. However, some conditions are excluded from the coverage. General health examinations, treatment for sexually transmitted diseases (STDs), HIV and AIDS medicines, treatment for hair loss, contraceptives, treatment for infertility, impotence, acne and any treatment related to obesity are not covered in the executive regulation of this insurance [36].

Regarding access to medicines, according to the Health Professions Act 2005, medicines can be kept and only sold in pharmacies. Moreover, by law, the pharmacist is the only healthcare professional who is authorized to dispense medicines. It is also prohibited for other healthcare professionals to dispense or keep medicines in their clinics or offices, except for emergency medicines [37]. Therefore, in the public sector, each hospital has its own pharmacy services department. A pharmacy department usually has an inpatient pharmacy, outpatient pharmacy and emergency pharmacy. For primary healthcare (PHC) centres, there is one pharmacy in each PHC centre. Similarly, in private hospitals, medicines are provided via the pharmacy department in the hospital. However, private polyclinics do not have a license to open pharmacies as part of the polyclinic. Therefore, patients who visit polyclinics need to get their medications from community pharmacies. For this reason, there are 7322 total community pharmacies in 2014 and they are run by 12,506 pharmacists [12].

16.7 Pharmaceutical Procurement and Distribution

In the public sector, the procurement of medicines is both centralized and decentralized. In the centralized system, which is the main procurement system, annual tenders are developed by government organizations and sent to the procurement

agency in the MOH. Recently, the government has established a major governmental company called a National Unified Procurement Company (NUPCO), which is responsible for the central procurement, storage and distribution of medicines and medical equipment to all hospitals and healthcare facilities in the public sector [38]. Beside the central tenders, the government organizations can procure some medicines via direct purchasing [24]. In fact, there is a written public procurement policy. Moreover, quality assurance of the procurement process is maintained through the pre-qualification of products and suppliers and sample testing of the products. The tender methods in public sector procurement include national competitive tenders, international competitive tenders and direct purchasing. In the public procurement, locally produced medicines are prioritized by legal provisions [24].

At the national level, the Central Medical Store facilitates the distribution of medicines in the government system. To ensure the quality of products during the distribution, national guidelines on Good Distribution Practices (GDP) are required to be followed. Moreover, the wholesalers and distributors in the public sectors should be GDP certified [24].

In the private sector, the procurement and distribution of medicines are processed via purchasing from wholesalers and distributors for the private sector. Similar to the public sector, there is a list of GDP-certified wholesalers and distributors in this sector [24].

16.8 National Health Policy Framework

In Saudi Arabia, there is a National Health Policy (NHP) and a National Medicines Policy (NMP). The implementation of pharmaceutical policy and the policies addressing medicines are monitored and assessed by the Saudi FDA. The Saudi NMP covers several components, as follows [24]:

- Selection of essential medicines
- Medicine financing
- Medicine pricing
- Medicine procurement
- Medicine distribution
- Medicine regulation
- Pharmacovigilance
- Rational use of medicines
- Human resource development
- Research
- Monitoring and evaluation
- Traditional medicine

16.9 Medicine Use in Saudi Arabia

16.9.1 Essential Medicines and Standard Treatment Guidelines

A National Essential Medicines List (NEML) exists in Saudi Arabia. The NEML had 183 medicines in its latest version in 2011. Moreover, there are Standard Treatment Guidelines (NSTGs) for the most common illnesses. These guidelines are produced and/or approved by MOH. In fact, NEML is aligned with these NSTGs [24]. Additionally, recently, the Saudi Center for Evidence-Based Healthcare (EBHC) under the umbrella of Ministry of Health published clinical practice guidelines (CPGs) for several diseases, such as stroke, atrial fibrillation, deep vein thrombosis and osteoporosis. However, currently, there are only ten evidence-based guidelines published by the EBHC [39].

16.9.2 Use of Generic Medicines

The Saudi medicine market is heavily dominated by original and patented medicine brands. On the other hand, utilization of generic medicines is relatively low, and there is much room for improvement [14]. Therefore, to confront the escalating healthcare cost in general and pharmaceutical expenditures, it is particularly essential to promote the use of generic medicines in the Saudi healthcare system. In fact, according to the WHO [40], a national medicine policy should ensure not only the availability and accessibility to high-quality, safe and effective medicines but also promote the cost-effective use of medicines to healthcare professionals and consumers. Therefore, the promotion of generic medicines is recommended to be included as part of the national medicine policy [41]. This step has helped to achieve the goal of a comprehensive and sustainable healthcare system in developed countries [42], whereas have improved affordability and accessibility of medicines in developing countries [43].

In Saudi Arabia, generic substitution by pharmacists is legally allowed. According to article no.23 of the Health Professions Act [37], pharmacists are allowed to perform generic substitution. Moreover, as stipulated by this article, the prescriber's permission or approval is not a legal requirement but patient consent is required. However, the executive regulations of this act [44] excluded Narrow Therapeutic Index (NTI) drugs from substitution. Hence, pharmacists are not allowed to perform generic substitution for NTI drugs [44].

Generic substitution is not a common practice in community pharmacies in Saudi Arabia. However, it has been noted that the selective generic substitution is practiced by some community pharmacists [45, 46]. It is also important to note that prescribing generic medicines by physicians is still relatively low compared to other countries [47].

Therefore, generic medicines should be promoted through a coherent generic medicine policy that involves all relevant stakeholders, including pharmacists, physicians and patients. Additionally, because there are misconceptions about generic medicines among some physicians [47], pharmacists [45] and patients [48], there is a need for educational interventions and promotional campaigns to promote the quality use of generic medicines.

16.9.3 The Role of Community Pharmacists in Quality Use of Medicines

The current community pharmacy practice is business oriented; this in turn affects the society's image of community pharmacists as a healthcare professional [49, 50]. A study conducted by Bawazir showed that 56.1% of consumers considered community pharmacists to be more concerned with business as compared to health [51]. However, the role of community pharmacists in educating the patients about their medicines is essential. This is particularly important in the context because the studies have shown that the general public lacks adequate knowledge about their medicines, including simple information, such as the names of their medicines. A study conducted by Khan and Ibrahim reported that only approximately 30% of consumers were familiar with the names of the medicine they requested. It is not uncommon for the pharmacist to try to guess the medicine by asking the patient about the shape, colour and/or price, in case the patient does not know the name of the medicine [52].

16.9.4 Dispensing Medicines Without Prescriptions

In community pharmacies, prescription-only medicines (POM), including antibiotics, antihypertensive drugs antidepressants and other prescription medicines, are provided over-the-counter without a prescription. Although legally not allowed, it is a common phenomenon and has been a point of concern in Saudi Arabia over the last three decades [52–57]. A study conducted in Riyadh by Abdulhak et al. [53] by using simulated patients showed that 77.6% of community pharmacists provided antibiotics without a prescription. This indicated that dispensing medicines and particularly antibiotics without prescription is still a serious issue in community pharmacies in Saudi Arabia. This leads to irrational use of medicines and especially in case of antibiotics, it increases antimicrobial resistance. Antibiotics use is very common in Saudi Arabia especially when compared to other countries [58]. Therefore, this necessitates the stricter enforcement of the laws governing medicines sales and dispensing.

16.10 Conclusions and Way Forward

Saudi Arabia has a well-developed national medicine policy as well as a well-established drug regulatory framework. Moreover, there is a well-defined pharmaceutical pricing policy, and medicine prices are strictly controlled. The Saudi pharmaceutical market is the largest market in the Middle East and in the African (MEA) region. Moreover, it is heavily dependent on imported medicines and dominated by patented and original medicines.

Due to lack of implementation of some policies and regulations, there are several issues regarding rational use of medicines that need to be addressed. These include unrestricted access to medicines at the community pharmacies. Moreover, the involvement of community pharmacists in promoting rational use of medicines is currently limited. Additionally, despite the rapid escalation of pharmaceutical expenditure, generic medicines are still underutilized in the healthcare system.

The way forward is to ensure that all the policies and regulations are fully implemented. More investments are needed to boost the local pharmaceutical industry. Furthermore, there is a need to promote the use of generic medicines to contain the steadily increasing pharmaceutical expenditures. Finally, appropriate interventions, including educational campaigns, are needed to promote the rational use of medicines in the country.

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Chapter 17
Pharmaceutical Policy in Trinidad and Tobago

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Abstract This chapter describes the pharmaceutical policy landscape in Trinidad and Tobago. The Republic of Trinidad and Tobago is a twin-island democratic nation located off the north coast of Venezuela in the Caribbean. The country is experiencing an epidemiological transition with a decline in the incidence of communicable diseases, and increases in chronic, noncommunicable diseases. Therefore, it is critical that pharmaceutical polices are reflective of our new health realities.

This chapter sets the base for examining the country's polices by exploring its health and regulatory system. It takes an in-depth look at the processes, which are in place and identifies gaps and best practices, which takes place in Trinidad and Tobago. The authors delve into identifying the county's procurement and distribution system of pharmaceuticals within the public sectors and how are these processes financed.

The role of the pharmacist and prescribing practices of doctors are also examined with a view to gain an understanding of the entire system. Trinidad and Tobago has significant policies, processes, and agencies in place to encourage best pharmaceutical practices. However, there continues to be gaps with implementation of some policies and processes, which hinders compliance. This chapter finally details these challenges.

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17.1 Introduction

The Republic of Trinidad and Tobago is a twin-island democracy located off the north coast of Venezuela, in the Caribbean. The country achieved independence from Britain in 1962, and became a republic in 1976. However, it remains a member of the British Commonwealth. Trinidad and Tobago has maintained the Westminster style of parliamentary governance, with the election of its President through an Electoral College of members of the House of Representatives and the Senate. The Judiciary is independent of the parliament, as upheld by the constitution, and the administration of Tobago is under the purview of the Tobago House of Assembly [1].

The population of Trinidad and Tobago is 1.33 million, with 4% residing in Tobago. There is an equal proportion of male and female residents, and a variety of ethnic groups: East Indian 41%, African 40%, and other groups 19% (Chinese, European, and Middle Eastern). In 2014, life expectancy at birth was estimated at 69.42 years for males and 75.24 for females, which is similar to estimates of some developed countries [2].

Trinidad and Tobago has maintained a reasonably stable economy, which relies heavily on oil and gas exports [3]. In spite of this stability, there are pockets of poverty. The 2005 Survey of Living Conditions reported that 16.7% of the population was poor [4]. The socioeconomic status of people is positively associated with the level of education achieved. Education is provided free of cost by the government from primary to tertiary level, with high levels of enrolment at primary (97%) and secondary (75%) educational institutions. This is reflected with high literacy rate of 98.8%, reported in 2011 [2]. The total expenditure on health per capita as of 2012 is US$ 1663. The total expenditure on health as percentage of Gross Domestic Product (GDP) is 5.5% [5].

The developmental challenges identified are diverse, but the priority challenges may be classified by critical areas including planning and policy development of the regulatory framework; health information systems, epidemiological surveillance, data analysis, and the use of information for decision making. Human resources in the public and appropriate competencies; the development of health system and services; and the coordination, follow-up, and networking at the local level for regional and global commitments are some other issues, which are being identified [1, 6]. Areas that require additional support include review of pharmaceutical evidence, health technology assessment, information technology, drug utilization research, laboratory capacity, and formulary review.

In 2005, the Government of Trinidad and Tobago made a policy decision to achieve the status of a developed nation by 2020. The country has developed a strategic framework to implement this vision and a separate subcommittee on health was established. The mission statement articulated by this subcommittee was the creation of a nation of individuals, families, and communities empowered to achieve and sustain the highest standards of health and well-being through the provision of efficient, effective, equitable, and collaborative services that support good health.

Seven goals for health were identified and some notables ones were related to improve the general health status of the population, reducing the communicable and noncommunicable diseases, and improving the quality and performance of health-care services [7].

This chapter aims to analyze the pharmaceutical policy in Trinidad to identify scope for improvement. It begins with an overview of Trinidad's health system and pharmaceutical situation. A section follows on regulatory environment, highlighting the function of Trinidad's medicines regulatory authority, the drug quality control system, the pharmacovigilance and situation of substandard and counterfeit medicines in the country. This chapter continues with sections on the supply system, financing and use of medicines, analyses the problems within the pharmaceutical sector, as well as the issues impacting on rationale medicines use in the country.

17.2 Health Indicators

Trinidad and Tobago is experiencing a transition with reductions in the incidence of communicable diseases, and a rise in chronic diseases. Within the Caribbean, Trinidad and Tobago has reported the highest morbidity and mortality rates for chronic noncommunicable diseases (CNCDs) [8]. Ischemic heart disease was the leading cause of death in 2012, followed by diabetes mellitus and stroke [9]. Table 17.1 identifies the top ten causes of death in Trinidad and Tobago in 2012.

Complications due to prematurity and congenital anomalies are the primary causes of death in children under 5 years (see Table 17.2).

Trinidad and Tobago has maintained a high Human Development Index (0.772), and was ranked 64th out of 169 countries in the 2015 Human Development Report [10]. There have been improvements in some health indicators. A comparison of Millennium Development Goals achieved in 1990/2000 and 2012 indicates improvements in infant mortality, maternal mortality, deaths due to HIV/AIDS (see Table 17.3) [10].

Table 17.1 Top ten causes of death in Trinidad and Tobago [9]

Cause of death	Percentage of deaths in year 2012
Ischemic heart disease	15.3
Diabetes mellitus	14.6
Stroke	7.5
Interpersonal violence	4.9
Hypertensive heart disease	4.2
Prostate cancer	2.9
Lower respiratory infections	2.2
Kidney diseases	1.9
Road injury	1.9
Colon and rectum cancers	1.9

Table 17.2 Distribution of causes of deaths in children under 5, 2013 [9]

Cause of death	Percentage of total
Prematurity	28
Congenital anomalies	26
Other causes	18
Birth asphyxia	9
Acute respiratory infections	7
Injuries	7
Neonatal sepsis	4
HIV/AIDS	1
Diarrhea	1
Malaria	0
Measles	0

Table 17.3 Millennium Development Goals (MDGs) [10]

Indicators	Statistics	
	Baseline (1990/2000)[a]	2012/2013[b]
Under-five mortality rate (per 1000 live births)	31	21
Maternal mortality ratio (per 100,000 live births)	89	84
Deaths due to HIV/AIDS (per 100,000 population)	41.6	15.3
Deaths due to malaria (per 100,000 population)	0.0	0.0
Deaths due to tuberculosis among HIV-negative people (per 100,000 population)	1.9	2.2

[a]1990 for under-five mortality and maternal mortality; 2000 for other indicators
[b]2012 for deaths due to HIV/AIDS and malaria; 2013 for other indicators

17.3 Health Systems and Services

The Ministry of Health is the prime authority charged with oversight of the entire health system in Trinidad and Tobago. The Ministry plays a significant role in the protection of the population's health and in ensuring that all organizations and institutions that produce health goods and services conform to standards of safety. It also provides effective leadership for the health sector by focusing on evidence-based policy making, planning, monitoring, evaluation, collaboration, and regulation. The Ministry of Health is responsible for establishing national priorities for health and ensuring an environment for the delivery of a broad range of high quality, people-centered services from a mix of public and private providers [11]. Responsibility for the provision of healthcare services in Trinidad and Tobago was devolved from the Ministry of Health to Regional Health Authorities (RHAs) with the passing of the Regional Health Authorities Act No. 5 in 1994 [11]. RHAs are autonomous bodies that operate health facilities in their respective regions. Presently, five [5] RHAs deliver public healthcare services to the population of Trinidad and Tobago. They are North West Regional Health Authority (NWRHA), North Central Regional Health Authority (NCRHA), South West Regional Health Authority (SWRHA),

Eastern Regional Health Authority (ERHA), and Tobago Regional Health Authority (TRHA) [11].

While the Ministry of Health does not manage health facilities directly, it plays a key role in ensuring that they are properly run, primarily through the development of policies, goals, and performance indicators for the RHAs. The Ministry also allocates resources to the RHAs to finance their operations [11].

Trinidad and Tobago has been a member state of both the Pan American Health Organization (PAHO)/World Health Organization (WHO) and since 1963 [12]. It receives programmatic technical cooperation from these organizations. PAHO/WHO has developed a technical cooperation (TC) program in close collaboration with the Ministry of Health. This is based on an assessment of the health situation and reflects the health priorities of the Government of Trinidad and Tobago. The selected strategic priorities under this program are (i) strengthening the health system and services, (ii) improving the health status of the population, and (iii) reducing threats to health [12].

17.4 Health Personnel and Infrastructure

In Trinidad and Tobago, there are approximately 3500 physicians, 1050 registered pharmacists, and 5500 nursing personnel registered with their respective boards. The ratio of doctors to nurses and midwifery personnel is 1:3. There are approximately 21 hospitals (11 public, 10 private) and 27 hospital beds per 10,000 population in the country [13].

Health professions education at the tertiary level is offered by the Faculty of Medical Sciences (FMS), The University of the West Indies (UWI), St. Augustine campus, situated at the Eric Williams Medical Sciences Complex, Champs Fleurs. The faculty comprises of schools of medicine, dentistry, veterinary medicine, pharmacy, and nursing, and a unit of optometry. The FMS UWI offers undergraduate and postgraduate degrees in the health professions, which allow interested graduates to develop practical and research skills in various medical and allied disciplines including public health. The curricula of each program are based on problem-based learning approaches and are periodically reviewed for quality assurance. Research priorities are determined by local and regional needs with an international prospective through the development of research collaborations with renowned research institutions across the world [14].

17.5 Country Regulatory Environment

In Trinidad and Tobago, the Drug Inspectorate Division (DID) and the Chemistry Food and Drug Division (CFDD) under the Ministry of Health (MOH) are responsible for the regulation of pharmaceutical practices. The CFDD monitors all aspects

of import, manufacture, storage, distribution, sale, fraud, and deception in labeling and marketing, and the disposal of food and drugs. This process ensures the quality, purity, and safety of food and drugs imported or manufactured in Trinidad and Tobago [13].

17.5.1 Marketing Authorization/Registration of Pharmaceuticals

The Blue Book (WHO 2011) describes Marketing Authorization/Registration (MA) as the legal permission granted by the local regulatory authority for a product to be put on the market. Product registration involves evaluating technical and administrative data submitted about a product [15]. It aims to ensure that pharmaceuticals have been adequately tested and evaluated for safety, efficacy, and quality, and that the product information provided by the manufacturer is accurate.

Local regulations require marketing authorizations for all new pharmaceuticals on the market, and existing marketing authorization holders (MAH) are required to provide information about any variations to existing products. However, there is no legal requirement for expiry or renewal of market authorization. In addition, a Summary of Product Characteristics (SPC) of each registered medicine is required to be published by the government in *The Gazette*. Although the registration process is computerized, it is unknown how many pharmaceutical products are registered in Trinidad and Tobago. Moreover, the CFDD is not legally required to publish a list of registered pharmaceutical products. Although provisions are made to waive the cost for essential medicines, there are still no mechanisms for the exception or waiver of registration. Therefore, these medicines undergo a similar waiting period of 3 months for issuance of authorization [13, 15].

17.5.2 Inspection

Inspections are used to monitor the quality of products in the distributing channels to eliminate the threats posed by the infiltration of counterfeit medicines, and to ensure that medicinal products being manufactured are compliant with the Good Manufacturing/Distributing Practices (GMP/GDP).

