I. Ralph Edwards
Marie Lindquist *Editors*

Pharmacovigilance

Critique and Ways Forward

Adis

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Foreword

As an answer to the challenges posed by the thalidomide tragedy in the early 1960s, the World Health Assembly endorsed the concept of an international collaborative project aimed at the early detection of possible drug-related problems. This was a seminal moment. Countries found they could join together and discuss safety problems in an open and collaborative manner and create a world data repository for the collected reports of suspected drug harms.

Starting in 1968, 10 countries were actively involved in the development of what in 1970 became the WHO Programme for International Drug Monitoring (PIDM), under the leadership of Prof. Jan Venulet. Amongst these early pioneers of drug safety, years later 'rebranded' as 'pharmacovigilance', were Drs. Hans Halbach and Bruce Royall from WHO Headquarters; Professor David Finney, who first had the basic idea of collating international case reports; and Dr. Ed Napke whose 'pigeon hole system' was the forerunner of the disproportionality methods used today to find signals based on pooled medical experiences.

By 1978, the operational activities were transferred from Geneva to the WHO Foundation Collaborating Centre for International Drug Monitoring, established for

WHO Programme for International Drug Monitoring
Founding members:

Australia (headed by Dr. Anette Welshe)
Canada (Dr. Ed Nakpke)
Czechoslovakia (Prof. O. Smahel)
Germany (Dr. G. Homann)
Netherlands (Dr. Leo Canta)
Ireland (Dr. A. Scott)
New Zealand (Dr. G. McQueen)
Sweden (Dr. B. Westerholm)
UK (Dr. W. Inman)
USA (Dr. A. Ruskin)

this purpose in Uppsala, Sweden. This foundation that was to become the Uppsala Monitoring Centre (UMC) has since been responsible for the maintenance of the database and the development of pharmacovigilance science and technology.

The first years to 1985 and even to 1990 were largely concerned with scientific and practical developments, always considering the best ways to harmonise and standardise tools and services, as well as to discuss global drug safety-related issues. Country representatives met at annual meetings organised by WHO, where work tasks for the Foundation Collaborating Centre were discussed and agreed. Any country could appoint a national pharmacovigilance centre to be a part of the PIDM after satisfying basic criteria of competence.

It was the mid-1980s when the pharmaceutical industry became actively involved in pharmacovigilance in a global sense. Two difficult pharmacovigilance challenges were responsible in part – practolol and keratoconjunctivitis plus sclerosing peritonitis and benoxaprofen and persistent skin photosensitivity with renal/hepatic failure. The global involvement of the pharmaceutical industry and regulators was essential, and pharmacovigilance dissolved into several complementary, sometimes dissenting, groups. The Council for International Organizations of Medical Sciences (CIOMS) and the specially created, industry-supported International Conference on Harmonisation (ICH) both served as platforms for industry and regulators to share views and ideas. Initially, both sides (industry and regulators) were suspicious of each other but agreed that, to achieve effective and cost-efficient processes, standards needed to be developed and rules adhered to.

As some of the large countries' databases expanded and there were increasing inflows of reports, the initial careful assessment of each report clinically, as if making a remote differential diagnosis, became too taxing. In essence, this led to a trend in the USA to consider a more and more public health epidemiological approach to drug safety, and the desire for pharmacoepidemiology to perform observational studies on collated data, rather than use clinical manpower on detailed evaluation of individual case reports. To bring together the scientific expertise, the International Society of Pharmacoepidemiology (ISPE) was started, for the first years being almost an entirely US enterprise.

In Europe, to tackle the same challenges, regional centres were created within countries to decentralise the workload. This regional clinical development was most advanced in France, and the natural desire for scientific but particularly joint clinical and pharmacology meetings led, from an annual national meeting in France, to the development of the European Society of Pharmacovigilance in 1984 and finally to the International Society of Pharmacovigilance (ISoP) in 2000.

From this, it is easy to see how two major groups have formed in pharmacovigilance: those with a public health epidemiology perspective and those who are more concerned with clinical analytics. The former rely on pharmacovigilance to deliver the best approximations of truth based on observational studies and a public health perspective; the latter consider collections of clinical cases and do individual case diagnosis and make clinical assessments of collated data on any safety issue.

Logic and experience tells us that both approaches have their place; the pioneers' vision that early signs of previously unknown medicine-related safety problems

would be identified promptly can only be realised by the use of different tools to create and evaluate hypotheses.

The use of pharmacoepidemiological methods has become popular with both regulators and industry because of their apparent robustness. Pharmacoepidemiology gives an apparently accurate numerical relative probability that event occurrence is not due to chance or is different between those exposed and unexposed to the drug, and a probability of real difference is generally accepted as equal or less than 0.05 or 0.01. These conventions are difficult to interpret with small effect sizes, and the probability for error makes it impossible to rule out rare effects. An important question is, 'What is an acceptable level of risk, and when should we stop putting resources into confirming the probability of risk from drug harm'?

For too long, the idea that case reports are the 'worst level of evidence' or 'just anecdotes' has predominated despite most hypotheses, and indeed decisions on regulatory action, being based on such evidence, and that is even considering 95 % under-reporting of suspected adverse reactions.

Where an expert group considers that the harm of one or more adverse effects caused by the drug is greater than the effectiveness, the drug is likely to be removed from public use or from publicly funded systems. Whilst it is clear that such actions are sometimes beneficial, we have little idea of how often or to what extent.

ISoP, amongst others, has taken the view that there are likely to be critical limitations to a system that makes top-down decisions on availability of drugs to a very heterogeneous group of patients in an even more heterogeneous population. It has also been well demonstrated that normative information focussing on public health findings to healthcare professionals or patients has had limited educational value.