Pharmaceutical inspections are conducted annually, under the control of the CFDD. Legal provisions permit annual inspection of all premises where pharmaceutical activities are performed. This is also a prerequisite for licensing of public and private facilities. Inspection works in hand with the marketing authorization as well as licensing by the inspection of samples of medicines to ensure quality and safety for the consumers [13].

17.5.3 Import Control

The import control ensures the quality of medicines by preventing the infiltration of illicit products into the supply system. The marketing surveillance activities should be complemented by administrative procedures aimed at ensuring that pharmaceutical products are imported only if they have been authorized or have received an import license before reaching the country [16].

The importation of medicines requires prior authorization, which is granted by the CFDD. Laws also allow for sampling of imported products for testing. In addition, legal provisions are in place, requiring import of medicines through authorized ports of entry as a means of controlling and monitoring of import activities. In addition, there are other mechanisms in place to prevent illegal import of medicines into the country by having inspectors posted at import stations [13].

17.5.4 Licensing

Licensing entails the approval of a product for sale once it has met the criteria of effectiveness and safety. The medicine should be made to the standard specified in the official British Pharmacopoeia, with all clinical information required to use it appropriately and to be provided as part of the packaging and labeling.

Pharmaceutical manufacturers, importers, distributers, and wholesalers are required to obtain a license before becoming operational. In addition, local and international manufacturers, as well as wholesalers/distributors must adhere to Good Manufacturing Practices (GMPs) and Good Distribution Practices (GDPs), respectively. However, the Trinidad and Tobago government does not publicly publish these GMP/GDP guidelines [13].

17.5.5 Quality Control

Quality Control activities are implemented to ensure that medicines are safe, of high quality, and demonstrate therapeutic efficacy through testing and reporting of defects to the regulatory authority prior to distribution and use by the public.

Within the CFDD, the quality of medicines is tested via an in-house laboratory. In addition, the Caribbean Regional Drug Testing Laboratory (CRDTL) is also available for the testing of pharmaceuticals. Products are sampled and tested in response to complaints or problem reports, and for postmarketing surveillance. However, the results of the tests are not made publicly available [13].

17.5.6 Market Control

Market control involves the monitoring of the quality and safety of medicines by ensuring that dangerous, low-quality or counterfeited drugs do not reach the consumer. In Trinidad and Tobago, The Dangerous Drugs Act of 1991 governs the control of the pharmaceutical market in the country [17]. These laws primarily address postmarketing surveillance, which aids in detecting products that do not meet the requirements of the respective compendia, or the manufacturer's specifications [17].

17.5.7 Medicines Advertising and Promotion

In Trinidad and Tobago, there are laws regarding medicines advertising and promotion including prescription medicines [13]. The promotion and advertisement of medicines is governed by the Medicines Regulatory Authority under the Food and Drug Act, which prohibits the deception or misleading of the general public with regards to drugs and medicines. The act also has legal provisions relating to the maintenance of the standard of a drug when advertising or promoting. In addition, provisions exist in the control of promotion or advertising of prescription medicines only [11]. These laws are generally adhered to. There are no guidelines or regulations concerning nonprescription medicines. The PAHO/WHO report also stated that the preapproval for medicines, advertisement, and promotional material is not a requirement.

17.5.8 Clinical Trials

In Trinidad and Tobago, there are no laws that require authorization for the conduct of clinical trials, but ethical review of proposed human research is undertaken by institutional review boards of various health facilities and universities [13].

17.5.9 Pharmacovigilance

In Trinidad and Tobago, legal provisions exist for pharmacovigilance practices, and for marketing authorization holders to continuously monitor the safety of their products, and report to the regulatory authority. There is an official standardized form used for reporting adverse drug reactions (ADRs); however, in practice it is not routinely used and the reporting practice is not very common [13, 18].

17.5.10 Counterfeit Medicines

In Trinidad, there are legal frameworks that govern the import and sale of pharmaceuticals [19]. Within these frameworks, there is no provision for parallel importation [19]. Yet, there exists an informal, parallel trade in pharmaceutical supply chain management. Traders involved in this practice are known as suitcase traders. These suitcase traders are not authorized distributors of medicines, but there are published reports that they procure medicines at lower costs than the authorized agents [19–22]. Pharmacy owners may assume that they are authentic suppliers, and the medicines distributed by them have passed the necessary inspections of the regulatory bodies, i.e., Customs & Excise and Chemistry, Food and Drugs Divisions. However, this may not be necessarily true. This practice has resulted in unauthorized agents importing medicines not registered for use in Trinidad [22].

17.5.11 Supply and Distribution in Trinidad and Tobago

The tendering process is a process whereby suppliers are invited to send in their requests for supplying goods and services. The National Insurance Property Development Company Limited (NIPDEC) conducts an open and competitive tendering process annually for supplies for the list of vital, essential, and necessary (VEN) medicines [23]. Invitations to tender commence on May 1 and extend up to 3–5 weeks. The deadline is very specific; it has a date and time. Once a request for tender is made, all interested suppliers must submit a tender electronically within 3 weeks for pharmaceuticals and within 5 weeks for nonpharmaceuticals. With respect to nonpharmaceuticals, samples must be provided [23].

All tenderers are required to be registered with NIPDEC and pay an application fee of $300 (Trinidad and Tobago dollars, TTD) before an application could be processed. Following submission, each bid is evaluated by the Ministry of Health's Drug Advisory Committee, which includes representatives of the Regional Health Authorities, and pharmaceutical specialists for quality and product specifications. The tender is awarded to the supplier that meet the product-specific criteria, and who guarantee the most efficient delivery at a lowest price. The results of tender are usually published at the end of September and the procurement cycle extends over a 1-year period from October to September [23] (Figs. 17.1 and 17.2).

In the private sector, the list of drugs to be acquired is determined by the pharmacy manager, with potential input from other pharmacists, where necessary. Medicines and medical supplies are procured from local distributors, who obtain their products from foreign manufacturers. The government, through NIPDEC central medical stores, also distributes chronic disease medicines at no cost to patients, via private pharmacies enrolled in the Chronic Disease Assistance Programme (CDAP) [23–25] (Fig. 17.3).

In the public sector, any medicine to be purchased must appear on the Ministry of Health's formulary. The pharmaceutical division of the NIPDEC manages the

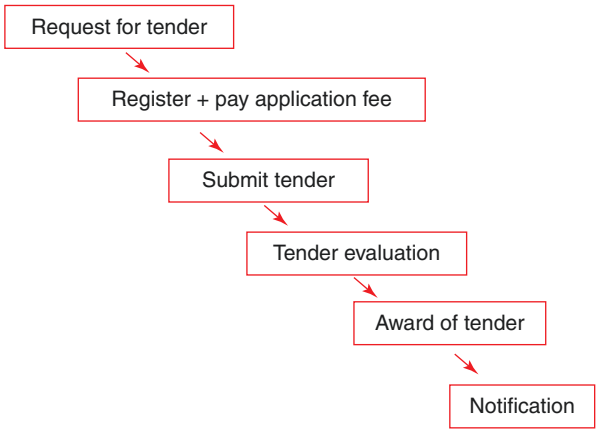

Fig. 17.1 The tendering process in Trinidad and Tobago

procurement of pharmaceuticals for the public sector, under contract with the government of Trinidad and Tobago. This division liaises with the local agents of foreign manufacturers (drug distributor companies) who have successfully tendered to supply certain pharmaceuticals. The supplier having won the tender will be able to supply that drug to the government for a period of 1 year until tendering is done again. There are pre-set bulk re-order times in the public health sector based on the patterns of drug consumption at each facility [23, 25].

17.6 Medicines Financing

Trinidad and Tobago operates under a two-tier healthcare system, for both private healthcare and public healthcare facilities. Public healthcare is free to everyone in Trinidad and Tobago, and is funded via taxes [11]. Healthcare services are provided on a walk-in basis, with estimated yearly expenditure of approximately 1.3 billion USD [26]. The Ministry of Health is responsible for administration of policy in the health sector, whereas delivery of health services is administered by the Regional Health Authorities (RHAs) [11]. In addition to policy development, the Ministry of Health is also involved in regulation, financing, monitoring and evaluation, and research related to health and its commodities. Within this context, the government is developing the National Health Service in which a package of services is delivered to the public, along with a suitable financing strategy [25].

17.7 Medicine Expenditure in General

During the fiscal year 2013/2014, the Government through the NIPDEC spent $441 million TTD (Trinidadian dollar) on pharmaceuticals. However, the total dollar value of requisitions sent to NIPDEC from all the RHAs was actually

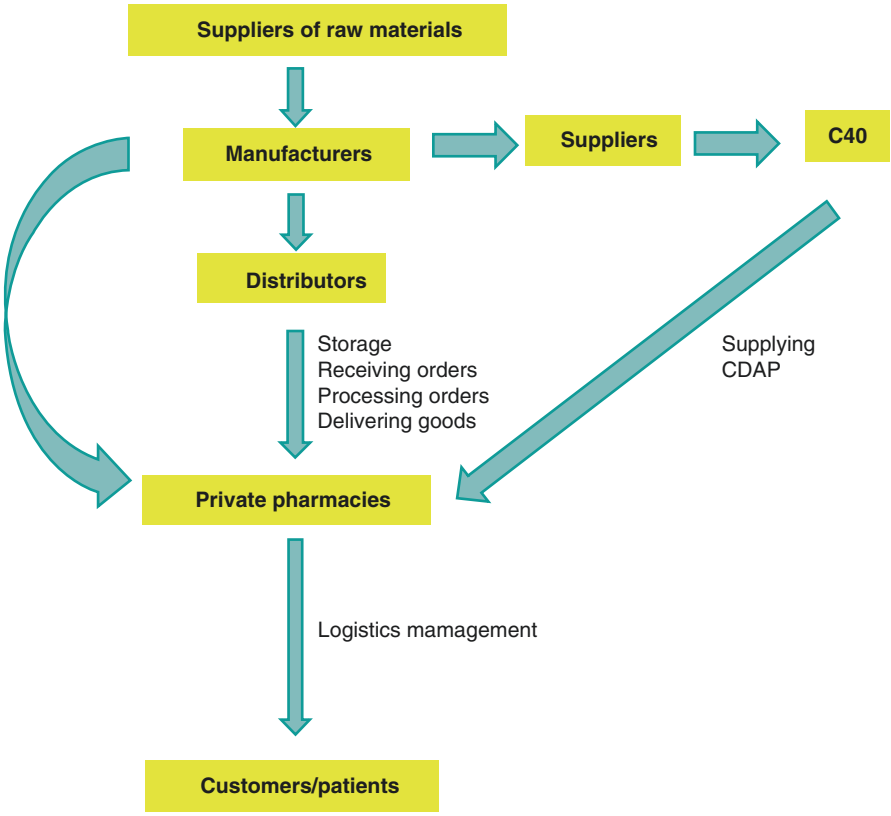

Fig. 17.2 Supply chain of the private sector of Trinidad and Tobago

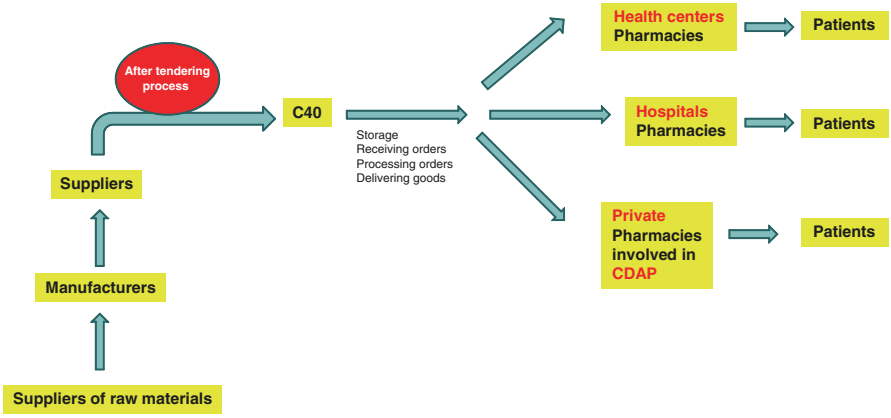

Fig. 17.3 Supply chain of the public sector of Trinidad and Tobago

$1.2 billion TTD, indicating that only 36% of the demand for medicines in the public sector is being met [27].

17.8 Pharmacoeconomics, Medicines Pricing, and Access

All patients accessing treatment within the public health system in Trinidad and Tobago access medicines free of charge. The CDAP program provides access to a basket of 52 pharmaceuticals and medical devices free of charge, for the treatment of 11 specific noncommunicable chronic diseases, via approximately 275 private pharmacies nationwide [24]. In an effort to handle the dramatic increase of persons accessing the program, the Ministry of Health in collaboration with The Pharmacy Board and NIPDEC acquired a new computerized system to streamline the processing of CDAP prescriptions. The CDAP program is extended to all eligible persons as defined by the Ministry of Health.

There is currently no data for the quantum spent in the private sector but approximately 42% of the overall health spend comes from the household [26]. There are legal or regulatory provisions within the private sector for pricing of medicines at the level of manufacturers, wholesaler, and retail outlets [13]. However, there is no active price monitoring system. Also no national and international affordability study has been conducted so far at the national level [13].

17.9 Generic Medicines

Substitution of generic equivalents at the point of dispensing is allowed in public sector facilities only if prescription is written with the International Non-Proprietary Name (INN)/generic name but not in private pharmacies [13]. On the national formulary there are several generic medicines, which are dispensed in public pharmacies. This trend is also seen in the private pharmacies. However, studies have found that generics may possess the same active ingredient and amount of drug but may show significant differences *in vivo* [28, 29].

17.10 Medicines Use

17.10.1 Medicines Use in General

In Trinidad and Tobago, medicine prescribing and dispensing are regulated. Legal restrictions exist in terms of physician dispensing; however, this still takes place in the private sector. There are no mandatory regulations concerning the setting up of drug therapeutic committees at hospitals but over 50% of them already have them

instituted. An Essential Medicines List and standard treatment guidelines are under development in Trinidad and Tobago [13].

Prescribing in the public sector falls strictly within the domain of the physicians. There is a concern, however, regarding the dispensing of antibiotics without prescription and this certainly has the potential to contribute toward antimicrobial resistance [30].

17.11 Role of Pharmacist

In Trinidad and Tobago, there are approximately 1050 registered pharmacists with the Pharmacy Board of Trinidad and Tobago and there are 271 community pharmacies. Pharmacists in public sector are expected to compound, prepare, and dispense medicines routinely. The concept of pharmaceutical care is relatively new and yet to be evolved into clinical pharmacy practice in hospitals settings.

Community pharmacists share a similar role to hospital pharmacists in compounding, dispensing and counseling. However, within their practice, there is greater focus on the treatment of minor illnesses with over-the-counter medicines, and primary care services. Some community pharmacies also maintain patient profiles, and educate patients on the importance of maintaining a healthy lifestyle. A small proportion of pharmacists pursue higher education either locally or internationally to develop competencies and skills in clinical pharmacy practice (e.g., Doctor of Pharmacy), and/or research (e.g., Master of Philosophy). Some graduates also enter the fields of sales and marketing with drug companies [31].

17.12 Summary and Way Forward

There are a number of medicine policies in place in Trinidad and Tobago. However, implementation of these policies is a challenge. There is a need to decentralize the health services system as it will help to better use of scarce resources.

The recent introduction of the health card system by the Ministry of Health has been slow to get off the ground; however, full implementation could increase surveillance and can better inform pharmaceutical policy. Development of clinical pharmacy in the area of oncology, diabetes, and noncommunicable diseases in general are critical at this point in time and a systematic human resource health planning is also required for the pharmaceutical sector.

Finally, for the overall system to be developed, there needs to be greater coordination between all healthcare stakeholders including the tertiary care educational institutions, the Ministry of Health, the Regional Health Authorities, and developmental agencies to ensure that effective, relevant, and sustainable pharmaceutical polices are implemented.

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Chapter 18
Pharmaceutical Policy in the UAE

Ranya Hassan, Hafiz Alam Sher, Rabia Khokhar, and Rabia Hussain

Abstract The United Arab Emirates (UAE) is a consortium of seven states, located in the region of Middle East and North Africa (MENA); it has the second largest economy in the Arab world. In 2012, it has a gross domestic product (GDP) of $377 billion. Due to the support of the ruler of the government, tremendous advances have been made in the field of oil, gas, tourism, and healthcare since its independence. Health is identified as a prime concern of the country; hence, remarkable advancement and phenomenal growth have been exhibited by the healthcare industry of the UAE. As a result of increase in the immigration population, the UAE healthcare system is striving to meet the expanding healthcare needs. Ministry of Health (MoH), Health Ministers' Council for Gulf Cooperation (GCC), Health Authority of Abu Dhabi (HAAD), and Dubai Health Authority (DHA) are the major regulatory bodies of the UAE. Various pharmaceutical legislations and policies majorly concerning accessibility, availability, affordability, quality, and pricing of medicines have been devised by these bodies; however, implementation is still a concern. This chapter describes the health system of the UAE, its regulatory structure, and present challenges with prime focus on pharmaceutical policies and medicines regulation in the UAE.

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18.1 Introduction

The United Arab Emirates (Dawlat al-Imārāt al-'Arabīyah al-Muttaḥidah) is located in the southeast end of Arabian Peninsula on the Persian Gulf bordering the Kingdom of Saudi Arabia to the south and the Sultanate of Oman to the east. It lies in the region of Middle East and North Africa (MENA). It also shares sea borders with Qatar and Iran. The UAE works in close coordination with its neighboring countries. The UAE is a consortium of seven states: Abu Dhabi, Ajman, Dubai, Fujairah, Ras Al-Khaimah, Sharjah, and Umm al-Quwain [1]. Since the independence of the UAE in 1971, it has made tremendous progress in oil, gas, and tourism. Flourishing tourism, strengthening economy, and large number of expatriates are the factors contributing in improving healthcare system of the UAE [2].

The United Arab Emirates has a population of 9.156 million according to 2014 estimates and GDP of 399.451 billion USD, which makes it a high-income country. The native population of the country is much less and most of the residents are expatriates, which constitute the major workforce of the country [3]. The expatriates are about 7.8 million; they constitute 90% of the population and 95% of the total workforce of the country [4]. The total health expenditure of the country is 3.6% of the GDP. It is estimated that the government provides 71.6% of the healthcare expenditure and the rest 28.4% is through out-of-pocket expenditure. The majority of these private expenditures (77.9%) are out of pocket [5].

Since the past few years, there is a continuous increase in the overall healthcare demand in the UAE. This demand is due to the rise in the influx of expatriate workers, the increasing level of aging population, and the rising costs of healthcare technology. As a result, the publicly funded healthcare services are overburdened, and the UAE Ministry of Health's budget has increased to 4.5% per year [5].

18.2 Health Sector in the UAE

The healthcare sector of the UAE, which emerged in the late 1970s, has matured over the years, and the healthcare standards are being strengthened [6, 7]. According to WHO, the total expenditure in the UAE on health per capita was 2405 US$ in 2014, whereas 3.6% of GDP is being spent on health. Life expectancy at birth was reported as 76 years for males while 79 for females (2015) [5].

The UAE spends more on healthcare when compared with other Arab countries. The UAE government is committed to provide world-class healthcare services by improving governance in the healthcare system. The 2021 vision of the UAE commits the government to ensuring a universal access to healthcare services by all Emiratis through availability and accessibility of quality health and personal care services in order to meet the growing needs of the population. There are various government agencies in the UAE including Ministry of Health (MoH), Health Ministers' Council for Gulf Cooperation (GCC), Health Authority of Abu Dhabi (HAAD), and Dubai Health Authority (DHA). These agencies are involved in regulation including

Table 18.1 Healthcare organization in the UAE

State	Total hospitals	Government	Private	Capacity (beds)	Population
Abu Dhabi	39	14	25	4226	2.5 million (2.7 beds per 1500 population)
Dubai	38	06	32	3857	2.1 million (1.0 bed for 532 population)
Sharjah	15	05	10	898	1.5 million (1 bed for 1670 population)
Ras Al-Khaimah	05	04	01	562	300,000 (1 bed for every 33 population)
Ajman	03	01	02	189	240,000 (1 bed for 1269 population)
Fujairah	03	02	01	538	200,000 (1 bed for 558 population)
Umm al-Quwain	01	01	–	165	100,000 (1 bed for 606 population)

accreditation, professional licensing evidence-based care, and health services surveillance [8]. Also, Dubai Healthcare City (DHCC) has been built which is a free zone independent authority in terms of its health services regulation [9].

In the UAE, the healthcare facilities are extended to both public and private sectors including delivery of basic healthcare services to far-flung countryside regions. All seven emirates provide healthcare to all citizens through infrastructure of hospitals and clinics, where the service delivery is done via a large number of foreign healthcare professionals. Public healthcare services are managed and regulated by federal and emirate-level government entities such as the Ministry of Health, Dubai Health Authority, the Health Authority Abu Dhabi, and Abu Dhabi Health Services Company, whereas the private healthcare service providers like the New Medical Center are nongovernment hospitals and clinics that provide specialty and full spectrum care to the UAE population. These private healthcare services are very important for the long-term healthcare system development in the UAE (Table 18.1).

Healthcare services are provided free of charge to the local citizens of the UAE. In case of expatriates, it is necessary for them to have compulsory health insurance. It is stated in the UAE law that the employer is responsible to furnish health insurance coverage to its employees. The healthcare intuition of the UAE has been highlighted in Economic Vision 2030 for Abu Dhabi as well as in the Executive Council's Policy Agenda 2007–2008 with special emphasis on health facilities' upgradation and regulatory strengthening [7].

18.3 Pharmaceutical Sector in the UAE

The UAE is the second largest pharmaceutical investor in the region. In 2013, the UAE pharmaceutical market was worth $2.4 billion which is anticipated to hit $3.7 billion by 2020. Similarly, the medical device market of the UAE was worth

733.3 million USD in 2013 and is estimated to reach 978.9 million USD by 2020 [10]. In case of the country's pharmaceutical sale, it is projected for 2016 as 3.170 billion USD and is likely to be 3.410 billion USD, 3.670 billion USD, 3.940 billion USD, and 4.220 billion USD for 2017, 2018, 2019, and 2020, respectively [11].

In the early 1980s, with the establishment of the Julphar (Gulf Pharmaceutical Industries) in the Emirate of Ras Al-Khaimah, pharmaceutical manufacturing sector laid down its foundations in the UAE [1, 12]. Since then, the Gulf Pharmaceutical Industries diversified and many other pharmaceutical manufacturing plants like Neopharma, Globalpharma, and Medpharma were established. Currently, there are about ten drugs and disposables (syringes) manufacturing units in the UAE [1]; however, the majority of medicines are imported at high prices in the UAE. The UAE is benefited with the presence of many of the world's largest pharmaceutical companies including Eli Lilly, Johnson and Johnson, Sanofi Aventis, Bayer, Astra Zeneca, MSD, and Merck Serono [8]. A number of private Emirati distribution and manufacturing pharmaceutical companies also contribute toward innovations in pharmaceutical sector, which includes Pharmatrade and Neopharma [11].

Health Authority of Abu Dhabi has made generic prescribing mandatory in 2009 [13]. In the UAE, generic prescribing is encouraged in order to reduce the overall healthcare cost. The dispensing pharmacists in the UAE are allowed to select a brand of their choice from multiple available brands, keeping in the domain of generic prescribing. Through Thiqa insurance system, the citizens of the UAE are entitled to have free medicines [14, 15]. For expatriates, it is necessary to get private health insurance. As discussed earlier, it is the prime responsibility of the employer to get his employees and his family insured [1]. The UAE is mainly benefiting from health-related free zones such as Dubai Technology and Research Park (Du-Biotech). The companies in Du-Biotech receive 100% waiver for corporate and personal taxes guaranteed for 50 years [16].

18.4 UAE Health Regulation

The legal matters are furnished via decree in the UAE; decrees are the official orders and laws. The UAE President or Vice President and Prime Minister hold the authority to issue federal decrees after negotiation with the Federal Supreme Council. Decrees related to a specific emirate are issued by the respective ruling Sheikh [6].

The healthcare in the UAE is regulated at the level of federation as well as at the emirate level. The first consumer articles that were regulated (with reference to licensing, registration, and pricing) in the UAE were medicines. In the 1970s and 1980s, the healthcare legislations were promulgated and the aim was to promote, develop, and strengthen the healthcare industry in the UAE. The UAE Federal Law number 4 of 1983 for Pharmaceutical Professions and Institutions regulates the medicines and pharmacy in the UAE [1].

18.4.1 Medicine Regulatory Authorities in the UAE

The healthcare system of the UAE is chiefly regulated by the collaborative efforts of different authorities, which include Ministry of Health (MoH), Health Ministers' Council for Gulf Cooperation (GCC) [17], Dubai Health Authority (DHA) [18], and Health Authority of Abu Dhabi (HAAD) [19]. The prime regulatory authority of the UAE is the Ministry of Health, MoH. Abu Dhabi is the capital of the UAE among the seven emirates where the Health Authority of Abu Dhabi (HAAD) and the Ministry of Health (MoH) are responsible for regulating the healthcare system. Likewise, in Dubai, the Dubai Health Authority (DHA) and the Ministry of Health (MoH) perform the medicines regulatory function, the rest of the emirates (northern) is regulated by the MoH alone [1]. In the UAE, community pharmacies are all privately owned which are either small independent facilities or chain-franchised shops [20].

18.4.1.1 Ministry of Health

The Ministry of Health (MoH) is the federal authority responsible for unifying the UAE's health policies, developing a comprehensive, nationwide health service, ensuring that healthcare remains accessible across the country [21]. The MoH is also the primary healthcare regulator in the Northern Emirates. The Northern Emirates do not have the necessary healthcare infrastructure and rely heavily upon the MoH for health system administration and regulation [8]. The Federal Health Authority (FHA) handles the executive responsibilities for the MoH, with a focus on increasing the efficiency and competitiveness of the UAE health system.

The foundation of the Ministry of Health (MoH) was laid in accordance with the Federal Law No. 1 of 1972 [22]. The ministry of health is mainly responsible to provide and manage the healthcare facilities to the people of the UAE and to regulate the practice of health professionals according to Cabinet Resolution No. 10 of 2008 [23]. The ministry of health is the leading regulatory body in the UAE that regulates the health system. As mentioned earlier, MoH works in collaboration with HAAD and DHA to achieve the healthcare objectives in Abu Dhabi and Dubai, respectively. Though some new regulatory bodies have recently emerged in Sharjah like the Sharjah Health Authority by Sharjah Amiri Decree No. 12 (2010) [15], still the responsibility lies on MoH to improve the healthcare system in Ajman, Sharjah, Ras Al-Khaimah, Umm al-Quwain, and Fujairah.

Various federal healthcare laws are governed by the ministry of health that includes:

- Federal Law No. 4 (1983): controls the activities concerning the regulation of pharmacy profession, establishments and that of pharmaceutical products (i.e., manufacture, distribution, and import of pharmaceuticals) [17].
- Federal Law No. 5 (1984) and Federal Law No. 7 (1975): regulate the licensing and registration operation of healthcare professionals [18].

- Federal Law No. 7 (1975) and Federal Law No. 2 (1996): details the specified requirements for establishments and licensing of medical facilities (i.e., hospitals, clinics, and medical testing laboratories) [18].

The MoH has simplified the health regulations for the UAE into levels of health policies and health standards. The health regulations collectively help translate and simplify the federal UAE laws, and there are efforts to improve patient compliance, quality, and cost-effectiveness across the healthcare system.

18.4.1.2 Council for Gulf Cooperation

A broader consortium of health ministers of Gulf States named as Health Ministers' Council for Gulf Cooperation (GCC) is one of the specialized councils of GCC [19]. It was established in 1976. It is comprised of seven Gulf States: the Kingdom of Bahrain, the State of Kuwait, the Sultanate of Oman, the State of Qatar, the Kingdom of Saudi Arabia, the United Arab Emirates (UAE), and the Republic of Yemen [19]. The basic aim of the Health Ministers' Council for GCC States is the establishment of cooperation and coordination among the member countries [24].

18.4.1.3 Dubai Health Authority

The Dubai Health Authority (DHA), the regulator and operator of the Emirate of Dubai's healthcare sector, oversees and sets healthcare policy and strategy, develops medical education and research, and regulates and issues licenses to all healthcare facilities and services in Dubai and its free trade zones. Universal healthcare expected to be fully implemented in Dubai by 2016 is its key priority [8]. The DHA serves the dual role of regulator and operator of the Emirate of Dubai's healthcare sector.

18.4.1.4 Health Authority of Abu Dhabi

The health system at Abu Dhabi is primarily regulated by the Health Authority of Abu Dhabi (HAAD). HAAD along with MoH ensures the efficient working of the health system by keeping check on the health-related services and facilities and ensuring the proper implementation of healthcare policies [25].

In December 2012, HAAD has published its policy manuals with the aim to improve the healthcare delivery and to strengthen the healthcare system in Abu Dhabi. These manuals contain guidelines for health regulators, healthcare professionals, healthcare providers, and healthcare insurers. This encourages them to work in harmony to strive toward a common objective of universal health [26].

Few other regulatory bodies also contribute in regularization of the UAE healthcare system like the Emirates Health Authority (EHA) in Sharjah. This was established under the Federal Law No. 13 (2009), with the fundamental goal to

consolidate the liaisons among the federal health authorities, local bodies, and private health division. EHA possess comparable aims and objectives as DHA and HAAD [15].

Another organization, the Abu Dhabi Health Services Company (SEHA; an Arabic word meaning "health") founded in 2007 by law in Abu Dhabi works in collaboration with HAAD is involved in managing the government healthcare facilities as well as the implementation of HAAD's policies and procedures [15].

18.5 Quality Control

The pharmaceutical quality is growing in the UAE with the support of governmental policies, which facilitate quality pharmaceutical manufacturing. Ministry of Health (MOH) is the federal regulatory authority in the UAE and is responsible for insurance of pharmaceutical quality system [27]. The pharmaceutical manufacturer and the pharmaceuticals it produces must be registered either with the GCC or with the national regulatory authority. Inspection of the manufacturing premises as well as the quality control testing is also executed to ensure quality, efficacy, and safety of medicines. The validity of the registration of the product is 5 years after which it must be renewed. Registration is also mandatory prior to medicines marketing in the UAE, which further empowers the quality control system [15].

18.6 Pharmacovigilance

Concerns over patient safety, frequency of known ADRs, and occurrence of new ADRs are the factors that have favored the development of ADR reporting system in the UAE [28]. Adverse drug reactions (ADR) reporting is of primary concern in any pharmacovigilance system. Spontaneous and voluntary reporting system is an integral part of the UAE's healthcare system [28].

Variation is seen in the ADR reporting infrastructures worldwide. The UAE possesses national pharmacovigilance centers, which solely focus on the receiving of ADR reports with negligible involvement in active provision of drug information. Though the UAE has operational drug and poison information centers in its Emirate, they are not coordinated with the government's pharmacovigilance system [29]. The UAE has set the legal requirement for all drug manufacturers to report ADRs of their products. ADR reporting by hospitals to pharmacovigilance centers is also necessary. Standard ADR reporting form which is a part of emirates hospital formularies and can be accessed through pharmacies or via Internet are employed to report any adverse drug event. Besides ADRs, the pharmacovigilance centers also report on safety concerns related to vaccines and biologicals [30].

18.7 Counterfeit Medicines in the UAE

Medicine counterfeiting is a serious threat all around the world as presence of wrong or absence of the desired active pharmaceutical ingredient in the formulation can result in patient morbidity and mortality [31]. The UAE not only suffers from the issue of counterfeit medicines but also there are reports that the medicines are transported through this route. It was reported that approximately 750,000 fake medicines were identified to be transported via the UAE in 2008 which is amounted to a value of 5.5million in 2009 [31]. HAAD reported sexual stimulants and anti-obesity drugs were the most common counterfeit medicine. The government of the UAE has felt the seriousness of the issues and is actively playing its role in fighting against this menace. The Ministry of Health is functioning in collaboration with the Ministry of Interior, Custom Authorities, and Dubai Police where periodic checks are performed in pharmacies [32].

The MoH also advises to the citizens of the UAE to watch out for fake medicines and actively discourage the online purchase of pharmaceuticals [33]. The sale of medicines over Internet is the most underregulated domain of pharmacy federal law. Illegal sale of medicines is increasing online, and this is an issue which is difficult to deal with. Consumers are encouraged to timely report the concerned regulatory authorities regarding the presence of these medicines. In April 2015, the Emirates International Conference on Combating Drug Counterfeiting was held in Dubai where experts from WHO discussed ways to counter the issue of drug counterfeiting with special emphasis on fake drugs [32].

18.8 Medicines Financing

The UAE spends approximately $1200 per capita on healthcare, ranking it among the top 20 countries in quality healthcare spending per capita [8]. The government spends 71.6%, while the private sector spends 28.4% on the UAE health sector. Out-of-pocket expenditure accounts for 77.9% of the total private health expenditures (28.4%) [1].

In order to sustain all of its healthcare costs, the country has been moving toward a universal healthcare system. A law passed in 2005 required all expatriates and their families living in Abu Dhabi to have private medical coverage [34]. By law, in 2007, HAAD has been given the mandate to develop insurance policies and to provide health insurance regulation services in the country [35]. Today, universal healthcare insurance is in place in Abu Dhabi and Dubai but only actively enforced in Abu Dhabi. Dubai is in the process of rolling out its universal healthcare insurance system and recently indicated that the population of the entire emirate must be covered by 2016 [35].

Health services provided by private or government facilities and medications dispensed to expatriates are paid for by insurance companies [35]. All insurance schemes must cover payment for basic healthcare services and medicines prescribed by doctors. For the UAE nationals, healthcare services and medicines are paid for by the

National Health Insurance Company – Thiqa and Daman [36]. The Ministry of Finance (MoF) is the responsible federal body for the financial reconciliation of all healthcare services offered to the UAE nationals and paid for by Thiqa and Daman [8, 37]. Another body, the Federal Health Insurance Authority (FHIA) is also involved in managing health insurance matters in the UAE [8]. HAAD and DHA also have their own insurance policies for the residents of the respective regions. Whereby, expatriates are required to purchase annual healthcare cards to receive subsidized healthcare services. However, this does not include pharmaceuticals. Private health insurance in the remaining six Emirates is voluntarily available to consumers and patients depending on their affordability or if they can pay for it [38].

Daman (the UAE National Health Insurance Company) is the first and largest specialized health insurance company to be formed in the United Arab Emirates and was established in September 2006. It is a joint project of Abu Dhabi government and Munich Re [39]. It currently provides comprehensive health insurance solutions to more than 2.4 million members in the UAE [40]. Daman provides health insurance for both individuals and organizations, and exclusively manages the UAE government's healthcare program, Thiqa, for UAE nationals, and the Abu Dhabi Basic Plan, for low-income expatriates. The expatriates in emirates, other than Dubai and Abu Dhabi, can get the insurance facility on voluntary basis [8].

18.8.1 Medicines Pricing

In order to exercise an efficient price control in its member states, a centralized body has been instituted in May 1999. The name of this body is the GCC Gulf Central Committee for Drug Registration (GCC-DR) [41].

A number of pricing policies have been developed to ensure the provision of safe and effective medicines to the local community at reasonable prices.

In the UAE, approximately 80%, of the consumed medicines in the UAE are imported [42]. Bearing high costs, the pharmaceuticals import put undue burden on healthcare; however, the government is trying to increase local pharmaceutical manufacturing capacity to reduce the healthcare expenditures [43].

The Kingdom of Saudi Arabia's pricing procedures and policies are used as reference by the UAE like other GCC member countries [13]. The Middle East Medicine Prices Database (MedPrice) has been established by the pricing division of Food and Drug Authority of Saudi Arabia which is basically a medicines prices repository covering a range of countries [13]. In the UAE, the medicine pricing is the responsibility of the Medicine Regulatory Affairs Section, particularly the Registration and Pricing Unit, of the Drug Control Department (also known as Medicine and Pharmacy Control (MPC) Department, MoH [44].

A survey in 2006 led to the discovery that a sample of 25 medicines in the UAE were priced higher than the international reference prices, leading to activities designed to lower prices of drugs especially for chronic diseases [45]. Prices are set using external benchmarking (international reference pricing or external reference

pricing or ERP) in the UAE. It is a method to control pharmaceutical prices wherein policy and decision makers specify a basket of countries, whose prices they use to finalize their national target prices. EPR is in practice worldwide, though countries vary substantially how they execute EPR. It mostly results in narrow corridor of pharmaceutical prices for innovative medicines [46]. It is important to note that the prices of similar available drugs, the medicine's production cost, and the prices in respective neighboring and GCC member countries are considered when fixing prices of pharmaceuticals in the UAE [44].

18.9 Medicines Use in the UAE

The primary, secondary, and tertiary health centers have made healthcare available to all residents of the UAE. In the UAE, strict regulations are exercised in the areas of drug prescribing and dispensing [47]. The UAE health regulation precludes the dispensing of medicines without a prescription [58]. The concerned prescriber and the dispensing pharmacist are answerable in case of any incomplete prescription prescribing or dispensing. An ideal prescription should contain all core elements concerning patient and prescriber, as per the UAE health regulations [47]. National Standard Treatment Guidelines (by MoH, UAE) and Local Health Authorities guidelines (by HAAD and DHA) covering the most prevalent medical conditions of the UAE can be utilized as reference by the UAE practitioners which can then perhaps assist them in judicious medical practices. Failure of compliance to these standard guidelines could greatly impact on the standards of healthcare delivery.

18.9.1 Generic Prescribing

Health Authority of Abu Dhabi, in 2009, instructed the medical practitioners to follow the generic prescribing of medicines [48]. Generic prescribing aims to reduce the financial burden related to medicine cost on the patient's pocket and to rationalize the use of drugs. It also facilitates the pharmacist in medication stock management [47]. According to a survey, little adherence, as low as 4.4%, is observed toward the generic prescribing policy [49]. The marketing activity of the pharmaceutical industry is identified as the most common factor that impedes significant adherence to such prescribing strategy [47]. Special attention should be given to prescription writing, essential drugs list and prescribing by generic names to ensure rational use of drugs, reducing the events of medication errors, and refining the therapeutic effects [47]. An electronic prescribing system, Wareed (in Arabic, means life-supply) has been introduced by the UAE government. It is hoped that this system would regularize the generic prescribing in the country in future [50].

18.9.2 Rational Medicines Use

The concept of rational drug use (RDU) was first highlighted by WHO which has later become the point of focus of healthcare agendas all around the world [51]. Understanding the importance of the issue, HAAD along with WHO, MoH UAE, and East Mediterranean Regional Office (EMRO) organized the first national conference on the theme in May 2008 [29]. The prime objective of the conference was to promote the safe and effective use of medicines with special attention to antimicrobial resistance. Strategies were also set forth to combat the issues of medicine misuse [29]. In May 2012, Ministry of Health together with the collaboration of Sharjah University organized another conference "Join hands to promote rational use of medicines." MoH utilized the WHO guidelines and the UAE Ministry of Health policies to develop an essential medicine list (EML) [52].