ISoP membership is more of the view that the best public health results in pharmacovigilance can be achieved by optimising each patient–health professional interaction about therapeutics and that all aspects of therapy, as well as trust, patient empowerment and good communication practices, need to be considered to achieve this.

Accordingly, too much focus on methodology becomes counterproductive when instead much more effort needs to be put into transforming the results of scientific evaluation and risk assessment into practical information and knowledge that really helps health professionals and patients in their decision making.

Since the early years, pharmacovigilance has evolved from its initial focus on detection of new adverse reaction signals towards the improvement of rational therapeutic practice throughout the world. In order to improve overall public health, improved clinical patient safety should be the prime objective. To reach this ultimate aim, efforts are needed not only in the further development of pharmacovigilance as a science but also in the areas of communication and education.

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Preface

This book arose from a series of discussions of the International Society of Pharmacovigilance (ISoP), culminating in a strategic planning meeting in Berlin in 2012, with the Executive Committee members and all past-Presidents of ISoP present to talk about the future.

From the Berlin meeting, there was a common view that there were movements in society in general and medicine in particular that would affect the practice of pharmacovigilance. A long list of future issues that needed addressing was identified: ranging from the utilisation of richer data sources as a complement to case reports, to anti-counterfeiting measures, and the need for transparency of both assessment and decisions.

It was thought that over the last decade in particular, there had been a great increase in media attention paid to issues of drug safety. Also, there are an increasing number of stakeholders with active interests in different broad aspects of safety: all expressing views that the current system is not delivering optimally to improve therapeutics in clinical practice.

Perhaps the major concern is that a concentration on intrinsic problems with drug products means that there is not enough awareness and activity in improving patient care which will need a much more holistic view of risk and benefit in the use of drugs.

No one can be in any doubt about the magnitude of the tasks and changes needed to achieve better pharmacovigilance practices in the future. On the other hand, there is little doubt that the overall high level of iatrogenic illness must be addressed, nor is anyone complacent about the increasing costs of health care, partly due to medication issues.

Several ISoP members have been critical of the largely public health approach to pharmacovigilance – a top-down approach which respects neither the patients' needs and wishes, nor those of highly trained and much overworked professionals who take huge pains and responsibility to give individual patients the best care.

So it is that the idea of this book was born: Why not ask ISoP members to give their views on where pharmacovigilance should go, and what it should leave behind (at least in part)?

We are grateful to all the members of ISoP who have given up their time to talk to us and give us ideas and support. We are particularly grateful to the ex-Presidents and Executive Committee members of ISoP who have shared their thoughts with us. Most of all we are thankful to the chapter writers who have had the courage and imagination to express their thoughts about how the future might be better in pharmacovigilance, and taken the time to write it all down and to keep to deadlines (more or less!).

One person who deserves our special thanks is Sophie Spence, who is ISoP's administrative heart. Without her efforts in bringing us all together happily in Berlin and then supporting us tirelessly with all the correspondence, a few reminders (!), and general organisation, all would have been chaos and loss (at least for one of us – IRE).

You will see that the contributions vary in length and style, and that is deliberate. We did not want to be in any way restrictive, and we hope that this book is just the start of a dialogue that will bring in many more individuals and groups that can add their contributions to progress. We hope this can be done via a web-based version of this book, so that this work will be living for time to come – for the improvement of clinical benefit and avoidance of harm.

Finally, we would like to express our thanks to our ever cheerful, diplomatic and strong supporter who encouraged us to 'go for it' with this book, who is, of course, Nitin Joshi. Nitin has remained enthusiastic on the sidelines even after he recommended us to go ahead practically with the excellent publishing team from Springer, Prasad Gurunadham, Ellen Blasig and Cameron Wright, whom we also thank heartily. They have kept us on the straight and narrow pathway to the finished product, but miraculously made our job painless as well. David Elek at Springer also has been in the background and we thank him for his general support of this project.

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Contents

Vigilantiae, quo vadis ?

Introduction

In this chapter, we have considered the present and future developments of pharmacovigilance. Some of the ideas are our own, but the main purpose is to introduce the concepts and provide a framework around the different chapter authors and the content of their chapters. We cannot realistically do justice to all the contributors' ideas, and our strong recommendation is to enjoy reading them all for yourselves!

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

See Elizabeth Storz and Willibert Franzen; both of these chapters discuss practical difficulties faced in managing work under the current bureaucratic system in the EU.

Pia Caduff talks about the sound scientific work that has been done to improve pharmacovigilance but points to the limitations of the top-down public health approach and the surrounding bureaucracy.

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development and also points to the general need for vigilance – alertness – in all medical practice.

Marco Tuccori and Magnus Wahlberg give an account of the problems associated with evaluating ICSRs and observational studies. They review current work being undertaken and make suggestions for the future.

Giovanni Furlan talks about improvements that can be made to cut down duplication of effort in managing and analysing safety issues.

Bruce Carleton talks about the importance of individualising drug treatment and the need for more information and use of phenotypes and genotypes.

Ulrich Hagemann talks about the 'neighbourhood' of pharmacovigilance concepts and activities to include the medical, drug marketing and supply chain environments, as well as the impact of new drugs and scientific advances.

Emmanuel Okoro talks about the clinical scene and how supply issues, the medical context and other factors affect pharmacovigilance particularly in a resource-poor setting.

Alfonso Carvejal strongly proposes further attempts at global harmonisation of pharmacovigilance efforts with a patient focus but also autonomy for those who work in pharmacovigilance towards prevention.