Though the health regulations are strict in the UAE, still prescription drugs are available over the counters. This is also being reported in a study on self-medication practices [53].

18.10 Role of Pharmacist in the UAE

According to law, a pharmacy in the UAE can only be owned by a UAE citizen with compulsory supervision of a qualified registered pharmacist [1]. In recent past, community pharmacists were supposed to practice the roles of compounding and dispensing medications. However, the rapid advances in health technology and research and due to varied cultural/socioeconomic status of the country and consumer's demands pharmacist's traditional roles are changing [20]. In an attempt to adapt to these changes, community pharmacy system is being upgraded, and patient's preferences, monitoring, and drug selection have been introduced in community pharmacies. It has led to the beginning of the shift in the role of community pharmacist toward patient care in the UAE [20]. This global shift is creating a stress on pharmacist community to better equip themselves with unique set of skills and knowledge for effective execution of the additional roles [20, 54]. This extension of roles of pharmacists, however, may culminate to an increase in their workload [8]. Hence, the role of pharmacist is extending in the UAE with the aim to improve quality of care and drug therapy optimization and decrease in workload of other healthcare professionals. This will ultimately result in reduction of long-term healthcare costs [20].

Currently at community pharmacies in the UAE, most of the dispensing tasks are done by the pharmacy technicians [1]. Monitoring and reviewing of controlled substances, dealing with approvals and rejections of insurance companies, keeping track of shelf-life expiry as well as the stock, and double-checking for errors (prescription and dispensing) are a few major responsibilities performed by pharmacists in the UAE [55].

HAAD is a strong supporter of continual education (CE) of pharmacist and hence supports such activities in the region. Since February 2008, it is compulsory for all pharmacists practicing in Dubai to attend a CE program [56].

18.11 Conclusion

The UAE has one of the most rapidly growing healthcare sectors among the GCC states. In order to meet the growing needs of population, the UAE is actively expanding its healthcare sector with leading medical centers and academic institutions. These organizations are playing a vital role to improve the quality of healthcare. All seven emirates provide healthcare to all of the citizens in both public and private sectors through an infrastructure of hospitals and clinics. This service delivery is mostly done by many expatriate workforce (doctors and nurses).

Availability of more than one health regulatory authority has provided the advantages of promoting and enhancing medical and pharmacy professional practices, and improving health quality standards. Despite the improvements in healthcare system over the years, there are issues related to rational drug use and generic prescribing. Development and implementation of novel mandatory healthcare policies, the rigorous implementation of existing policies, and their timely upgradation are the key elements that will result in reinforcement of the health division of the UAE.

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Part IV
Further Perspectives

Chapter 19
"Repurposing" Medicines: A Case for Low- and Middle-Income Countries with Developing Healthcare Systems

Warren Kaplan

Abstract Medicine developers are looking to medicine repositioning (also referred to in this chapter as as 'repurposing') as a cost effective, reduced-risk strategy for developing new medicines. Repurposing refers to the concept or process of taking a medicine developed for one indication and applying it to another. This chapter discusses whether low and middle countries could potentially benefit from such repurposing. In particular, the chapter investigates the possibility of developing new uses for generic and/or failed medicines. The chapter concentrates on repurposing anti-infective medicines, rather than those for chronic conditions. There is a relative paucity of anti-infectives in FDA withdrawn clinicial trials . Repurposing new uses for medicines withdrawn from clinical trials would seem very risky indeed. Furthermore, repurposing a new indication for some already-approved generics is possible but has other challenges. If a repurposed generic medicine works in a new disease indication using its existing formulation and doses, it may be controversial for the company to charge a higher price for the new disease indication, while patients continue to pay a lower price for the same medicine for the old disease indication. Typically, what is needed is a sufficiently large number of patients to make a drug profitable so, in this regard, repurposing medicines for 'neglected' or even more common diseases in LMICs are clearly a challenge where the market may exists but patients are not insulated from the cost of medicines. Successful repurposing of medicines for LMICs will not happen without policy alignment and synergies of expertise that are created through collaborations between academia and industry. Unlike use of failed medicines, the investigation of new targets and mechanisms for existing drugs with known safety profiles may add value to the business model and bring more therapies to market for patients in LMICs.

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19.1 Introduction

In early December 2013, in the midst of legal wrangling about India's granting of its first compulsory license (CL) on a pharmaceutical product (Bayer AG's kidney and liver cancer drug sorafenib Nexavar), Marjin Dekkers, the CEO of Bayer, was quoted as saying that the CL was unwarranted and "… essentially theft." Further, he said Bayer did not "… develop this product for the Indian market…" but for "… Western patients who can afford this product… "[1]

There are many reasons why medicines are both expensive and, for the most part, developed for "Western" patients. It is by now a truism that for medicines that primarily affect populations with weak purchasing power, there is insufficient incentive for industry to invest in research and development (R&D). Further, under the present biomedical R&D system of high-income countries (primarily the United States, Europe, and Japan), therapeutic advances are still a rarity with the majority of new drugs showing little to no added value compared to previously available treatments [1].

In brief, many commentators have suggested that there is an ongoing failure of the R&D system to address the needs of patients globally. Medical knowledge has the potential to be a global public good—that is, knowledge produced in one country can benefit the entire global community (it is "nonexcludable"), and disclosing that knowledge does not reduce the amount of knowledge left for others to enjoy (it is "nonrival"). The public goods nature of medical knowledge can generate important health advances but how the burden of paying for such knowledge should be distributed globally is challenging. If one country can benefit from the investment of another, there is a powerful temptation to "free ride" on the other's efforts; the end result may be aggregate global underinvestment in R&D [2].

In the area of innovation, there have been many proposals to deal with this global underinvestment. There has been increased funding for specific neglected diseases [2], a variety of technology transfer initiatives to build capacity in low- and middle-income countries (LMICs) [3, 4], creation of a market for children's formulations of ARVs [5] and adapted pneumococcal vaccines [6], a priority regulatory review voucher granted in exchange for bringing a neglected disease drug to market [7], milestone prizes and proposals for large end-product prizes (see, e.g., [8]), patent pools [9], and open-source approaches [10].

Medicine developers have also looked to medicine repositioning (also referred to in this chapter as "repurposing") as a cost-effective, reduced-risk strategy for developing new medicines. Repurposing can mean new life for shelved or abandoned medicines that have never been on the market, or extended life for marketed medi-

[1] As of late 2014, about 17,000 persons in India needed this medicine. The Indian Supreme Court's final ruling in December 2014 upholding the CL put an end to the legal battle. See, Supreme Court Says No to Bayer, Upholds Compulsory License on Nexavar (Dec. 15, 2014) Available: http://infojustice.org/archives/33690. See also Knowledge Ecology International online. Available: http://keionline.org/node/1910

cines via new indications or formulations. Repurposing refers to the concept or process of taking a medicine developed for one indication and applying it to another. Medicine repurposing is increasingly being pursued as a policy solution to the problem of dwindling pharmaceutical pipelines; it is being proposed in both industrial and academic medicine development settings [11–13].

More specifically, medicines or candidates suitable for repurposing include those in clinical development whose mechanism of action is relevant to multiple diseases; medicines that have failed to demonstrate efficacy for a particular indication during phase II or III trials but have no major safety concerns; medicines that have been discontinued for commercial reasons; marketed medicines for which patents are close to expiry; and medicine candidates from academic institutions and public sector laboratories not yet fully pursued [14].

It has been suggested that medicine repurposing, especially of old and/or generic medicines not under patent protection, may be an attractive approach to medicine development for patients in low-income and middle-income countries [15]. Many medicines are sufficiently expensive but not particularly innovative [1, 16]. By investing in efforts to find "positive side effects" of inexpensive old medicines, it is hoped that really transformative medicines could be made available for a majority of the citizens of LMICs [15].

Successful repurposing of medicines for LMICs will require collaboration between industry and academia. Unlike the use of failed medicines for new indications, the investigation of new targets and mechanisms for existing drugs with known safety profiles may add value to the private sector business model and bring more therapies to market for patients in LMICs.

19.2 Purpose of Chapter

This chapter discusses whether LMICs could potentially benefit from such repurposing. In particular, this chapter investigates the possibility of developing new uses for shelved and/or failed medicines. This chapter concentrates on repurposing anti-infective medicines, rather than those for chronic conditions, although the latter will be briefly discussed as well. This chapter provides a brief descriptive analysis of all the US and overseas clinical trials in which the test medicine was withdrawn, that is, all "failed" medicines.

This chapter also investigates whether new uses can be found for certain medicines by reviewing these medicines and their biological targets. These particular medicines are nearing the end of their patent life and are considered of sufficient importance such that a generic drug company would be willing to bring patent infringement legal proceedings in the United States against the "pioneer" company holding the original patent in order to get on the market. These are the so-called Paragraph IV medicines, as discussed below in Sect. 19.3.

This repurposing approach is promising but, like medicine development generally, many barriers must be overcome in order to repurpose medicines for uses

in LMICs. After a medicine's initial FDA approval, the US patent system provides some market exclusivity protection over new indications that are later developed for use with that medicine. Nonetheless, the development of new, and usually patented, medicines that have never previously gone through the FDA approval process still remains the dominant pharmaceutical business model, with much less spent on developing new uses for recently approved medicines, and virtually no investment in new uses for medicines available as generics or those withdrawn from clinical trials. This is the conundrum faced by those who wish to create a viable model for repurposing old/generic medicines for LMICs. This chapter will also review these barriers and suggest some feasible approaches to overcome them.

19.3 Methods

19.3.1 Medicines Withdrawn from Clinical Trials

Data were downloaded from the website ClinicalTrials.gov [17] in early March 2016. This site contains the registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. All interventional clinical trials that were deemed "withdrawn" were downloaded. Clinical trials involving devices, behavioral interventions, surgical procedures (except those including medicines), and those labeled "phase 0" were removed, but those categorized as "radiation" were not removed. Interventions categorized as "other" were not removed if the intervention used a medicine.

Data were analyzed according the clinical phase (1.1/2, 2 or 2/3), the age group of the participants (child, adult, senior, or various combinations of these), and the medical condition. Many medical conditions are the subject of clinical trials, so this descriptive analysis is limited to those withdrawn clinical trials from a range of disease conditions that are relatively easy to search, that is, HIV, chronic obstructive pulmonary disease (COPD), diabetes, Ebola, infections, and cancer.

In the database, "cancer" as a medical condition has many manifestations. I searched the database using the terms "adeno" plus any condition with "oma" (e.g., myeloma, blastoma, lymphoma), "cancer," "neoplasm," "leukemia." The search for conditions caused by infections used the terms "it is," "infect*" (where * is a wildcard) plus specific microbes. No attempt was made to identify specific medicines in these withdrawn trials. The entire dataset of these withdrawn trials are in Appendix 19.1.

19.3.2 Generic: or Soon-to-Be Generic Medicines- and Their Protein Targets

19.3.2.1 Protein Targets and Medicines Attacking These Targets

Many medicines considered for repurposing bind specific proteins. Over time, many of these protein targets have evolved to have similar features such as binding and active sites. Thus, protein targets can potentially be matched with homologous targets that have been pursued for drug discovery for other indications [18]. As an example, one front-line treatment for human African trypanosomiasis (HAT), eflornithine, is an inhibitor of its target ornithine decarboxylase. Eflornithine was initially studied as a human cancer therapeutic, but it was found to have poor efficacy in cancer and the clinical development was stopped. However, it was recognized by others that trypanosomes utilize a similar ornithine decarboxylase enzyme [18].

The Therapeutic Target Database (TTD) [19] was used to provide information about therapeutic protein and nucleic acid targets, the targeted disease, pathway information, and the corresponding drugs directed at each of these targets. Links to relevant databases containing information about clinical development status are also included in this database.

The name of a particular medicine (e.g., nevirapine) is entered into this database. The structure of the drug, whether the medicine is FDA approved and the therapeutic condition (HIV) is provided. A link provides the therapeutic class, formula, and the target for this medicine (in this case: HIV-1 reverse transcriptase). Significantly for our purposes, a further link provides information about any other medicines (besides nevirapine) attacking this identical target, whether these other medicines have market approval, the clinical phase they are in or whether their clinical trials have been withdrawn/discontinued.

In this example of nevirapine, there exist seven different approved medicines attacking HIV-1 reverse transcriptase – all 7 for HIV, although one of these, emtricitabine, is also approved for hepatitis C. Fifteen different medicines attacking HIV-1 reverse transcriptase target are in various clinical trial stages for HIV-1 infection, hepatitis B, breast cancer, and solid tumors. Five different medicines against this same target have been withdrawn from clinical trials – 4 of them for HIV-1 infection. In principle, the "primary" medicine nevirapine and its 14 family members attacking HIV-1 reverse transcriptase presently in clinical trials and those in withdrawn trials could potentially be repurposed for hepatitis and various cancers.

Using this database, it is possible to identify a "primary" medicine, determine its therapeutic target, and see if there are other medicines in clinical trials or those withdrawn from clinical trials that attack this same target and the indications for these other medicines. These other medicines, including the primary medicine, may be suitable for repurposing to develop a new indication. Medicines used as "primary"

compounds to search in the TTD database were selected from the group of medicines described immediately below in Sect. 19.3.2.2.

19.3.2.2 "Paragraph IV" Medicines: List of Off-Patent or Soon-to-Be Off Patent Medicines That Generic Manufacturers Think Are Important

The US FDA maintains a list of medicines products for which an Abbreviated New Drug Application (ANDA) has been received by the Office of Generic Drugs (OGD) containing a "Paragraph IV" patent certification [20].

ANDAs are one way that generic medicine manufactures expedite the approval of their medicines. In the ANDA process, the generic drug company may rely upon the clinical safety and efficacy of the "pioneer" pharmaceutical company. The pioneer company must have previously filed a New Drug Application (NDA) which is required to have information on the pioneer drug's safety and efficacy obtained from clinical trials. The NDA applicant must also identify all patents, if any, covering their approved drug (or use of this drug), and this list is published in FDA's Orange Book [21].

When seeking approval of an ANDA, and if there is a patented drug (or patented use of a drug) involved that is listed in the Orange Book, a generic drug maker must make one of four types of patent certifications [20]. Paragraph I certification is that no relevant patent is listed in the Orange Book. Paragraph II certification is that the listed patent has expired. Paragraph III certification asserts that the listed patent, plus any other exclusivity, will expire before the requested approval. There is no obvious list of Paragraph I, II, and/or III medicines.

For our purposes, a Paragraph IV certification is a document in which the generic medicine manufacturer asserts that the listed "pioneer" company patent is at least one of the following: (a) invalid; (b) not infringed; or (c) unenforceable [22].

The mere filing of a Paragraph IV Certification is treated as a statutory act of patent infringement, so the pioneer medicine must be of sufficient importance such that the generic company would be willing to risk a lawsuit initiated by the patent holder. Upon providing the reasons why it thinks the patent on the pioneer medicine deserves a Paragraph IV certification, the pioneer patent owner/NDA holder can sue on all, some, or none of the patents included in the Paragraph IV Certification [22]. If the patent owner does not bring suit within a certain time period, the FDA may issue final approval of the ANDA. If the patent owner decides to bring suit against the generic company within this same period, approval of the ANDA is held up for 30 months. After that time, the FDA can approve the ANDA or earlier if the patents involved are judged invalid or not infringed [22].

To incentivize generic drug makers to challenge suspect Orange Book listed patents, the first company to file a Paragraph IV Certification gets a 6-month marketing "bonus" in which it will be the only generic company on the market with that product regardless of whether it establishes that the Orange Book patents are invalid or not infringed by the drug described in its ANDA [22]. Not surprisingly, Paragraph

IV Certifications under US law have spawned a tremendous number of legal conflicts between the generic drug makers and the owners of those patented drugs (or patented uses of those drugs) [23].

The Paragraph IV certification list (March 5 2016) was used in two ways:

(a) The list was searched for all USAN stem names to specifically identify the anti-infective products (e.g., antibiotics, antivirals, antifungals, antihelminthics, and the like) on this list. Briefly, USAN (United States Adopted Names) is a US organization that selects unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships [24]. The listing of USAN stems represents common stems for which chemical and/or pharmacologic parameters have been established. These stems and their definitions are used in coining new nonproprietary names for drugs that belong to an established series of related agents. In other countries, requests for INNs are submitted directly to the World Health Organization (WHO). Where there are national nomenclature commissions, such as those for the United States, Britain, France, and Japan, national INNs are usually identical to the WHO-managed INN.
(b) Fifty medicines on the Paragraph IV certification list were randomly selected for searching and searched in the TTD database. This search reveals the molecular target of this "Paragraph IV" medicine, any other medicines (and their indications) against this same target, and whether any of these medicines are approved, are in clinical trials, are withdrawn from trials, or are removed from the market. The total number of different approved medicines was divided by the number of different indications as a rough estimator of the number of medicines/disease indication. The same was done for withdrawn medicines.

19.4 Results

19.4.1 Failed/Withdrawn Medicines in Clinical Trials: Potential Repurposed Medicines?

As of 5 March 2016, there were in total 1740 withdrawn clinical trials in the US clinicaltrials.gov database and 1516 after removal of nonmedicine interventions and clinical "phase zero." The majority (83.4%: $n = 1265$) of these 1516 trials enrolled either only adults (18–65 year) or both adults and seniors (66+ year) and 4.8% ($n = 74$) only to children (birth–17 years). Only two withdrawn trials had enrolled only seniors. Figure 19.1 shows that among these individual age groups, most clinical trials were withdrawn in Phase 2, with the exception of clinical trials directed to adults only which were primarily withdrawn in Phase 1. On average for all ages, however, about 55% of all clinical trials were withdrawn in Phase 2 and about 30% in Phase 1. One can therefore infer that at a minimum, at least one quarter of all withdrawals in these 1516 withdrawn clinical trials were based on medicine safety considerations.