Bruce Hugman reflects on the culture of pharmacovigilance and need for much more dynamism. He argues that communications outwards reflect the state of inner culture.

Shirley-Anne van der Spuy begins with the general concept of health and states that politics should facilitate the right to health and pharmacovigilance as a part of that. For her, the prime stakeholders are patients, but there are several other important stakeholders as well. The interrelationships are challenging, but she proposes some ways forward.

Souad Skalli talks about the use of traditional herbal remedies making the point that pharmacovigilance is just as important for alternative therapies.

Giampaolo Velo raises the issues of ecopharmacovigilance. The negative effects of drugs are not only felt directly by susceptible patients but also via their appearance in the environment as waste or excreted materials. The risks are both direct and indirect.

Brian Edwards discusses the various aspects of patient safety that are of concern with the use of drugs. He points out many inconsistencies in what is regarded as 'safe'. He argues that we currently have confused practices which are unclear and dysfunctional, perhaps because our basic thinking and processes are unclear.

Luis Alesso and Raquel Herrera talk about education for healthcare professionals and the public. For the former, they cover undergraduate and postgraduate education that must be related to specific healthcare settings.

The Aim of Pharmacovigilance

Definition of Pharmacovigilance
The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. [WHO, 2002]

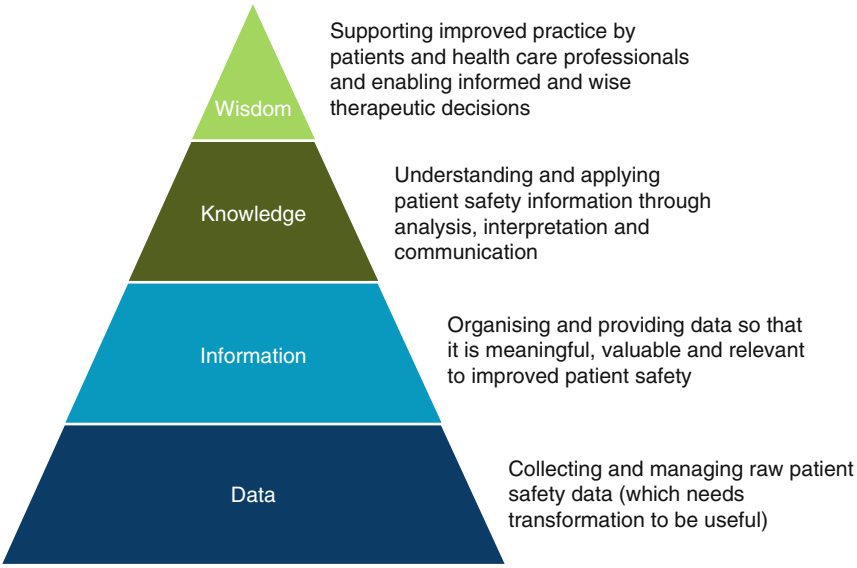
What is the prime objective of pharmacovigilance? Since the early years, pharmacovigilance has evolved from its initial clinical focus on detection of new adverse reaction signals towards the improvement of rational therapeutic

practice throughout the world. Following from this, there is naturally a major public health aspect to pharmacovigilance where the concentration is on improving therapeutic practices, in general, and reducing the overall burden of problems in relation to drug use. To achieve these public health goals, there must be an expressed political will and adequate funding to set up and maintain sustainable and cost-efficient systems for data collection, analysis and communication, and these systems need to be supported by a robust legal and regulatory framework.

Whilst we agree that the public health perspective is important and must be given adequate resources and support, the pharmacovigilance system must never be an end in itself. Our view is that improved clinical therapy for each individual patient should be the prime objective of pharmacovigilance; only if the results of pharmacovigilance activities meet the needs of the individual patient and their health professionals, and support the best possible decision making in each specific therapeutic situation, will there be a real and lasting impact on public health.

To achieve the vision of a world where all patients and health professionals are empowered and able to make wise therapeutic decisions in their use of medicines, we need good-quality data, but that is only the starting point. The key challenge is our ability to transform it into useful, timely and accessible knowledge at the point of care.

In this chapter, we shall concentrate on the scientific and methodological challenges and prospects ahead, but in proposing ways forward, we will also argue that pharmacovigilance can only seriously develop if there is open and constructive debate and a genuine will to work together, across stakeholder groups and borders.



The Starting Point

We need data to be able to determine any unusual clinical features coming during therapy of patients. With this data, we hope to assemble knowledge of any sort that may eventually lead to the better diagnosis, management and prevention of problems with therapy and to better learn about the real-life clinical uses (incl. off-label) of products so that effectiveness risk information will guide therapeutic decisions.

After collecting and collating case data, we need to do causality assessment to determine the likelihood of chance or otherwise spurious associations and so develop hypotheses about the harm that may be related to drug therapy. In order to do that, we need to determine the nature and strength of the causal relationship between a therapy and any clinical event. Such causal relationship will be most often a probability, not a certainty (only a very few medicines and clinical event relationships can be assumed to be near certain).

In essence, the assessment of causation is the same as the process of clinical diagnosis at the bedside. The difference is that the background expertise of the person reassessing the diagnosis is likely to have greater familiarity with causation by drugs and have more time and facilities for checking general information than the average healthcare professional or patient. On the other hand, the healthcare professional(s) making the original diagnosis has first-hand information about all aspects of the patient.

In either situation, the individual diagnosis depends upon:

- The relative probabilities of the cluster of signs, symptoms, their evolution and investigations that have been found to point to a pathophysiological diagnosis
- The relative probabilities of various possible competing diagnoses within the patient's community

Clinical diagnosis of apparently serious disorders is an iterative process usually with peer reviews and sometimes involves long periods of follow-up with reassessments noting the evolution of signs and symptoms, any divergent opinions, supporting investigations and more:

- The nature, and particularly the sensitivity and selectivity, of the diagnostic process overall has not had great enough attention in pharmacovigilance.
- Neither have the reasons behind under-reporting of suspected adverse reactions nor possible ways of improving the number and quality of case reports.

In addition to clinical case assessment, we need to quantify the drug/harm incidence to determine the broad public health impact of the possible harm. The usual tools that are used are often variants of the four groups below. Each of them has advantages and disadvantages, so that they must be used according to the needs of each situation:

1. Prospective controlled interventional studies:
   (a) Placebo-controlled double-blind clinical trials
   (b) Comparative post-marketing studies

2. Prospective observational cohort studies with controls:
   (a) Prospective self-control studies
3. Retrospective case control studies:
   (a) Retrospective self-control studies
4. Monitored consecutive exposed cohorts with retrospective community data as controls

These are the basic approaches to developing a hypothesis of harm and the first analysis to try to understand the causal attributes of the clinical effect as competing probabilities, as well as quantifying the incidence of the effect.

A view has developed that pharmacoepidemiology can both find signals (raise hypotheses) and validate them (confirm hypotheses). This standpoint must be reviewed critically and in particular must be considered against the numbers of exposed people involved in epidemiological studies and the very nature of epidemiology and proof of causation.

Risks up to ~1:1000 are often seen and evaluated in clinical trials, though that depends upon human exposures during clinical trials and their duration. For exposed groups ~ 1:1000 – 1:10 000 and more rare, spontaneous reporting becomes the main way of first finding signals – and it is often the only way of evaluating the risk. This is because of the rarity of the effect (versus other probable causes – confounding) and the challenges of assembling enough patients with well-documented exposures and other necessary details (e.g. for propensity scoring).

It is clear that new hypotheses can appear, by chance, as a result of epidemiological studies, but that depends upon the data being of good quality, the numbers being sufficient and the observers of the study being alert to new possibilities. On the whole, the number of subjects exposed in even observational studies is too limited to find harms that occur less frequently than around 1:5000. Studies are designed to confirm hypotheses, and the data they use is selected for that purpose. All observational studies have the same problems with data quality as spontaneous reports since the data is collected during the routine work of clinicians; therefore the diagnostic data may be inaccurate and incomplete, particularly those data that are not the focus of the study.

We should therefore not rely on statistical significance: adverse reactions to marketed drugs are relatively too rare. Longitudinal patient healthcare records have the potential to improve this situation, but collection of suitable controls remains a challenge. The process is not short, and the length of time from first signal to public health action causes concerns when serious adverse effects are involved.

At the rarer end of the risk probability spectrum, it seems likely that many, perhaps serious, adverse reactions will remain ‘unverified’ because of lack of power. Instead of trying to find statistical probability as a gold standard alone, we should invest more effort into considering causation using the proposals of Bradford Hill, and so producing a logical argument for causal relationship, and not waiting for a statistic which cannot itself disprove a rare causal association. Also it follows that

any effectiveness – risk evaluations will have limits of confidence that must always be made known to caregivers and patients.

Some Current Problems and What Needs to Be Done

Data and Methodology

The chapters in this book confirm the current status of pharmacovigilance as an almost uniquely public health exercise in which pharmacoepidemiology is considered as the higher level of evidence that is regarded as essential for sound decisions. The collected clinical stories and suspicions that were (and in fact still often are) the basis of both pharmaceutical company and regulatory decisions are derogated to mere 'clinical anecdotes'. Far more important, the writings confirm the extensive level of bureaucracy that surrounds the collection and analysis of 'clinical anecdotes'.

It is usually considered that reported case reports of actual experiences of harm with drugs need to be assessed before they are regarded as a 'signal' for further attention or regulatory action. This process normally includes an assessment of the plausibility and credibility of the reported association.

The European Medicines Agency (EMA) has in their guidance described the concepts 'signal validation' and 'signal confirmation'. However, it is not easy to understand what exactly is meant by a validated signal and how that differs from a 'signal'. Should it be interpreted that a 'signal' is not a signal but instead a tentative/potential signal? Also, the difference between a 'validated' signal and a 'confirmed' signal is obscure. If 'signal confirmation' means 'communication via EPITT, within 30 days', then it is not that the signal has been transformed in the process from one concept to another (from 'validated' to 'confirmed') but that it is just that the 'validated' signal has been posted and made available.

Excerpt from EMA Guidance Document Questions & Answers on Signal Management

Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis. The clinical significance of the signal, its previous awareness, the biological and temporal plausibility and any relevant sources of information supporting the association are taken into consideration. Signals validated by the EMA or Member States are entered in the European Pharmacovigilance

Issues Tracking Tool (EPITT). EPITT is a database developed by the EMA to promote the communication of pharmacovigilance and risk management issues between the EMA and Member States. Signals for which the validation process was not supportive of a new potentially causal association, or a new aspect of a known association, are not entered in EPITT.

Signal confirmation means communication via EPITT, within 30 days of its receipt by the Rapporteur, the lead Member State or a national competent authority that the validated signal is confirmed or not confirmed. Any confirmed signal should be analysed and prioritised by the Pharmacovigilance Risk Assessment Committee (PRAC).

(http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/09/WC500150743.pdf accessed April 4, 2016)

These are the very basic issues that underpin how pharmacovigilance functions. If there are misunderstandings possible at this level, the risk is obvious that the confusion will continue.