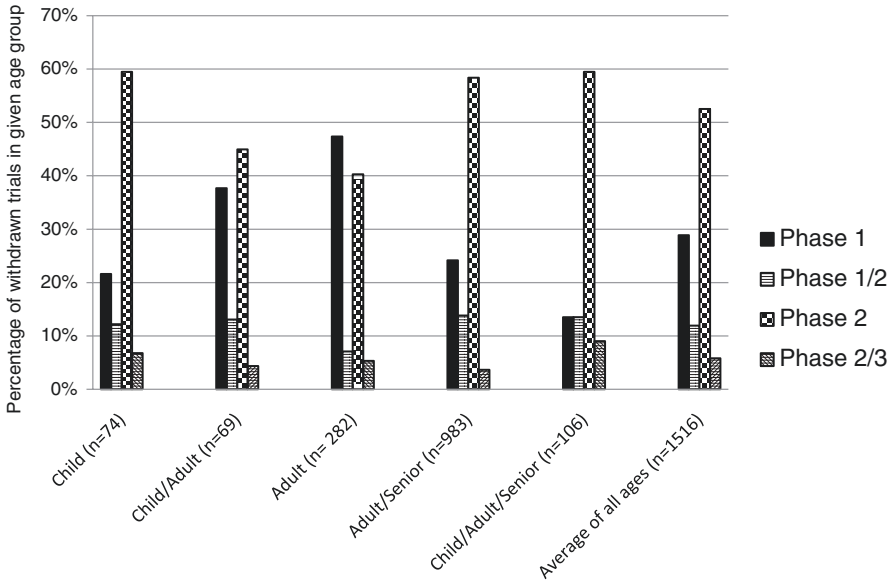

Fig. 19.1 Percent of clinical trials in a given age group withdrawn: Impact of clinical phase on withdrawals

Table 19.1 Examples of anti-infective indications (exclusive of HIV) in withdrawn clinical trials

Infection	Number of withdrawn trials
Hepatitis C	18
Influenza	13
Cytomegalovirus	3
Pneumonia/mycoplasma	3
Upper respiratory infections (rhinitis, bronchitis, sinusitis)	4
Hepatitis B	2
Urinary tract infections	3
"Bacterial" infection	3
Herpes	2
Heliobacter pylori	2
Clostridium difficile	1
Rotavirus	1
Smallpox	1
Equine encephalitis	1
Staphylococcal infections	1

Of these 1516 withdrawn interventional trials, almost 44% ($n = 664$) were trials testing cancer medicines. About 2.6% ($n = 40$) of withdrawn trials utilized medicines for HIV and AIDS-related conditions, about 2.3% ($n = 35$) for diabetes and related

conditions (e.g., neuropathies) and about 0.03% (n = 5) for malaria. Exclusive of HIV, of all withdrawn trials, 58 (3.9%) involved a medicine directed to a viral or bacterial infection. Of these 58, about one third involved hepatitis C medicines, by far the most common infection (aside from HIV) in these withdrawn trials. These results for anti-infectives are summarized in Table 19.1.

19.4.2 New Uses for Off-Patent (or Soon to Be Off-Patent) Medicines: Paragraph IV Certification

There are 1059 Paragraph IV medicine products, including duplicates which are the same medicine but different dosages and/or strength. that is, different products but the same active ingredient. See Appendix 19.2 for the complete dataset. Using the USAN stem names as a search strategy, it appears that there are few anti-infectives on this list of potential generic medicines. Of all 1059 "Paragraph IV" generic medicines, only 98 (9%) are anti-infectives and of these 98, 21 were antiviral products. See Annex 19.1 at the end of this Chapter.

Of the 50 randomly chosen "Paragraph IV" medicines, and excluding antiretrovirals, only three medicines (fluconazole, gatifloxacin, pralatrexate) were directed to anti-infective indications. Pralatrexate in particular has family members which include proguanil, pyrimethamine, trimetrexate and trimethoprim, all of whom inhibit dihydrofolate reductase.

The 50 randomly selected Paragraph IV products attacked 45 different protein targets. Full data are provided in Appendix 19.3 for these 45 targets. For example, meloxicam is a common nonsteroidal anti-inflammatory for osteo- and rheumatoid arthritis, pain, and dysmenorrhea and the subject of Paragraph IV certification as a potential generic. The TTD database identifies it as an inhibitor of the prostaglandin G/H synthase 2 enzyme. Other medicines (including meloxicam) attacking this same target are in clinical trials for arthritis, plus asthma, cancer, and Alzheimer's disease. Various medicines attacking this target have been withdrawn from clinical trials for arthritis, Alzheimer's, inflammation, various cancers, type 2 diabetes, pain, and colon polyps. All these indications could be potential candidates for meloxicam repurposing.

For the medicines attacking these 45 targets, only seven medicines (7/45 = 6.3%) are for various anti-infective indications (fungal infections, HIV, malaria, schistosomiasis, Hepatitis C, amebiasis, "respiratory tract/bacterial infections" flu virus); the remaining 38 medicines are directed to chronic conditions.

Figure 19.2 below lists the medicines directed to these 45 different targets on the X-axis. As mentioned previously, the TTD database shows all the related medicines that attack the same target. In Fig. 19.2, the Y-axis plots two separate numbers: (a) total number of different medicines that have been FDA approved which attack this protein target/all indications for these medicines (solid line) and (b) total number of different medicines that have been withdrawn from trials which attack this target/all indications for these medicines (dashed line).

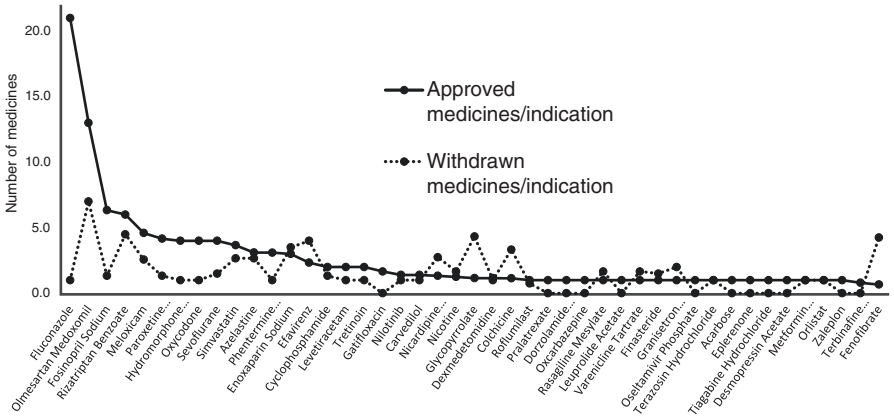

Fig. 19.2 45 Medicines attacking 45 different protein targets: Solid line: Total number of FDA-approved medicines attacking this target: Dashed line: Total number of withdrawn medicines attacking this target

There are almost always multiple approved medicines per indication. Fluconazole has 21 different FDA-approved "family member" medicines attacking the same target, but everything is for fungal infections. Simvastatin has 11 different statins attacking the same target but with a more diverse suite of approved indications, that is, hypercholesterolemia, lipid disorders, myocardial infarction, cerebrovascular ischemia.

For some medicines, however, the number of medicines per indication that have been withdrawn is greater than the number approved per indication. For instance, fenofibrate (an agonist of peroxisome proliferator activated receptor alpha protein) has four different approved medicines attacking this target which are directed against six different indications (Diabetes Type 2, hyperlipidemia, high cholesterol/trigylcerides/lipoprotein, atherosclerosis: ratio = 4/6 = 0.66). Yet 17 different medicines directed against this same target were withdrawn from clinical trials for four indications (ratio = 17/4 = 4.25). In total, 14 of these "Paragraph IV" medicines (14/50 = 13%) each had between 3 and 7 medicines per indication withdrawn from clinical trials (Fig. 19.2).

19.5 Discussion

19.5.1 Limitations of the Analysis

Because there are many different conditions, for example, different cancers, in this dataset of withdrawn clinical trials, Fig. 19.1 might be considered a lower limit as some conditions might have been missed in the search. Nonetheless, the overall interpretation of this Figure should not change. Indeed, some of these withdrawn clinical trials might have been themselves for repurposing, but that number is not known.

Similarly, there exist many more medicines already off patent than those on this rather specialized list of "Paragraph IV" medicines but the latter are the most recent ones that generic drug companies are willing to go to court over and would be considered very important from a clinical and market viewpoint. Even among the "Paragraph IV" medicines, there are likely more medicines not randomly chosen that have great potential for repurposing. For instance, analysis of the existing "Paragraph IV" antiprotozoal metronidazole (a DNA blocker) revealed 56 approved medicines attacking this same target: 46 for cancer, 1 for dietary shortage, 8 antimicrobials (e.g., malaria, bacterial infections, amebiasis, sepsis, urinary tract infections, schistosomiasis), and 1 for psoriasis. Four medicines against this target were discontinued in trials: two for lupus nephritis/systemic lupus erythematosus and two for cancer.

19.5.2 Repurposing Medicines from Failed Trials: Should We Bother?

There is a relative paucity of anti-infectives in FDA withdrawn clinical trials (Table 19.1), and this is mirrored by the relative lack of anti-infectives in the "Paragraph IV" list as well as their related medicines that attack the same target. This is likely a consequence of several well-known factors, including inadequate market incentives for companies to invest in R&D and bring new antimicrobial/anti-infective products to market at the right time [25].

Second, at first glance, repurposing new uses for medicines withdrawn from clinical trials would seem very risky indeed. Fourteen of the randomly chosen Paragraph IV medicines (14/50 = 13%) each had between 3 and 7 medicines withdrawn from clinical trials per indication (Fig. 19.2). More importantly, between January 1, 2003 and December 31, 2011, there was only a 10–15% probability that any given drug will advance from phase 1 to FDA approval [26]. Thus, 85/100 trials will not advance out of phase 1. The crude analysis presented here (Fig. 19.1) shows that 60% of all withdrawn clinical trials were withdrawn in phase 2. This is roughly consistent with the fact that of all the medicines attacking the 45 "Paragraph IV" therapeutic protein targets, nearly 30% were withdrawn in phase 1, 55% in phase 2, and 15% in phase 3. See also Appendix 3.

Nevertheless, it cannot be denied that failed medicines can be successfully repurposed. Two failed cancer drugs that were successfully repurposed include zidovudine (AZT), the first antiviral approved for HIV/AIDS in 1987 and, more recently, farnesyltransferase inhibitors (FTI), which were used to successfully treat children with the rapid-aging disease, progeria, in a 2012 clinical trial [27]. Tamoxifen was intended to be a contraceptive clinical trial were terminated and it was repurposed as the "gold standard" of antihormone therapy for prevention and treatment of all stages of breast cancer. Some 30 years after approval for cancer, researchers discovered that it also helps people with bipolar disorder by blocking

the enzyme PKC [28]. This does nothing to blunt the evidence that overcoming the clinical trials attrition rate is very challenging.

19.5.3 Repurposing of Generics for LMICs: A Double Edged Sword

Obviously, many already-approved medicines can be successfully repurposed and repurposing can be of great public health benefit [15, 27–29], but it exposes the tensions inherent in the current global R&D and intellectual property systems. As a preliminary point, repurposing a new indication for some approved generics would still seem ill-advised. As mentioned above, fluconazole has 21 different FDA-approved medicines attacking its therapeutic target, but each one is for fungal infection. Olmesartan has 13 different FDA approved medicines attacking its therapeutic target, and each is for hypertension.

More significantly, if a repurposed generic medicine works in a new disease indication using its existing formulation and doses, it may be controversial for the company to charge a higher price for the new disease indication, while patients continue to pay a lower price for the same medicine for the old disease indication. Typically, the "pioneer" medicine had market exclusivity from patents on the original product structure and methods of use. Unless a now, or soon-to-be, generic molecule is structurally reconfigured, from a business viewpoint only a second method of use and a possible new formulation patent would be obtainable.

If a generic company can secure a new "method of use" patent for a repurposed indication, meaning it is the first to discover a new use for an off-patent generic, it still might not be able to profit from it. If the generic is widely available from many manufacturers, a physician could prescribe a different drug from another manufacturer "off-label" for the repurposed indication, and the patent owner may not see any profit on sales, even though it holds the patent on the new use [30]. This is because it is often difficult to enforce this patent on a "use" as the patent infringing activity takes place in private, as it were [30].

In this regard, recent experience in the United Kingdom is on-point and instructive. Warner-Lambert (Pfizer being its parent company) has expended considerable effort to protect a patented market for its pregabalin (Lyrica®) product. Pregabalin is used for three indications: epilepsy, generalized anxiety disorder (GAD), and neuropathic pain. Patent protection for the active ingredient has expired yet Warner-Lambert holds a European patent (EP 0934061B) directed to use of this now off-patent medicine for treating pain.

In early 2015, generic drug manufacturer Actavis obtained marketing approval for generic pregabalin (under the trade mark Lecaent) for treating epilepsy and GAD, that is, the indications not covered by the claims of Warner-Lambert's use patent. Significantly, the pain indication accounts for about 70% of the pregabalin

market. Understandably, Warner-Lambert/Pfizer feared that doctors would prescribe pregabalin for the treatment of neuropathic pain, and the pharmacist would dispense the Actavis product for pain “off-label” [31]. After much legal maneuvering, Pfizer was granted an order compelling the UK healthcare authority National Health Service England (NHSE) to issue central guidance to prescribers and pharmacists in relation to Warner-Lambert’s pregabalin product [31].

Actavis had to notify superintendent pharmacists that Lecaent was not licensed for the treatment of neuropathic pain. Notably, in addition to writing to over 7500 superintendent pharmacists, Actavis also wrote to every Clinical Commissioning Group (CCG) in England and corresponding bodies in Wales, Scotland and Northern Ireland advising that Lecaent is not licensed for pain [31]. In compliance with the Court order, UK healthcare authority, National Health Service England (NHSE), issued guidance to CCGs, advising that pregabalin should be prescribed for pain under the brand name Lyrica, and that dispensers – when pregabalin is prescribed for pain-only dispense Lyrica. Software packages used by GP practices within the UK have now been updated to provide warnings of the existence of patent rights when pregabalin is prescribed for the treatment of pain [31].

The UK, and many LMICs, have healthcare systems which generally favor the prescribing and dispensing of less-expensive generic versions of a drug [32]. Actions taken by Actavis, Pfizer, and various healthcare bodies illustrate the lengths taken to avoid mis-prescribing or mis-dispensing of Actavis’ generic pregabalin for the pain indication [31].

It remains to be seen if a more formal system could be created to actually separate the patented market for a substance from the nonpatented market. Notwithstanding, it is not clear that many LMICs have the regulatory, legal, and IT infrastructure to manage such notification activities, even if the situation warranted such action. It is important to note that this pregabalin example of “off-label use” is based on therapeutic method of use patents, which are available in the United Kingdom. However, as the global framework for intellectual property rights (TRIPS) does not require LMICs to grant therapeutic “method of use” patents, the Actavis-pregabalin scenario in the United Kingdom may never arise in LMICs [33, 34].

In brief, a lack of clear exclusivity (typically afforded by the composition of matter patents for new drugs) for new uses creates challenges for innovator firms, generic manufacturers, and investors, making it difficult to fund drug development activities required for market approval, irrespective of whether for LMICs or not [35].

The situation is even less sanguine if we consider LMICs with a dual burden of NCDs and infectious diseases [36]. Indeed, of the 1059 medicines on the Paragraph IV list, there are 55 antibiotics and 0 antihelminthics (Appendix 19.3). In short, medicine repurposing, especially for the so-called “neglected” diseases which are prevalent in LMICs [37], does not ordinarily provide the same economic returns as does new drug development, with its patent protections and secured market exclusivity (1) so their scarcity on this list is not surprising.

Until a new system is implemented, which allows a company to reasonably recoup its investment on repurposing a generic medicine, it may well be that little generic medicine repurposing for LMICs will actually take place in the pharmaceutical industry. Investors focus on areas where they can make a profit from their drug discovery investments.

19.5.4 Recommendations for Improving the Situation

One approach is to get more companies to allow compound screening for potentially relevant off-target activity and to contribute more failed drugs. Efforts to do compound screening are ongoing and extensive. For example, since 2009, AbbVie (formerly Abbott) has shared with the Drugs for Neglected Diseases Initiative (DNDi) with thousands of compounds on a pro-bono basis for research on Chagas disease, Leishmaniasis, and river blindness [38]. The Academic Drug Discovery Consortium (ADDC) has established a new screening partnership with AstraZeneca, the aim being to provide ADDC members access to a high-quality compound library and allow AstraZeneca the opportunity to access and collaborate with academic researchers [39] It is not clear how many, if any, of these compounds will have previously been withdrawn from clinical trials. Given the rate of clinical failures in phases 1 and 2, it is not immediately obvious why even more failed compounds could be usefully repurposed. Using failed compounds may not be the most cost-efficient way to approach the problem.

An even more ambitious approach might be to get companies to contribute their active pipeline candidates as well as their failed medicines. The search for new indications should be expanded to active drugs and not just withdrawn/failed or already-approved active ones that are not otherwise prioritized [13]. In the United States, the National Center for Advancing Translational Sciences (NCATS) [40] acts as a clearinghouse, to facilitate drug repurposing by enabling the exchange and distribution of drug information, initiate collaborations, and provide the infrastructure and resources for academia and industry to work together. In July 2015, NCATS announced nearly $3 million to fund cooperative agreements with four academic research groups with respect to Type 2 diabetes, acute myeloid leukemia, glioblastoma, and significantly, Chagas disease [40].

Another example is the AIDA Preserving Old Antibiotics for the Future Project [41] running until December 2016 which seeks to determine the optimal dosing regimens for five existing antibiotics in treating multidrug-resistant infections [42].

Governments could create alternative incentive mechanisms that tie the rewards for developing new indications to their therapeutic value which is necessary for linking rewards to social value. See, for example [43, 44]. Because the underlying problem is inadequate market demand for socially valuable drugs – whether

repurposed or not, the government can remedy it with consumer subsidies (perhaps through subsidized prescription drug insurance or advanced purchase commitments) to bolster market demand for those products. Medicine repurposing efforts should focus on unmet medical needs and not making medicines for which existing treatments are available [1, 30].

Increasing the public availability of data can accelerate the process of drug repurposing, but incentives are needed to encourage more scientists to share their data. Negative or less interesting data are still valuable and should be shared with the larger drug repurposing community so that the specific reasons for drug failures are clear [13]. Sequestering valuable data [45] limits its value by inhibiting its availability for use in the healthcare and R&D systems. Crowdsourcing of candidate compounds for repurposing can generate ideas about new mechanisms of action and potential applications [46].

19.6 Conclusions

A successful, innovative pharmaceutical R&D business model requires identifying the area of the Venn diagram where scientific innovation, unmet need, and commercial attractiveness overlap [13]. Typically, what is needed is a sufficiently large number of patients to make a drug profitable so, in this regard, repurposing medicines for "neglected" or even more common diseases in LMICs are clearly a challenge where the market may exist, but patients are not insulated from the cost of medicines.

Medicines in abandoned clinical trials are available for repurposing, but the analysis presented here, albeit limited, suggests there may be few obvious medicines available to treat conditions prevalent in LMICs. Generic medicine repurposing is attractive in principal, and there are many thousands of off-patent medicines that could be repurposed. Yet those generics that the generic industry is willing to go to court over are primarily not anti-infectives and thus not obviously useful for neglected diseases. About 85% of medicines found to attack the various therapeutic targets of 45 Paragraph IV medicines were withdrawn from clinical trials in phase 1 and phase 2 likely due to safety and clinical failures.

Successful repurposing of medicines for LMICs will not happen without policy alignment and synergies of expertise that are created through collaborations between academia and industry. Academics in rich and LMICs can provide innovative insights linking pharmacologic and disease mechanisms to drug indications. Industry can facilitate execution across stage development, regulatory approval, manufacturing, and commercialization. Unlike use of failed medicines, the investigation of new targets and mechanisms for existing drugs with known safety profiles may add value to the business model and bring more therapies to market for patients in LMICs.