The bureaucracy around the reporting of 'anecdotes' from industry to regulators and on the development of hypotheses from grossly under-reported clinical experiences seems paradoxical and almost grotesque when little or nothing is done to enhance the quantity and quality of those reported clinical experiences at source. Moreover the bureaucracy around the general evaluation and reporting by industry to regulators and the slow introduction of appropriate and agreed standards has been confusing and unproductive and has led to noticeable inefficiencies and increased workload in industry safety efforts.

For examples, see Elizabeth Storz and Willibert Franzen; both of these chapters discuss practical difficulties faced in managing work under the current bureaucratic system in the EU.

Pia Caduff talks about the sound scientific work that has been done to improve pharmacovigilance but points to the limitations of the top-down public health approach and the surrounding bureaucracy.

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development and also points to the general need for vigilance – alertness – in all medical practice.

Also there are inefficiencies in the separation of functions between pre- and post-marketing groups both in industry and regulators that cause duplications of data and resources.

Giovanni Furlan talks about improvements that can be made to cut down duplication of effort in analysing safety issues.

Under-reporting remains a problem with ICSRs. There are difficulties in getting good-quality data both for ICSR as well as observational studies. There have been many attempts to overcome the problems of the quality of data and the various biases and confounding that affect observational studies. Many improvements have been made but the power of studies remains a challenge. Studies will end up as large, cumbersome, time-consuming and expensive, or they cannot evaluate rarer suspected adverse effects. Certainly evidence from observational studies cannot exclude rare drug causes of harm.

These are areas that are continuously under review and improvement by very many academic and multidisciplinary groups.

See Tuccori and Wahlberg who give an account of the problems associated with ICSR and observational studies. They review current work being undertaken and make suggestions for the future.

New tools and approaches will need to be developed to collate and manage data from different sources and to analyse it for new knowledge. Some of the challenges are listed below and are mentioned in several of the chapters:

- Many harms may be related to medication errors that can in turn be due to environmental and organisational factors.
- Polypharmacy and interactions (this may be reported elsewhere than in the actual cases analysed) (e.g. food interactions and unusual drug interactions).
- Administration device problems (e.g. infusion devices and inhalers).
- Genotype/phenotype differences.
- Substandard, spurious, falsely labelled, falsified and counterfeit (SSFFC) product matters.
- Generics (may cause confusions in reporting and may have important differences in the chemistry of excipients and even active ingredients, e.g. biosimilars).

This new knowledge will be novel kinds of signals fulfilling the second part of the WHO definition ‘or any other possible drug-related problems’.

Bruce Carleton talks about the importance of individualising drug treatment and the need for more information and use of phenotypes and genotypes.

The list above annotates more recent areas that have been raised as important concerns that affect safe use of drugs. Given that around half of the adverse effects that are serious enough for hospital admissions are from older drugs and possible medication errors and the other issues mentioned, these should be receiving great attention in the future.

This will need close cooperation with groups involved in broader safety issues in medical practice and certainly the collection, collation and analysis of practices globally that we currently have in place for determining adverse reactions to drugs. We will also have to broaden our current gaze from just drug product data and its regular use to other data (e.g. drug poisoning, misuse, off-label prescribing and fraudulent products) in order to understand how drugs may cause harm and how it can be eliminated or minimised.

There are many more places where critical information about safety issues with drugs is recorded and investigated. Those data sources should be used to gain more information. Some examples are as follows:

- Poison control centres (for more information about human toxicology and pharmacokinetics).
- Drug information services (many adverse drug effects are the reason for queries about a drug).
- Electronic patient/health records contain much information about patients' clinical status that can be linked to the drugs they take by suitable clustering algorithms and useful chronological data.
- Social media/data posted on the web (as yet untested but patient concerns and the impact of drug effects on people are important information).
- Pre-marketing toxicology (links between toxicology and pharmacovigilance should be explored further for its value) and clinical trials data and others, such as the many sources of data in the private domains of health professional and patient organisations.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Main Points

- Knowing what method works for what situation:
  - The importance of good-quality case reports
  - The role of pharmacoepidemiology methods
- Incorporating new data:
  - Vaccines, medication error, SSFFC, patient-reported data, electronic healthcare records, active monitoring studies, etc.

- Analysing available data to identify safe use:
  - Influence of demography, drug combinations, diseases, and situations
- Redefining of 'signal' to take into account:
  - New types of data
  - That most problems are not ADRs as such but related to drug use
  - Patient outcomes (impact, duration, dose, benefits!)

Risk Management and Decision Support

Balanced Evaluations

In order to make decisions about both individual patients and public health, the good that a medicine can offer must be weighed against the bad. In our view, the correct balances, with explanations, are as follows:

- Efficacy is the result of preclinical work on pharmacology in humans and animals as well as in vitro methods that shows that a drug has a useful pharmacological effect, and hazard is the toxicological and early clinical testing result that indicates a potential for harm in clinical practice.
- Effectiveness is the clinical demonstration of useful effects in real-life clinical practice, just as risk is the probability of harm as assessed from ICSRs and observational studies during the routine clinical use of drugs.
- Benefit is the value of the drug as determined by individual patients, just as harm is the negative way in which a drug may affect them from adverse effects directly caused by the drug or from aspects of its use or misuse. These factors can only be judged by various kinds of outcomes research:
  - The phenomenology of illness and the way in which those matters affect the lives and decisions people make. These are critical factors in improving the care of patients and the possibility of providing decision aids to patients and their carers.
  - Quality-of-life measurement is an essential tool for the vigilance of patients, but so far very little has been done to determine what entities and phenomena the individual patient values most and therefore what should be primary considerations. Development of such a tool is possible:
    - Existential self-assessment by phenomenology.
      - Self-assessment tool should be developed in cooperation with other groups involved in outcomes research.