Annex 19.1

Stem	Definition	Examples	"Paragraph IV" medicine (# different products)
-ac	Anti-inflammatory agents (acetic acid derivatives)	Bromfenac	Bromfenac (1) Diclofenac (10) Etodolac (1) Ketorolac (6) Nepafenac (1)
-adox	Antibacterials (quinoline dioxide derivatives)	Carbadox	0
-antel	Anthelmintics (undefined group)	Carb*antel*	0
aril-,-aril,-aril-	Antiviral (arildone derivatives)	plecon*aril;* *aril*done; fos*arilate*	0
arte-	Antimalarials (artemisin derivatives)	*Arte*flene	0
-bendazole	Anthelmintics (tibendazole type)	Cam*bendazole*	0
-camra	Antivirals (intracellular adhesion molecules, icam-1 derivatives)	Trema*camra*	0
-carbef	Antibiotics (carbacephem derivatives)	Lora*carbef*	0
-catib	Cathespin inhibitors	Bali*catib*	Icatibant (1)
cef-	Cephalosporins	*Cef*azolin	Ceftaroline Fosamil (1)
-cidin	Natural antibiotics (undefined group)	Grami*cidin*	0
-cillin	Penicillins	Ampi*cillin*	Amoxicillin and Clavulanate Potassium, Piperacillin Sodium and Tazobactam Sodium
-citabine	Nucleoside antiviral or antineoplastic agents, cytarabine or azarabine derivatives	gem*citabine*; fia*citabine*; zal*citabine*	Capecitabine (1) Emtricitabine (3) Gemcitabine (3)
-cycline	Antibiotics (tetracycline derivatives)	mino*cycline*	Doxycycline (6) Minocycline Hydrochloride (5) Tigecycline(1)
-dapsone	Antimycobacterials (diaminodiphenylsulfone derivatives)	Ace*dapsone*	0
-dar	Multidrug resistance inhibitors	elacridar valspodar	0

Stem	Definition	Examples	“Paragraph IV” medicine (# different products)
-ezolid	Oxazolidinone antibacterials	eper*ezolid*; lin*ezolid*	Linezolid (4)
-fungin	Antifungal antibiotics (undefined group)	kala*fungin*	Caspofungin Acetate (1) Micafungin Sodium
-ganan	Antimicrobial, bactericidal permeability increasing polypeptide	ise*ganan*; pexi*ganan*	0
-gillin	Antibiotics (Aspergillus strains)	mito*gillin*	0
-kacin	Antibiotics obtained from Streptomyces kanamyceticus	Ami*kacin*	0
-micin	Antibiotics (Micromonospora strains)	madura*micin*; genta*micin*	Fidaxomicin
-monam	Monobactam antibiotics	gloxi*monam*; oxi*monam*; tige*monam*	0
-motine	Antivirals (quinoline derivatives)	fa*motine*	0
-mulin	Antibacterials, pleuromulin derivatives	Retapa*mulin*	0
-mycin	Antibiotics (Streptomyces strains)	linco*mycin*	Tobramycin Azithromycin(2) Clarithromycin Clindamycin (6) Daptomycin
-nidazole	Antiprotozoal substances (metronidazole type)	ti*nidazole*	Metronidazole (2)
-oxacin	Antibacterials (quinolone derivatives)	difl*oxacin*; ciprofl*oxacin*	Ciprofloxacin (3) Gatifloxacin (5) Gemifloxacin Mesylate Levofloxacin(5) Moxifloxacin Hydrochloride (4) Ofloxacin
-oxanide	Antiparasitics (salicylanilide derivatives)	Brom*oxanide*	0
-oxef	Antibiotics (oxacefalosporanic acid derivatives)	flom*oxef*	0
-parcin	Glycopeptide antibiotics	avo*parcin*	0
-penem	Antibacterial antibiotics (carbapenem derivatives)	imi*penem*	Doripenem (1) Ertapenem
-planin	Antibacterials (Actinoplanes strains)	mide*planin*; ramo*planin*; teico*planin*	0
-prim	Antibacterials (trimethoprim type)	ormeto*prim*	0

Stem	Definition	Examples	"Paragraph IV" medicine (# different products)
-pristin	Antibacterials, pristinamycin derivatives	quinu*pristin*; efe*pristin*	0
rifa-	Antibiotics (rifamycin derivatives)	*rifa*pentine; *rifa*mpin	Rifaximin
sulfa-	Antimicrobials (sulfonamides derivatives)	*sulfa*salazine	0
vir-, -vir- or -vir	Antiviral substances (undefined group)	ganciclo*vir*; en*vir*adine; *vir*oxime; al*vir*cept; dela*vir*dine	Tenofovir Disoproxil Fumarate (2) Valacyclovir Hydrochloride (3) Abacavir (2) Acyclovir Sodium (1) Adefovir Dipivoxil (1) Atazanavir Sulfate (3) Darunavir Ethanolate (2) Efavirenz (2) Rilpivirine,(1) Entecavir (1) Famciclovir (1) Fosamprenavir Calcium (1) Ganciclovir (1) Lopinavir/Ritonavir (2) Maraviroc (1) Nevirapine (1) Oseltamivir Phosphate (3) Raltegravir (1) Ribavirin (2) Ritonavir(2)

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Chapter 20
Pharmaceutical Policy in Countries with Developing Healthcare Systems: Synthesis of Country Case Studies

Warren Kaplan, Nikolina Boskovic, Daniel Flanagan, Serafina Lalany, Chia-Ying Lin, and Zaheer-Ud-Din Babar

20.1 Introduction

This chapter attempts to synthesize information taken from the various country chapters in this volume. To do this, we created a template (see Appendix 20.1) from which information is extracted from the various country profiles. Each of the country profiles generally followed a preset format, and the template was designed to mimic this by having various "domains" (see below). We searched the documents for key terms to aid in filling out the template. Data used to generate the figures in this chapter were compiled from both the completed templates and from data generated by the World Health Organization (http://www.who.int/healthinfo/statistics/en/) and the World Bank (http://data.worldbank.org/indicator).

There are several key limitations inherent in this analysis. Not all the country profiles contained sufficient information to populate the data template. The fact is that no response to a question on the template (e.g., presence of a pharmacovigilance system in country X) is not evidence that such a system is nonexistent.

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We also present summaries of the various challenges faced by the pharmaceutical systems in these countries with regard to the various domains. The completed data template is found in Appendix 20.2.

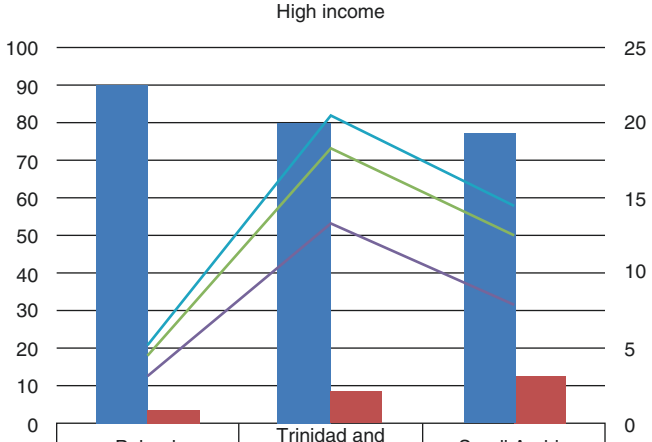
20.2 Overview: Health System

20.2.1 High-Income Countries

In these countries (Fig. 20.1), there is primarily an NCD burden of disease (left hand Y axis: 80–90% of reported conditions are noncommunicable). There is a three- to fourfold gradient of increasing infant/neonatal/under-five mortality (right hand *Y* axis) from Poland to Trinidad and Tobago.

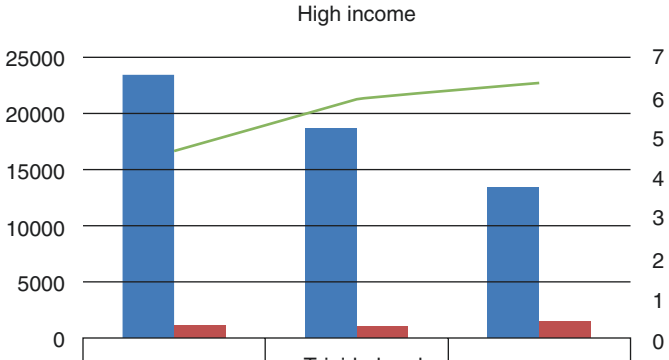
All three countries shown in Fig. 20.2 (below) are ranked according to their per capita Gross National Income (all called Gross Domestic Product or GDP) (left hand *Y* axis). These countries have per capita health government expenditures ranging between $1100, about $1500 annually (left hand *Y* axis) and about 5–6% total health expenditure as a percentage of Gross Domestic Product (GNI: right hand *Y* axis)

Figure 20.3 ranks these countries by their per capita health spending (left hand *Y* axis). The majority of total annual health spending in these countries is in the public sector (right hand *Y* axis), with the largest fraction (74.5%) being in Saudi Arabia. In Trinidad and Tobago, the percent health spending in the private sector is nearly



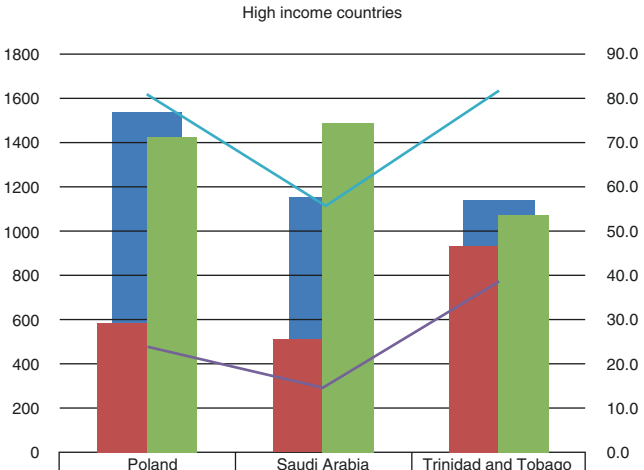
	Poland	Trinidad and Tobago	Saudi Arabia
% Burden of disease NCD	90.1	80.2	78
% Burden of disease ID	3.4	8.6	12.6
Infant mortality/1000 live births	4.5	18.2	12.5
Neonatal mortality/1000 live births	3.1	13.2	7.9
Under five mortality rate per 1000	5.2	20.4	14.5

Fig. 20.1 Burden of disease estimates in high-income countries



	Saudi Arabia	Trinidad and Tobago	Poland
GNI per capita, Atlas method (current US$) (2014)	23550	18600	13370
Per capita gov't health expenditure (dollars)	1,147	1,136	1540
Total health expenditure as % GDP	5	6	6

Fig. 20.2 Selected health expenditures in high-income countries



	Poland	Saudi Arabia	Trinidad and Tobago
Total annual health spending per capita ($)	1540	1147.445577	1136
% Total health spending PRIVATE SECTOR as % of THE	29.0	25.5	46.5
% Total health spending PUBLIC SECTOR as % of THE	71.0	74.5	53.5
Out-of-pocket health expenditure (% of total expenditure on health)	23.5	14.3	38.0
Out-of-pocket health expenditure (% of private expenditure on health)	80.8	56.2	81.7

Fig. 20.3 Selected health expenditures in high-income countries

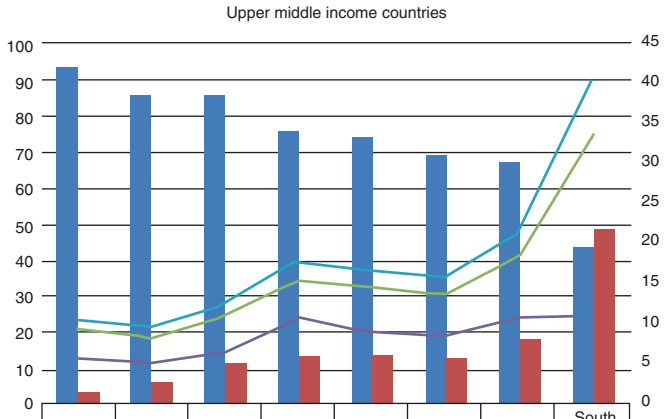
equal to that of the public sector (46.5%). There is an increasing gradient in out-of-pocket expenditures as a percent of total health expenditure and private health expenditure from Saudi Arabia to Trinidad and Tobago, the latter with over 80% of private health expenditure being out-of-pocket, the former with about 56%.

Healthcare in all three countries is primarily centralized healthcare, in which public healthcare is supported through government funded public health insurance. Saudi Arabia, in particular, has a large network of modern healthcare facilities, including hundreds of hospitals and thousands of primary care centers are currently established in the country to provide healthcare to all citizens and residents in the country.

Nonetheless, there is always an active private sector in which services provided are usually financed by cooperative health insurance schemes and out-of-pocket payments. All three countries face similar structural issues within their healthcare systems. Primary among these are escalating costs in providing healthcare services, plus local healthcare professionals. This is especially true in Saudi Arabia as the majority of healthcare professionals are expatriates. To more or less degrees, all three face a rapid population growth, the aging of the population, the high burden of chronic diseases, and a growing demand for healthcare services.

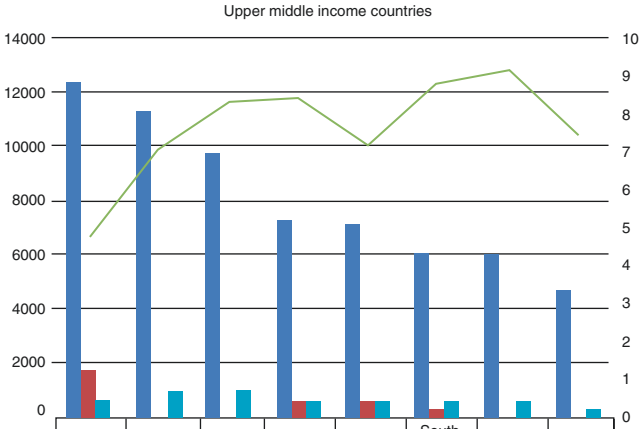
20.2.2 Upper Middle-Income Countries

In these upper middle-income countries (Fig. 20.4), there continues to be a primarily NCD burden of disease (left hand *Y* axis) with a decreasing gradient from Bulgaria (90% of reported conditions are noncommunicable) to South Africa (43%



	Bulgaria	Russia	Argentina	Jordan	Brazil	Colombia	Ecuador	South Africa
% Burden of disease NCD	93.7	85.7	81.4	75.6	74.2	69.3	67	43.4
% Burden of disease ID	3	6	11.3	13.2	13.5	12.6	17.8	48.5
Infant mortality/1000 live births	9.3	8.2	11.1	15.4	14.6	13.6	18.4	33.6
Neonatal mortality/1000 live births	5.6	5	6.3	10.6	8.9	8.5	10.8	11
Under five mortality rate per 1000	10.4	9.6	12.5	17.9	16.4	15.9	21.6	40.5

Fig. 20.4 Burden of disease estimates in upper middle-income countries



	Argentina	Russia	Brazil	Bulgaria	Colombia	South Africa	Ecuador	Jordan
GNI per capita, Atlas method(current US$) (2014)	12460	11400	9850	7220	7130	6050	6010	4680
Per capita gov't health expenditure (dollars)	1725			566	569	223		
Health expenditure per capita (current US$)	605	893	947	662	569	570	579	359
Total health expenditure as % GDP	5	7	8	8	7	9	9	7

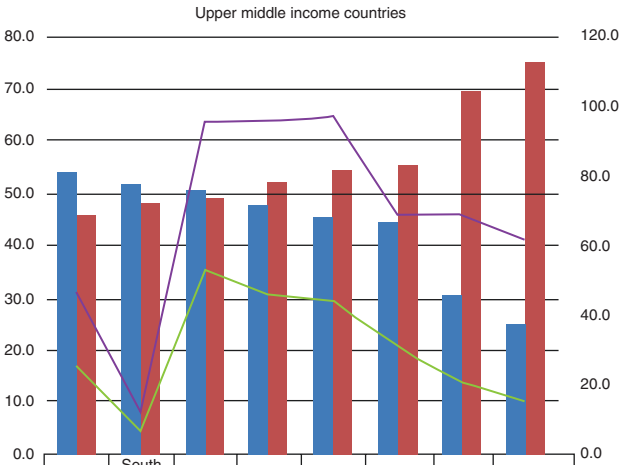
Fig. 20.5 Selected health expenditures in upper middle-income countries

are noncommunicable). In line with the increasing gradient of communicable diseases (left hand *Y* axis), there is a three to fourfold gradient of increasing infant/under five mortality from Bulgaria through Jordan to South Africa (right hand *Y* axis), although the neonatal mortality rate is about a twofold increase from Bulgaria to South Africa.

These countries have per capita health government expenditures ranging between $1725 annually to about $223 annually (Fig. 20.5: left hand *Y* axis), although only a few countries reported this statistic. Total health expenditure as a % of Gross National Income (right hand *Y* axis) is lowest in Argentina (5%) and highest in Ecuador and South Africa.

Among these countries, the majority of total health spending in these countries is very roughly split between public and private sectors (Fig. 20.6: left hand *Y* axis), with Jordan and Colombia being the outliers with the largest fraction (70–75%) being spent by the public sectors. Russia and Bulgaria have a remarkable 95–97% of out-of-pocket health expenditures (right hand *Y* axis) being in the private sector with South Africa being the least (12.5%). Between about 6.5% and 53% of total health expenditure is out of pocket, a very wide range, with South Africa having the least and Russia/Bulgaria the most.

Generally, the health systems of these countries are designed within a unified framework, while implementation of policies is quite often decentralized, in principle to ensure better management and greater geographical accessibility. Russia, with its centralized Federal Ministry of Health, is supported by the Ministries of Health in 85 regions, with their own budgets and regional development programs.



	Brazil	South Africa	Ecuador	Russia	Bulgaria	Argentina	Jordan	Colombia
% Total health spending PRIVATE SECTOR as % of THE	54.0	51.8	50.8	47.8	45.4	44.6	30.3	24.9
% Total health spending PUBLIC SECTOR as % of THE	46.0	48.2	49.2	52.2	54.6	55.4	69.7	75.1
Out-of-pocket health expenditure (% of total expenditure on health)	25.5	6.5	53.0	45.8	44.2	30.7	20.9	15.4
Out-of-pocket health expenditure (% of private expenditure on health)	47.2	12.5	95.3	95.9	97.3	68.9	68.8	61.7

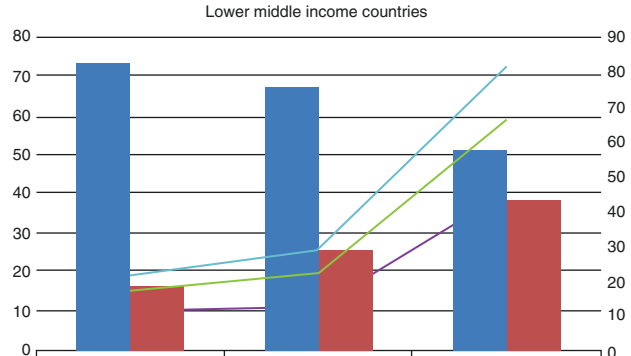
Fig. 20.6 Selected health expenditures in upper middle-income countries

There are active public and private sectors in all countries. Jordan in particular has an extensive private sector, which includes 61 private hospitals and many private clinics. The private sector in Ecuador comprises a diversity of nonprofit and for-profit hospitals, small clinics and out-patients physician's offices. South Africa as in the other countries has a private sector funded largely from insurance premiums (paid by individuals and employers), but also from out-of-pocket payments. It caters mostly, but not exclusively, for the needs of members of registered medical schemes.

20.2.3 Lower Middle-Income Countries

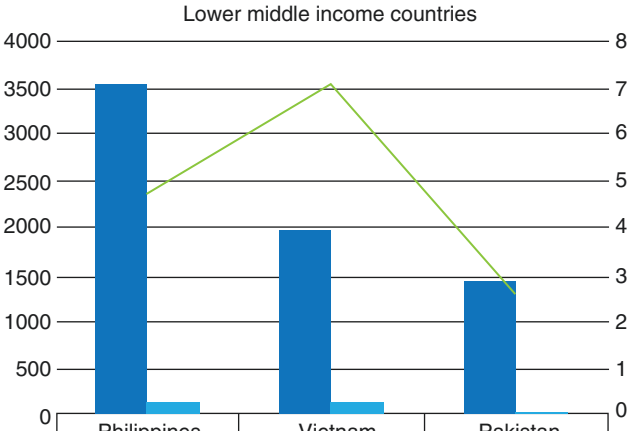
In these few lower middle-income countries (Fig. 20.7), there continues to be reported a primarily NCD burden of disease (left hand *Y* axis) with a decreasing gradient from Vietnam (73% of reported conditions are noncommunicable) to Pakistan (50% are noncommunicable). In line with this, there is a three- to fourfold gradient of increasing infant/neonatal/under-five mortality from Vietnam through Philippines to Pakistan (right hand *Y* axis).

These countries all have per capita health government expenditures of less than about $100 annually (Fig. 20.8: left hand *Y* axis). Total health expenditure as a % of Gross Domestic Product (Fig. 20.8: right hand *Y* axis) is lowest in Pakistan (just 3%) and higher in Vietnam and the Philippines (5–7%).



	Vietnam	Philippines	Pakistan
% Burden of disease NCD	72.9	67.1	50.5
% Burden of disease ID	16.6	25	38.3
Infant mortality/1000 live births	17.3	22.2	65.8
Neonatal mortality/1000 live births	11.4	12.6	45.5
Under five mortality rate per 1000	21.7	28	81.1

Fig. 20.7 Burden of disease estimates in lower middle-income countries



	Philippines	Vietnam	Pakistan
GNI per capita, Atlas method (current US$) (2014)	3540	1980	1440
Health expenditure per capita (current US$)	135	142	36
Total health expenditure as % GDP	5	7	3

Fig. 20.8 Selected health expenditures in lower middle-income countries

	Philippines	Vietnam	Pakistan
% Total health spending PRIVATE SECTOR as % of THE	65.7	64.8	45.9
% Total health spending PRIVATE SECTOR as % of THE	34.3	35.2	54.1
Out-of-pocket health expenditure (% of total expenditure on health)	53.7	56.3	36.8
Out-of-pocket health expenditure (% of private expenditure on health)	81.7	86.8	80.0

Fig. 20.9 Selected health expenditures in lower middle-income countries

In these lower middle-income countries, the majority of total health spending is in the private sector (Fig. 20.9: left hand *Y* axis), except for Pakistan. A very high fraction (80%) of out of pocket health expenditures (Fig. 20.9: right hand *Y* axis) is in the private sector. About 40–56% of total health expenditure is out of pocket.

20.3 Pharmaceutical/Industrial System

20.3.1 High-Income Countries

We note little information in these reports on medicine production capacities in high-income countries. In Saudi Arabia, local pharmaceutical companies produce only approximately 17% of the domestic pharmaceuticals as part of a 7.5 billion market. By value, patented medicines were 56.2% of the total medicine and 64.5% of the prescription medicine markets and generic medicines represented 30.9% and 35.5% of the total medicine and prescription medicine markets, respectively. This situation is in contrast to Poland, with a 66% market share of generics by value, being one of the highest rates in Europe. In October 2015, the value of sales of the

pharmaceutical market was nearly 7.8 billion, on the same order as Saudi Arabia. In Poland, about 2.7 billion USD or 41.7% of total medicine spending is on over the counter (OTC) medicines.

20.3.2 Upper Middle-Income Countries

The total value of the medicines market in seven of eight countries averaged 9.71 billion USD (range: Ecuador $1.5 billion–Brazil $28 billion). Six of the countries reported on their pharmaceutical industry, which averaged 80 local producers (range 20 Jordan–160 Argentina). Three countries reported an average of 22 foreign manufacturers (range 10 Colombia–30 Argentina). On average, local production by local manufacturers was 62.1% (n = 5) of the total pharmaceutical market volume and by value, the local producers were about 43% of the total market (n = 6).

Of the eight countries, five make APIs locally. Some, like Colombia are highly dependent on pharmaceutical imports (both finished products and APIs, as well as, chemical, biological and biotechnological products). In Ecuador, the local pharmaceutical industry only has a small share of the domestic market and exports are not substantial, which might be partly caused by the concerns on the quality of locally manufactured medicines.

20.3.3 Lower Middle-Income Countries

Of three countries, only two reported. Interestingly, the number of local manufacturers is higher than in "richer" countries, averaging 339 local producers (range 180 Vietnam–619 Pakistan) and 235 foreign ones (range 31 Pakistan–438 Vietnam). Vietnam has a domestic pharmaceutical industry characterized by limited R&D facilities, insufficient financial capacity, and poor management. Most local pharmaceutical manufacturers comprise small-scale operations with outdated manufacturing technology and duplicated production processes. About 90% of the raw materials used in Vietnam's domestic production are imported.

20.4 Trade and Public Health

20.4.1 High-Income Countries

All countries are members of the World Trade Organization (WTO) but provided little additional information.

Medicines from Poland have much lower prices than those sold in the Western European markets, and they are illegally exported to Western European countries by selling of a drug from a pharmacy back into a pharmaceutical warehouse.

20.4.2 Upper Middle-Income Countries

All are members of WTO and most countries are using the WTO TRIPS Agreement's (Trade-related Aspects of Intellectual Property Rights) so-called "flexibilities", with regard to intellectual property. For example, Argentina has compulsory licensing provisions that can be applied for reasons of public health, the ability to use patented methods and products in order to file for regulatory approval of generic versions (the so-called "Bolar exceptions"), as well as provisions related to parallel importing. Additionally, there are legal provisions on data protection for pharmaceuticals. Brazil is also following suit in this regard. In order to incorporate TRIPS nationally, Brazil requires that the granting of patents for pharmaceutical products depends on the prior consent of the National Health Surveillance Agency – ANVISA. Brazil's strategy to address high-cost, patented medicines includes aggressive price negotiations using the threat of compulsory licenses and local production of medicines.

Colombia, although a WTO member since 1995, has extensively exercised the right to use any TRIPS flexibility as safeguards to protect public health from patent rights' holders abuse. Colombia has requested drug compulsory licenses twice (Kaletra® in 2008 and Glivec® in 2014) but neither has resulted in a compulsory license so far. Instead, Colombia introduced data exclusivity protection, which is controversial because it delays the entrance into the market of competitors of the protected product, regardless of the patent protection's status. Subsequent free trade agreements with the United States and EU adopted the same standard, with a 5-year term of regulatory test data exclusivity.

Jordan is also a TRIPS signatory but, unlike Brazil or Argentina, has adopted more strict IP provisions than required by TRIPS. Prior to TRIPS, patent-protected medicines found in major industrialized countries were widely available in Jordan, usually at a lower price than the original patented drug. The copies were either manufactured by local companies in Jordan or imported, without having to ask the patent holders' permission.

South Africa has enjoyed use of TRIPS flexibilities. It has a long history with TRIPS, using it to gain access to medicines. Although not reviewed in the South African document, it is worth mentioning that on September 19, 2002, the Treatment Action Campaign launched a complaint with South Africa's Competition Commission against GlaxoSmithKline and Boehringer Ingelheim. The complaint charged these corporations with excessive pricing in respect of ritonavir, lamivudine, ritonavir+lamivudine, and nevirapine. GSK and BI were found to have contravened the Competition Act of 1998, and to have abused their dominant positions in their antiretroviral markets. On March 7, 2001, Indian pharmaceutical manufacturer CIPLA formally requested the South African Department of Trade and

Industry to issue compulsory licenses to patents on the following HIV drugs: nevirapine, lamivudine, zidovudine, stavudine, didanosine, efavirenz, indinavir, and abacavir.

Challenges
Jordan's agreement with the World Trade Organization (WTO) poses major challenges for the local pharmaceutical industry. Compliance with TRIPS provisions has resulted in adverse outcomes, such as increased medicine prices, and a dwindling local pharmaceutical industry, in part the result of Jordan's inability to access advanced, patented technology on reasonable commercial terms. The US–Jordan Free Trade Agreement (FTA) in 2001 limits the grounds under which a compulsory license can be issued far beyond those in Article 31 of the TRIPS Agreement. It only permits compulsory licenses to remedy anticompetitive practices, for public noncommercial use, for a "national emergency," or in case of "extreme urgency."

20.4.3 Lower Middle-Income Countries

All countries are members of WTO but provided little additional information.

20.5 Regulation/Legal

20.5.1 High-Income Countries

None of the high-income countries had a constitutionally based right to health, although all had a single national medicines policy. Pre- and postmarket product quality regulations and manufacturing Good Manufacturing Practice (GMP) standards were also followed but only Poland specifically mentioned the presence of a bioequivalence requirement for generic medicines. All had some type of pharmacovigilance system on the books but no mention of its implementation. Only Poland mentioned the presence of counterfeit and fake medicines but asserted that availability of counterfeit medicines "… does not seem to be a concern for Polish community pharmacies."

Challenges
Medicines regulation in Poland is expensive, complicated, and time consuming. Medicines that are not authorized for sale in Poland can be imported via direct import and the Ministry of Health, not the medicines regulatory authority, regulates this. Medicines imported in this way are illegally exported to Western European countries. The easiest and most popular way of illegal export is designated as "resale," which involves the selling of a medicine from a pharmacy back into a pharmaceutical warehouse.

It seems remarkable but in Trinidad and Tobago, the exact number of pharmaceutical products registered is, according to the report, "unknown." Furthermore, there are no laws that require authorization for the conduct of clinical trials. Also, unauthorized agents import medicines not registered for use in Trinidad, without the requisite license needed for such importation and distribution.

20.5.2 Upper Middle-Income Countries

Four of these countries had a constitutional right to health (Argentina, Brazil, Colombia, Ecuador) and a different set of four had a single medicines policy (Brazil, Colombia, Russia, South Africa). Argentina has multiple medicines policies. As expected, all countries had pre- and postmarketing product quality rules, GMP regulations, and three have bioequivalence requirements for generics (Argentina, Brazil, Jordan). All except Colombia mentioned the existence of a pharmacovigilance system on the books (with no mention of the extent of implementation).

With respect to substandard, spurious, falsely labeled, falsified, and counterfeit (SSFFC) medical products, just four countries had specific sanctions (Argentina, Brazil, Ecuador, Jordan). Jordan asserted that there is no problem with counterfeit medicines. In Russia, it was estimated that 7–8% of Russian pharmaceuticals are substandard and that 0.5–0.6% are counterfeit. In Argentina, in 2008, it was estimated that 10% of the medicines on the market were fake. Argentina does have a system of National Drug Traceability for presumed control and monitoring of medicines throughout the distribution chain and assigns each medicine a unique barcode identification. Argentina admitted that its counterfeit medicine market was around USD$ 120 million dollars and most were for "serious illnesses" such as cancer, HIV, and hemophilia.

Challenges

Argentina's healthcare system is very fragmented and lacks a unique list of essential medicines. Likewise, the country does not have a National Health Technology Assessment (HTA) agency or national health economic guidelines. Consequently, HTA activities are completely decentralized, and the medicines covered in each health system's subsector depend on different stakeholders. Similarly, Bulgaria does not require marketed medicines to have or imply evidence of satisfactory HTA and in Russia, there is no centralized HTA agency either as local state authorities can form their own budgets. Typically, Russian patients receiving medicines in community pharmacies report adverse events to their doctors, so that pharmacies cannot be considered as a reliable source of information for pharmacovigilance reporting.

In South Africa, there are apparently no data available on the extent to which SSFFC medical products have been detected or reported. Critically, there is no publicly accessible register of medicines, showing all products for which a marketing authorization has been issued by the South African medicines regulatory authority.

20.5.3 Lower Middle-Income Countries

None of these three countries mentioned that they had constitutional right to health, although all had a single medicines policy and pre- and postmarketing product quality regulations regulated largely by their respective national governments. Pakistan is a typical example as drug sales are regulated by provincial governments and drug manufacturing, registration, licensing, import, and export are regulated by the federal government. All had GMP standards but Pakistan asserted that GMP "malpractice" is common, which we might assume to mean the taking of bribes. The Pakistani medicines regulatory authority is underfunded. Only the Philippines mentioned the existence of a bioequivalence requirement for generics that is operating. Although Vietnam's regulations allow for a requirement of bioavailability and bioequivalence data, there have been only 12 active substances out of about 1500 required bioequivalence data submissions.

Challenges
While the Philippine National Formulary is reviewed through a process that nominally involves cost-effectiveness analysis, pharmacoeconomic capacity is weak and HTA is at an early stage. Pakistan's pharmacovigilance system is said to be "… largely neglected …". There is a dire need to establish an adverse drug reaction database on national level, and also a liaison to liaise with the WHO's Uppsala Monitoring Center for monitoring The Pakistan national regulatory authority seems to be ineffective; as it is working on a limited budget of only US$ 4.77 million with only 275 staff members, including drug inspectors. A common challenge in these countries is the inadequate number of pharmaceutical inspectors. Vietnam specifically mentioned that parmacovigilance activity is challenging because of an incomplete Drug Information Network from central to local level that lacks coordination throughout the system.

20.6 Financing/Pricing

20.6.1 High-Income Countries

All three countries have a mixed, two-tier healthcare system, for both private healthcare and public healthcare facilities. In Trinidad and Tobago, public healthcare if free and funded by taxes but only 36% of the demand for medicines in the public sector is being met and there is no active government or private sector price monitoring system and no pharmacoeconomic analyses.

In Saudi Arabia, healthcare is also provided via a dual system (i.e., public and private sector). The public sector is currently the main provider of healthcare and is funded from the government budget. Private sector services are financed by cooperative health insurance schemes and out-of-pocket payments. In Poland, the public

healthcare system is primarily supported through government funded public health insurance but with a significant contribution through out of pocket patient charges.

All three countries strictly control medicine prices. In Saudi Arabia, it is somewhat unusual that any drug product must be priced before marketing so that pricing is one of the essential steps during the medicine registration process. Pharmacoeconomic studies of a product (if available) are considered in pricing. Common pricing criteria and the pricing rules of generic medicines are complex but successive generic equivalents require step-wise reductions in price. Similarly, Poland's price controls have a significant impact on the pharmaceutical market as governmental pharmacoeconomic analyses are used to determine the prices of individual medicines, the amount of reimbursement, validity of registrations, and cost-effectiveness of preventive actions. Each holder of a Polish market authorization that applies for reimbursement of drugs must provide a cost-effectiveness analysis and a budget impact analysis. There is also a relatively complex pricing schedule.

20.6.2 Upper Middle-Income Countries

Financing of healthcare and medicines varies among each country but, with few exceptions, also follows a mixed public/private model. For instance, in Russia, healthcare is financed via state-funded programs using federal and regional budgets, various insurance funds, "out of pocket" expenses and nationalized industries (national air company "Aeroflot," Russian Railways, etc.) with their own budgets and structures.

In Argentina, Brazil, Bulgaria, and Colombia, healthcare services are provided by public hospitals and healthcare units, which are financed through national, provincial, and municipal resources funded by taxes, workers, employers, and retirees contributions. In South Africa, the public sector is largely funded from the treasury and caters for the needs of the uninsured. The private sector is funded largely from insurance premiums (paid by individuals and employers), but also from out-of-pocket payments. It caters mostly, but not exclusively, for the needs of the members of registered medical schemes. Ecuador's healthcare is funded primarily through the government, presumably by taxes. Only about 5.5% of the population is covered by insurance.

Jordan seems to be the sole exception to this two-tier financing. Here, the private sector is the largest source of health funding (57%) with the remaining 37.5% and 5.5% being covered by the private and donor sectors respectively.

All countries monitor and manage prices to some extent EXCEPT Argentina, which has "… no legal or regulatory provisions for medicine pricing." Prices are set by a market economy but there are some voluntary pricing agreements between the government and the pharmaceutical industry.

In Brazil, the Medicines Market Regulatory Chamber sets *ex factory* medicines prices, maximum consumer prices, and public sector prices. Brazil uses both external and internal reference pricing for generics, but the price may not exceed 65% of

the reference drug. Federal, state, and municipal levels share responsibility for financing medicines for primary healthcare. South Africa created its own Pricing Committee and introduced a single exit price (SEP) for all prescription medicines, in the form of a fixed *ex factory* price with a logistics fee component (and value added tax) for medicines sold to all purchasers other than the State. Internal reference pricing exists, external reference pricing is planned but not yet practiced. This has also been used to regulate the maximum dispensing fee charged by pharmacists and licensed dispensing practitioners, and to provide for annual reviews of these fees as well.

Bulgaria has external reference pricing for generics and, while a statutory price reduction is applied at the point of initial generic market entry, there is no mechanism to drive further price reductions within the off-patent market. In effect, the *ex factory* price of a generic medicine cannot be higher than 80% of the originator and must be no higher than the lowest price for the same medicine in any reference country. Colombia has a complicated system of external and internal reference pricing methodologies.

In 2011, Ecuador established a price regulation system, which is trying to more updated mechanisms, based on international price referencing. In the private sector, there appears to be therapeutic reference pricing, e.g., new medicines that have no therapeutic advantage over existing medicines for the same indication, will get a price no higher than the existing competitors.

For drugs manufactured abroad, the price in Russia can be established based on the price overseas but for locally manufactured medicines the price is based on the actual price of a medicinal product for a certain period of time and the actual production costs of drugs.

Most countries in this category (6/8) have some sort of government pharmacoeconomic evaluation for reimbursement and inclusion on the respective national drug list.

Challenges

The drawbacks of fairly complex financing systems (like Russia, Jordan) are related to accessibility, equality, duplication of services, poor coordination among major providers, unregulation of the private sector, low utilization rates in the private sector, limited quality improvement programs, inefficient use of available resources, poor management, and an inappropriate health information system.

Indeed, in Jordan, there are all manner of perverse economic incentives to keep medicines prices high. Wholesalers and pharmacies receive margins on the landed cost and on the wholesale price, respectively. These are cumulative. As a result, there are strong incentives for both wholesalers and retailers to promote and sell the highest priced drugs or brands as these attract the highest return in money terms. Moreover, the low demand in the small Jordanian market makes local manufacturers request the highest prices possible, as they depend on exports and the exportation market tends "… to request the country of origin price …" during price negotiations. Thus, the current policy encourages competition between generics and originators only, but not between generics. The reason behind the weak pricing

policy in Jordan may be due to the local generic industry and originator wholesalers influencing the policy. In South Africa, there has been a ban on off-invoice bonuses, rebates and various other marketing incentives but it has been difficult to enforce.

20.6.3 Lower Middle-Income Countries

In Vietnam, 72% of all medicines expenditure is financed by out-of-pocket patient expenses. This percentage is similar to Pakistan where the government funds public sector hospitals but overall the government funds 32% of total Pakistan health expenditure, whereas 64% is funded by the patients themselves. In the Philippines, government expenditure on health at 31.6% of total health expenditure and out-of-pocket expenditure on health was a remarkable 82.9% of private expenditure on health, revealing weak coverage of health insurance benefit packages.

Of these lower middle-income countries, only Pakistan does NOT monitor prices but all three attempt to set medicine prices, more or less successfully. The Government of Pakistan follows either SAARC (South Asian Association for Regional Cooperation) countries or international market price trends while setting the prices of medicines in the country. Vietnam has allowed pharmaceutical companies to set prices of their products based on market forces, subject to "stabilization" by the State, but this term was not explained.