So far, decisions have been the results of value judgement by groups of experts for broad public health matters and by individual clinicians for patients, and there has been too much focus on harm. The evidence basis for the public health decisions

is obscure or certainly neither made available readily nor much debated. There have been partial attempts made (e.g. NICE in the UK and public hearings in the USA), but little effort has been made to be rigorous about comparisons: efficacy is still often compared with risk and the whole is often labelled 'benefit/risk assessment'.

Once the basic understanding of the good and bad of drugs is applied more rationally, better decisions will be possible and better tools devised to replace judgements based entirely, or to a large extent, on expert opinion and values.

It will need to be also understood that so-called 'risk benefit' evaluations cannot be definitive but have to be iterative to ensure that comparisons between drugs remain current and that new findings and new therapies are incorporated.

It will be important (and always has been!) for the public to better be educated about the 'risk benefit' of drugs so that they can learn what to expect. Since this kind of evaluation is relevant for everyone, one could hope that it will be taught from school age. Good communications around drug safety issues, particularly using the media, will be most important.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Main Points

- Improving methods for deciding if (chance of) benefit > (risk of) harm
- Developing decision support for signal action and communication – what is an 'actionable' signal?
- Implementing trend analysis strategies and tools to deal with evolving issues
- Devising communication strategies for better understanding of concepts of risk assessment

Management and Prevention of Adverse Reactions

Diagnosis and Management

There are many factors that lead to failures in diagnosis, prescription and drug use. How do those failures affect subsequent management? If a patient has an adverse reaction, will it resolve if the drug dosage regimen is changed? And if a drug therapy is stopped, what alternative treatment is available? Will it have less adverse effects? The off-label use of drugs is another area for investigation: how often do they cause harm? How often do they provide useful information on new indications?

In order to develop a sound knowledge basis to support the best possible treatment options for each patient, we think it is necessary not only to collect more, and better, evidence of patient harm but also to start finding out what it is that works well and why.

Ulrich Hagemann talks about the 'neighbourhood' of pharmacovigilance concepts and activities to include the medical, drug marketing and supply chain environments, as well as the impact of new drugs and scientific advances.

Emmanuel Okoro talks about the clinical scene and how supply issues, the medical context and other factors affect pharmacovigilance particularly in a resource-poor setting.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Prevention

Despite many developments in pharmacovigilance and drug regulation, drug misadventures are still a major source of death, morbidity and financial burden in society. It has been estimated that about half of the adverse events causing hospital admission are potentially preventable and therefore represent avoidable patient harm. Medication error and drug–drug interactions (DDIs) are well-known causes of preventable adverse reactions, but the size of the problem, both in terms of patient suffering and costs to healthcare systems, is still very much under-researched.

Preventable adverse reactions pose a rapidly growing challenge also in resource-poor nations. Access to better healthcare brings access to more medicines, but inadequate knowledge about medication error and DDIs and their prevention dilutes the health benefits; this is compounded by the effect of SSFFC medicines, which hits already vulnerable populations the hardest but which is a growing problem globally.

This is an extremely important area where there is lack of data, under-developed methodology and even less data on impact. We believe that education and communication is very important at all levels of health professionals and for the public, but much more must be done and learned to prevent the preventable.

Alfonso Carvejal strongly proposes further attempts at global harmonisation of pharmacovigilance efforts with a patient focus but also autonomy for those who work in pharmacovigilance towards prevention.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

Main Points

- Develop methods for comparative risk profiles to aid patient and medication management.
- Collect and communicate success stories from data, HCPs and patients on how to mitigate harm, and alternative treatments.
- Establish tools for further research on preventable reactions and how to avoid them.

Regulation and Impact Assessment

In the last decade, as the political and public demand for rapid access to new medicines has increased, the need for more proactive, iterative safety management has been recognised by both regulators and pharmaceutical industry, and efforts have been made to improve regulatory processes and routines.

In resource-poor countries, with previously limited access to medicines, large populations burdened by the endemic scourges of communicable diseases can now be treated thanks to medicine donations. Real-time monitoring of their use for both safety and efficacy is a high priority, of particular importance since some are novel drugs, and others will be used in settings and populations which are very different from those of the original approval.

Withdrawing drugs from the market leads to substitution by others or non-treatment. We know little about the negative effects of such regulatory actions on those that take the drugs without problems and good benefit. We know little about the success or otherwise of the substituted drugs. We know that regulatory communications are not optimal, but there is little suggestion that the changes currently being made are effective.

Given that there is a continued large problem caused by adverse events related to medication, it is essential that the impact of pharmacovigilance should be audited for effectiveness. The emerging role of outcomes research in identifying shortfalls in practice and promoting strategies to improve healthcare is an increasingly important tool for organisations, governments and industry.

The profile of pharmacovigilance has been raised, and its role is under scrutiny and review globally. Both WHO and USAID-financed Management Sciences for Health (MSH) have developed indicators that provide measures that will enable the

assessment of the status of pharmacovigilance and the activities and their impact, nationally and globally, at all levels of the healthcare system with a view to ensuring patient safety. These must now be deployed and fine-tuned as needed and the identified gaps addressed!

Isah and Edwards present ideas of pharmacovigilance performance indicators

Pia Caduff talks about the sound scientific work that has been done to improve pharmacovigilance but points to the limitations of the top-down public health approach and the surrounding bureaucracy.

Main Points

- Establish, evaluate and develop routine assessment using pharmacovigilance indicators.
- Collect data and do research on impact, e.g. changed ADR incidence, changed practices, healthcare and patient-reported outcomes.
- Develop tools and strategies to provide feedback loop pharmacovigilance – healthcare practice.

Communication

Reaching Out to Patients (Communication)

There is a critical need for education and communication between stakeholders in pharmacovigilance. In the past, and currently, there has been secrecy and too much concern about patient privacy issues. That is not to say at all that patient privacy is not of utmost concern and must be protected, but rather it has been used as an excuse in situations where one major party wishes to find an excuse against sharing totally anonymised data. The reasons behind these actions seem to relate to political control, not for the benefit of patients who should be helped by the sharing of group data with experts whose sole intent should be to improve the safety of others who may be exposed to the same drug in the future.

It seems that a rather cynical battle between regulators, industry and other groups with competitive motives that hinder sharing of knowledge about safety has held up the development of pharmacovigilance for decades. Now is the time to begin real, thoughtful communication and education which must be the most important way of

moving forward as a global partnership for the best therapy for patients worldwide.

Luis Alesso and Raquel Herrera talk about education for healthcare professionals and the public. For the former, they cover undergraduate and postgraduate education that must be related to specific healthcare settings.

Main Points

- Develop communication tools and strategies to:
  - Engage with the media, public and decision makers to:
    - Raise the profile and status of pharmacovigilance
    - Enable a public dialogue
    - Get funding
  - Make the best possible information and knowledge available, useful and usable to all stakeholders

What Might We Do Next?

Pharmacovigilance and Rational Therapy

In response to a number of safety issues that the public (via the media) has been concerned about, regulatory agencies have been criticised for delays in regulation and industry for prevarication. Much bureaucracy has resulted from this in order to increase efficiencies in reporting safety problems and in openness to society.

Consequently private enterprise groups have developed for patient reporting, and patient groups have become more and more active. The Internet has also provided more and more information sources on drug safety issues that can be tapped but which need to be evaluated and used carefully. Very many patients are active users registering and communicating their concerns. The use of wearable monitoring devices is also exploding, with the resulting vast amounts of patient-generated data that may add useful information on drug use and responses.

At the same time, there have been a major concerns about the cost and delivery of healthcare – not only safety but effectiveness also. As mentioned above, as a response to these challenges, outcomes research projects have become increasingly practiced, and patient safety projects and monitoring have become more widespread and often performed by independent groups, using approaches and methods that

may or may not be better than those that are current, but there is a great need to investigate and harmonise these methods and to find ways of collating information to produce useful knowledge.

Particularly we need to consider how to measure the balance between efficacy and hazard, effectiveness and risk and benefit and harm using all relevant data and producing results that will be useful for both clinical medicine and public health decisions.

This is particularly so when increases in pharmacological and medical science knowledge have resulted in advances in therapy that make categorisation difficult. Is stem cell therapy a 'drug'? A biological? How do we consider devices used in drug delivery? How in individual patients do they all interact? Who are the patients who will best benefit from each and how are the treatments best used in combination? What are the negative aspects of combinations of treatment modes? These are the questions that clinicians face daily.

Ulrich Hagemann talks about the 'neighbourhood' of pharmacovigilance concepts and activities to include the medical, drug marketing and supply chain environments and includes the introduction of new therapeutic products.

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development. They also point to the general need for vigilance – alertness – in all medical practice.

Successful therapy and good patient outcomes must also take into account patients' perceptions and expectations – which may be totally different from, and sometimes even seemingly irrational to, those of health professionals or regulators who see things from a different perspective than the patient themselves.

In the overall evaluation of how therapy affects patients, many more questions must be asked and answered: What do patients expect from treatment? What is the best therapy? Is it drugs? Surgery? Physiotherapy? Acupuncture? Herbal medicines?

Medicines are just one mode of therapy albeit the most frequent one used by healthcare professionals. Other therapies need better assessments of their effectiveness and risks; for a single patient, there are good and bad interactions between therapies that need to be better understood, for example, by evaluation of phenotypes and then genotypes of those suffering adverse drug effects.

Souad Skalli talks about the use of traditional herbal remedies making the point that pharmacovigilance is just as important for alternative therapies.

Bruce Carleton talks about the importance of individualising drug treatment and the need for more information and use of phenotypes and genotypes.

Pharmacovigilance is the oldest continuous monitoring system for safer medicines practice and such alertness or vigilance should be a sustained and integral part of safe healthcare practice in general. This is happening as part of the drive to better patient safety, but the methodologies are very variable. This should change towards more harmonised vigilance in all areas, taking into account that all of medical care has overlapping responsibilities and professional territories

It seems very inefficient to have many unrelated and incompatible systems to collect and store data on continuously collected healthcare outcomes. Is there anything we can determine from the current medical treatments of patients and from pharmacovigilance?

Since pharmacovigilance has well-developed approaches to getting information on the negative aspects – and increasing the positive results – of drug therapy, perhaps the same methodology can be used for general therapeutic vigilance. Would it not be wise to broaden what we do in pharmacovigilance and start to record the good and the bad outcomes that patients experience from any of their therapies? Is that not a more rational way of approaching the management of disease? Isn't it so that outcomes research needs to operate in such a way continuously and that we in pharmacovigilance have many of the approaches and tools that will make a huge difference to collecting evidence from the first information on suspected harm and guiding work towards more definitive studies?

Ron Meyboom talks about the development and needs of pharmacovigilance and about the restrictive effects of too much bureaucracy on scientific development and also points to the general need for vigilance – alertness – in all medical practice.