It appears that only the Philippines has an active pharmaeconomic system in place. Two pricing schemes Maximum Drug Retail Price (MDRP) and Government-Mediated Access Price (GMAP) are applicable at all retail pharmacies in both public and private sectors. Under the Maximum Drug Retail Price (MDRP) scheme, five drug molecules (amlodipine, atorvastatin, amlodipine/atorvastatin combinations, azithromycin, cytarabine, doxorubicin) on a named product basis have ceiling retail prices set by presidential proclamation.

Challenges

The Philippine government has taken a number of measures to increase affordability of medicines, although there remains no systematic price regulation in either public or private sector. Under the GMAP scheme, a wider range of drugs have had their prices voluntary reduced by half. This was done after negotiation with the government; however, competitor products have also reduced their prices. Senior citizens and disabled persons are entitled to a 20% discount on retail medicine purchases but the discount is provided by the retailer out of their own operating income and is not funded through taxation. This may result in increased prices of medicines in general to compensate for losses due to the discount. The basis for the price reductions under these two schemes is unclear and the selection of drugs for inclusion under them has been questioned. An assessment of the effects of the price reductions has concluded that they did little to increase access to essential medicines for the poor and many of the medicines under these schemes are not those prescribed for them.

In Vietnam, price regulation initiatives did not address the need for reasonable prices or the need to differentiate between declared, published, and selling prices. Further, the provisions were not routinely monitored or effectively enforced. The medicine pricing policies are still in the start-up phase and there is currently no requirement for Health Technology Assessment to support medicine pricing.

20.7 Procurement/Distribution

20.7.1 High-Income Countries

All three high-income countries typically have a centralized public sector procurement system. Poland is experimenting with "Direct to Pharmacy" distribution, which leads to the omission of wholesaler activity, and products are purchased by pharmacies without intermediaries being involved. Poland's hospitals have the option of creating purchasing groups, thus lowering their costs through volume and preferred supplier arrangements. The downside of this approach is that it shifts the procurement focus to very standardized product orders and consequently there can be a significant reduction in the range of products available in Polish hospitals

Trinidad and Tobago conducts an open and competitive tendering process annually for supplies for the list of vital, essential, and necessary (VEN) medicines. In the private sector, the list of drugs to be acquired is determined by a pharmacy manager, with potential input from other pharmacists. Medicines and medical supplies are procured from local distributors, who obtain their products from foreign manufacture. In the Saudi Arabian public sector, the centralized procurement system, which is the main one, receives annual tenders that are developed by government organizations and sent to the procurement agency in the Ministry of Health (MOH). In the private sector, the procurement and distribution of medicines are purchased from wholesalers and distributors.

20.7.2 Upper Middle-Income Countries

All countries in this category, except Colombia, have strong centralized public sector procurement with variations. The private sector gets its medicines from manufacturers and/or wholesalers.

Notwithstanding the fact that Colombia created the first Latin American system based on managed competition with financing for a comprehensive package of personal health services, the government has not been able to implement centralized procurement. It also lacks mechanisms to measure registration of companies and organizations whose purpose is to purchase, sell and/or distribute medicines.

The South African centralized limited competitive bid (tender) system has been in place since 1985, where all public sector medicines are procured in terms of a national competitive bid (tender), and delivered either to provincial stores in the provinces or directly to public health facilities. In the private sector, wholesalers or distributors do medicines supply from manufactures to end dispensers. Public and private procurement is entirely separate.

Procurement in Brazil is carried out mostly at the municipal level. All government purchases are done through an open bid, with the exception of some large hospitals with managerial autonomy, public procurement is always centralized. The centralized procurement of medicines involves much bureaucracy (something not unusual in any of these countries) and in Brazil it is particularly "… not agile." In many cases, it takes around 9–12 months between the time a procurement list is prepared until medicines are delivered to the warehouse. Similarly, in Jordan, limited financial resources and lengthy bureaucratic procedures may lead to certain essential drugs becoming out of stock. Procurement is only open to companies registered by the Jordanian government.

In Russia, there are three main levels of procurement at the federal, regional, and at the level of individual medical institutions. The main criterion for selection is the lowest price compared to competitors. If two or more manufacturers from the Eurasian region are bidding, then parties with drugs manufactured in other countries are not permitted to participate in the tender process. In the case, that there is competition between brand name and generic drugs it is most likely that the generic will be successful. This algorithm makes it possible to decrease expenditures and manage within budgets. On the other hand, it does not take into consideration parameters such as efficacy, efficiency, or cost-effectiveness. In Russia, private healthcare institutions can purchase medicines according to their corporate procedures. However, this segment of the market is relatively small.

Challenges

The South African centralized limited competitive bid system is over 30 years old but accurate quantification of demand remains a challenge, with poor quality and noninteroperable information systems complicating the use of prior consumption data and preventing greater use of morbidity-based estimates.

In Bulgaria, vertical integration (manufacturer, wholesaler, retailer) is theoretically prohibited but the largest local producer Sopharma (supplying both originator and generic products, and the only local manufacturer of sterile injectables) is in fact one of several entities reportedly heavily vertically integrated with a wholesaling operation as well as owning a large number of pharmacies. While by law any one individual is permitted to own a maximum of four pharmacies, that same individual may own multiple entities each of which may, in turn, also own up to four pharmacies, thereby controlling a substantial network. In reality, one network of around 300 pharmacies is owned by a single entity, which also owns a wholesaler. The costs of medicines used in hospitals are ostensibly captured in the estimations of the costs using standard treatment guidelines but in practice, however, patients

with chronic diseases using medicines subsidized by the government are prescribed in outpatient settings and are frequently expected to bring their medicines with them when admitted to hospital.

20.7.3 Lower Middle-Income Countries

All these countries have both centralized and private sector decentralized procurement. Typically, like Vietnam, public hospitals purchase medicines using a tendering system. The tender may be conducted by the provincial government for all hospitals in the province, or at the individual hospital level. In the Pakistan mixed procurement system, the public sector hospitals contact the prequalified and registered pharmaceutical manufacturers for bids. The Pakistani Ministries have centralized procurement. In the Philippines, tenders are used for essential medicines in central and local government procurement. Procurement of essential medicines is largely the role of local government units (provincial and municipal governments).

Challenges
These mixed models need reliable storage conditions until the products reach the end user, but in Pakistan there are gaps in the country's drug supply management system. Some public sector drug facilities do not fulfill adequate storage conditions. In the Philippines, local governments have limited resources to fulfill their medicines procurement and distribution mandate. It has been noted that in the Philippines, procurement prices are unrelated to volume, distance of distribution, or hospital capacity with prices from the same supplier varying between hospitals for the same item. Similarly, in Vietnam, the current pharmaceutical supply chain needs reorganization. The many layers within the distribution network, each contributing a compounding mark-up along the supply chain, serve to inflate the final price of medicines to patients.

20.8 Prescribing/Dispensing

20.8.1 High-Income Countries

In all countries, pharmacists in the public and private sectors are expected to compound, prepare, and dispense medicines routinely. Pharmacists must be licensed. Doctors, registered nurses and midwives (limited list of drugs), and pharmacists (in emergencies) can prescribe in Poland, whereas in Trinidad and Tobago prescribing in the public sector falls strictly within the domain of the physicians.

As for medicines requiring a prescription, all countries requires one but in community pharmacies in Saudi Arabia, prescription-only medicines including antibiotics, antihypertensive drugs, and antidepressants and other prescription medicines,

are provided over-the-counter without a prescription. Although legally not allowed, it is a common phenomenon. Trinidad and Tobago was the only country mentioning legal restrictions regarding physician dispensing, but this apparently "… still takes place in the private sector."

Generic substitution in Poland is mandatory, such that the patient is guaranteed the opportunity to replace an original drug with a generic equivalent. It is not mandatory in Trinidad and Tobago, although generic substitution when medicines are dispensed is allowed in public sector facilities only if prescription is written with the International Nonproprietary Name (INN)/generic name. Similarly, generic substitution by pharmacists is allowed but not mandatory in Saudi Arabia. Nonetheless, generic substitution is not a common practice in community pharmacies in Saudi Arabia. Prescribing generic medicines by physicians is still relatively low compared to other countries.

Challenges

Notwithstanding its mandatory generic substitution, pharmacists in Poland rarely take part in making decisions about treatment of patients or recommend alternative medicines. This apparently is due to the high level of competition in the pharmaceutical market, a pharmacist must be focused on activities directed to increase the pharmacy's profitability (e.g., looking for discounts and low-cost warehouses). Further, patients are often not aware that pharmacists can have the oversight of their drug therapy. In Saudi Arabia, private polyclinics do not have a license to open pharmacies as part of the polyclinic. Therefore, patients who visit polyclinics need to get their medications from community pharmacies

20.8.2 Upper Middle-Income Countries

Argentina and Colombia require International Nonproprietary Name (INN) prescribing but, although permitted in Bulgaria, it is rare. In Argentina, doctors and dentists but also nurses, nutritionists, and pharmacists may prescribe medicines as in Brazil, where physicians and dentists are the main authorized prescribers, but nurses, nutritionists, and pharmacists may prescribe specific products when appropriate. In Jordan, physicians are the only prescribers as it is in Russia and South Africa.

In general, most countries in this category have a positive attitude towards generic medicines and are very willing to accept strategies that encourage generic utilization, INN prescribing and generic substitution. In half these countries (Argentina, Brazil, Jordan, South Africa), generic substitution is allowed in the public and private sectors. In the private sector in South Africa, it appears that generic substitution is mandatory. In most of these countries, the public sector challenge is in determining demand for certain medicines because of poor quality information systems and poor reporting mechanisms for disease burden.

Challenges

In Bulgaria, prescribing by INN is seemingly discouraged in most institutional settings. For government-subsidized prescriptions, pharmacies in Bulgaria are supposed to dispense only the brand specified by the prescriber. In practice, however, there is anecdotal evidence that because of the proportional nature of retail margins, substitution often occurs in favor of higher priced products. The latter also tend to be favored when medicines are dispensed without a prescription.

In both Ecuador and Colombia, there appear to be a lack of incentives for generic substitution. In Colombia especially, very few public and private services perform the full technical processes for dispensing medicines. In most cases, they are simply limited to medicines delivery, without providing information to patients or meeting the quality standards established by pharmaceutical service regulation.

20.8.3 Lower Middle-Income Countries

Although generic substitution is permitted in all these countries, there is little commonality and many challenges. Only the Philippines has mandatory INN prescribing but, perversely, prescription medicines are widely available without a prescription at community drugstores. INN prescriptions in Pakistan were emphasized (along with generics) until 1975 when law banning prescription of branded drugs was repealed.

Physicians, veterinarians and dentists are authorized to prescribe medicines in the Philippines but only physicians in Vietnam. Indeed, in Vietnam, the income of health workers is directly linked to prescribing patterns, both in the private sector and in the public. This has encouraged overprescribing with little concern for clinical need. "Prescription Only" medications are freely available for direct purchase in Vietnam contrary to the law with little accompanying information relevant to their use. Antibiotics are the "Prescription Only" medicines, which are most frequently purchased from private pharmacies without prescription or adequate user instructions.

Consumers in all these countries can buy medicines without prescription, leading to poor dispensing practices. In Pakistan, the pharmacist's role is not well established and they are not remunerated appropriately. In fact, most of the drug dispensing at pharmacies and medical stores is performed by untrained dispensers having no formal pharmacy education Standardized dispensing practices are missing in community pharmacies and hospital environments except for a few private sector hospitals which have well-established pharmacy systems and pharmacists to perform patient-oriented services.

The challenges existing in the Philippines are the usual ones in low- and middle-income countries: lack of support by physicians and other health professionals; lack of information technology support for data collection and documentation, lack of economic incentives and proper remuneration for providing pharmaceutical care services, absence of standards and guidelines, lack of time, and lack of patient demand for these

services Barriers cited are perceptions regarding quality of generics, lack of regulation, dispensing behavior of pharmacies, marketing of branded products, patient's choice and doctor's previous experience. Sources of influence of physician prescribing include the consultants under whom they are trained, perceived quality of generics, marketing practices of medical representatives, and the financial status of the patient.

20.9 Medicine Use/Selection

20.9.1 High-Income Countries

Two countries have essential medicines lists, with the apparent exception of Poland which has a list of medicines for reimbursement that receive fixed reference prices, reviewed every 2 months. All countries have clinical practice/standard treatment to encourage rational use but there little to no mention of implementation and monitoring of specific policies to encourage cost-effective use and/or programs to reduce waste and inappropriate use.

20.9.2 Upper Middle-Income Countries

Most countries (6/8) have a single national Essential Medicines List. Curiously, in Ecuador, industry-sponsored compendiums are still the main source of drug information. The Bulgarian regulatory authority has established and maintained a Preferred – also called a Positive Drug List (PDL). Argentina does not have a unique list of essential medicines as a result of the "… fragmentation of the health system." Three countries specifically mentioned promotion of generics as a national policy in the public sector (Argentina, Brazil, South Africa). All countries have clinical practice/standard treatment guidelines to encourage rational use of medicines.

Challenges
Argentina not only lacks a unique list of essential medicines but does not have a National Health Technology Assessment (HTA) agency or health economic guidelines so that HTA activities are completely decentralized, and the definition of the medicines covered in each health system's insurance subsectors depends on different stakeholders. In the private sector, the list of covered medicines varies according to the agreement made between the Obras Sociales and the insurance company. In turn, for the voluntary private insurance the medicines coverage depends on the beneficiaries' ability to pay. In short, there are different lists of essential medicines for each health system subsector

For Brazil, surveys on medicine access and rational use are supposed to be taken every 5 years and the country has invested to improve information systems specific to medicines and pharmaceutical services. It is unclear whether or not these

information systems are specifically targeted to evaluate availability/affordability, cost-effective use, inappropriate use, and so on. Similarly, South Africa lacks a clear monitoring and evaluation system capable of tracking what medicines are available and how these are being used across the country, even in the public sector. In the South African public sector, the selection of medicines is decided separately by each of the provincial Departments of Health but for preventive and promotive services, selection is done by the National Department of Health. Overall, these selection processes reflect the biases of individual prescribers and academics. The private sector functions separately from that in the public sector. It may lean on/follow many similar guidelines but is not required to do so.

20.9.3 Lower Middle-Income Countries

All these countries have national Essential Medicines Lists. Two mention having clinical practice/standard treatment guidelines but, like most other country reviews, there is little specific mention of Implementation and monitoring policies to encourage cost-effective use or to reduce waste.

Challenges
In some countries, the rationale for the selection of some medicines is open to question. In Pakistan, the presence of antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone, and escitalopram) are available under the Mental Health medicines access program but this "… appears to be contrary to the essential medicines concept and recent evidence." Consistent Issues in Pakistan, Philippines and Vietnam include irrational combinations of medicines, overprescription, sharing of prescriptions among family members and friends. The inability of prescription controls to work in community drugstores support these practices. Patients are buying antimicrobials piecemeal without physician prescription and doctors are often prescribing maximum doses of antibiotics for longer periods of time when the first-line antimicrobials are unavailable.

20.10 Transparency

Overall, there is very little information available on specific policies dealing with medicines promotion and, advertising.

20.10.1 High-Income Countries

All countries have policies related to medicines promotion and advertising, although only Poland specifically prohibits direct to consumer advertising. Unfortunately, this prohibition in Poland to advertise prescription only drugs does not apply to over

the counter drugs and this leads to a high degree of self-medicating on the part of Polish citizens. We suspect this is not an unusual circumstance in any country, regardless of income category.

20.10.2 Upper Middle-Income Countries

Most countries mentioned having some type of policy with regard to regulating advertising and promotion. Argentina and Ecuador have specific provisions regarding direct to consumer advertising. Only over-the-counter (OTC) medicines are allowed to be advertised in the media. Additionally, the advertising of prescription medicines can be targeted only to health professionals. In Argentina, there is a national code of conduct concerning medicines advertising and promotion. The code applies to both domestic and multinational manufacturers and includes a formal process for complaints and sanctions. Adherence to it is mandatory.

Russia appears to have a particular challenge with lack of transparency and conflicts of interest. In practice, many GPs prescribe those medicines that they use in daily practice. They also receive information from representatives of pharmaceutical companies but this information can obviously be biased. It is thought that only a relatively small proportion of doctors actively look for information across a range of sources. The large majority of doctors accept information from the pharmaceutical industry through communication with medical representatives. Medicines' promotional practices include medical conferences around specific themes and interaction between company representatives and doctors.

In Jordan as well, barriers to the prescribing and dispensing of generic drugs are due to advertising campaigns by originator companies. In Ecuador, although the regulation exists, the ex-postcontrol activities are weak, leading to frequent unethical promotion messages in the mass media. In 2013, a law was enacted to regulate communication activities in general and the Ministry of Health (MoH) was tasked with producing a list of medicines that could be directly advertised in the mass media. The MoH never used this option and recently the Ecuadorian Parliament has decided to revoke this regulation.

20.10.3 Lower Middle-Income Countries

All countries have policies with regard to advertising and medicines promotion but, in all three countries, there appears to be no institutionalized national system to measure or monitor drug utilization research in the country and research is lacking. Most studies are usually initiated by academic institutions, either with small funding or as student projects and the fragmented nature of the medicines supply chain in the countries would make such studies difficult.

Challenges

It is understood that in Pakistan, most companies "… spend 20–30% of their revenue on marketing …" and this has led to multinational companies dominating the market. In addition, heavily funded marketing schemes are often launched, targeting prescribers. In private sector hospitals, medicine's brands are selected by the hospital administration, which is somewhat influenced by the pharmaceutical companies and the prescribing is almost always based on the promotional activities of the medical sales representatives. This is typical of other countries in this category as well.

In Vietnam, the pharmaceutical industry had direct marketing activities, plus the income of many health workers is linked to prescribing practices. In Vietnam, studies have shown that economic pressures in an imperfectly competitive market forced both pharmaceutical companies and prescribers to be linked financially. A lack of transparency and accountability and poor legislative enforcement continue to be important factors perpetuating unethical practices in all these countries.

20.11 Conclusions

As this relatively simple analysis has shown there are clearly similarities in funding, procurement, distribution, price regulations among countries of the same income type, and even between high- and upper middle-income countries. For instance, pharmacovigilance systems are in place in most high- and upper middle-income countries – although we do not know if they are being implemented. Most countries have a multitier health system with public healthcare funded via taxes and/or citizen contributions via insurance and the private sector financed by cooperative health insurance schemes and out-of-pocket payments. Some countries have more of an out-of-pocket contribution than others. Almost all countries have both centralized and decentralized medicines procurement.

Nevertheless, the details will differ and the details are important but we cannot say at this time which are important and which are not. For instance, we note that high income and lower middle-income country profiles were less forthcoming about IP/Trade aspects. This may reflect the bias of the authors and/or the fact that in none of these countries is there extensive use of many TRIPS "flexibilities."

Upper middle and lower middle-income countries continue to struggle with the usual health system dysfunctions related to lack of medicines access and availability and many low- and middle-income countries have health systems still designed to treat acute episodes of illnesses and injuries. They are not prepared to meet the challenge of the rise in chronic diseases. We are not the first to suggest that countries, if they have not done so already, develop legislation to ensure universal coverage, access to cost-effective health services, and creation of a means of financial protection.

We are not yet capable of understanding the relationship between presence or absence of a policy and quantitative aspects of a healthcare system. For example, is there a threshold of total health expenditure, above which a country is capable of developing a comprehensive, and functioning, pharmacoeconomic system? Perhaps a more quantitative reanalysis of information from these country profiles would provide more insight.