All of the above may seem idealistic and out of our reach. It is not – the technology to help us do all of this is available. It is only human will that is required to recreate and develop David Finney's and WHO's idea of a global system for the early warning of problems with therapy and which takes the earliest possible action to improve patients' well-being around the world. Such a cooperative system would be economically efficient as well.

Eugene van Puijenbrook and Linda Harmark talk about a broader consideration of the harmful effects relating to drugs. They want to know more about the details surrounding a report of harm, what patients think about risks and how they can be more involved in gaining new knowledge about therapy and its risks.

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Emmanuel Okoro talks about the clinical scene and how supply issues, the medical context and other factors affect pharmacovigilance particularly in a resource-poor setting.

Why We Need International Collaboration

The chapters in this book, apart from being critical over the status quo, propose ways forward for pharmacovigilance. It is very clear that in the last 10–15 years the interest in the safety of medicines has increased both amongst the public as well as health professionals of all kinds. As a result, there are a number of new stakeholder groupings, some with broad interests and some having specific focus. Much more pharmacovigilance work is now being undertaken by groups outside the global efforts of WHO, CIOMS and ICH.

There is a large overlap in the requirements for long-term, continuous oversight of therapy/management of patients and a need for harmonisation of methods. To do all of this, there is a need of a global, continuous system for assessing the outcomes of healthcare therapy, particularly safety, in a harmonised way that can be used by any domain expert. This is not supplied by any current global organisation.

Global cooperation seems to be essential if we are to find suspicions of problems, investigate them and take appropriate actions. Global cooperation is as necessary now as it was at the start of the WHO programme: we need global data and different ways of looking at it. If we are to be efficient in eliminating or mitigating harm, we need to be sure that all useful information is available, and relevant knowledge transferred, to empower patients and their health professionals worldwide. (*See Alfonso Carvejal.*)

The global coordination of groups concerned with effectiveness and risk in patient care will be essential in the future for the limitation of even greater expansion of healthcare costs.

Main Points

*International collaboration is needed to***:**

- Optimise use of different competencies and resources:
  - Possibility for prompt and open exchange of information.
  - Working towards common goals brings people together.
  - Learning from each other's experience.
  - Sharing workload.
- Increase understanding and ability to interpret results across countries/regions
- Bring results together instead of duplicating efforts

Conclusion

Our world is full of data of variable quality about virtually the whole of human knowledge but the path from data >>>>information >>knowledge>wisdom is complex. The first and perhaps most extensive/expensive step is to transform data into meaningful information. It has been shown that it is possible to automate data collection satisfactorily for pharmacovigilance (though not with complete agreement) by the work of WHO, CIOMS, ICH and various public–private partnerships to create agreed, usable data sets for information, and there are also methods for knowledge finding within that data.

However, in recent years, we have seen a multitude of new stakeholders taking an interest in pharmacovigilance, and then there is the big data revolution, with vast amounts of patient-generated data and reported outcomes becoming available. From the experience of previous international standardisation work, it would be surprising to have complete global agreement about a single process or formats for collecting, managing and analysing all data. This suggests that repeating the process that took decades, for new clinical data sets and safety purposes, which have links with pharmacovigilance anyway, would be wasteful.

We propose that a better way of expanding our knowledge base is to accept a higher level of heterogeneity in terms of data and information sources and concentrate on collaboration efforts instead of knowledge-finding tools (and those may only need some limited adjustment), better methods for decision support and an open and constructive debate of what the knowledge tells us and how we should use it wisely.

Main Points

- Safer use of medicines for all populations can be achieved.
- New methods and data sources need to be integrated into robust and scientifically sound evaluation processes:
  - There is no one-size-fits-all for evaluation of data, but techniques for data management, outcomes vigilance and data analytical support are common:
    - There is a good case for broad health outcomes vigilance.
- We need to get past our preoccupation with standardisation of data and collection processes and move rapidly towards optimising useful knowledge transferred to patients and their healthcare professionals so that they might make wise decisions that improve peoples' lives.
- Openness, good communication practices and win-win international collaborations are essential for success.

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Chapter 1
Teaching Pharmacovigilance in University

Raquel Herrera Comoglio and Luis Alesso

The aim of Pharmacovigilance (PV) is to avoid, to the greatest possible extent, the harmful effects of medicines, both for individuals and populations. Pharmacovigilance covers not only the study of adverse drug effects and medication errors, but also drug overuse, abuse and misuse, and harms caused by adulterated or fake medicines [1]. Teaching of PV in universities is one of those essential activities that is required if we are to move forward with the objective of detection, evaluation, and prevention of the adverse effects of medicines on patients and on populations.

Pharmacovigilance, "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [2], is a multidisciplinary science. The transmission of knowledge and the development of practical skills needed for contributing to or working in PV can be approached from several perspectives, some of which may be different from others. Content of teaching may arise from sources as diverse as pharmacology, pharmacy, molecular biology, clinics, pharmacoepidemiology, regulatory and legal information, public health, and traditional herbal medicines [3]. A comprehensive understanding of how healthcare systems work allows the identification and detection of many medication errors. The therapeutic use of medicines, risk perception, and acceptability of drug adverse effects also involves sociologic aspects. These aspects are sometimes very complex and, in contemporary societies, susceptible to be strongly influenced by a wide range of communicational strategies – and media – as well as modified by regulatory actions and educational interventions.

PV methods cover spontaneous reporting and a broad range of occasionally complex strategies for detecting and analyzing data. In spite of underreporting, impossible quantification, and lack of comparative controls, spontaneous reporting of adverse drug reactions (ADRs) is the most effective and practical way for postmarketing

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surveillance of the safety of medicines and remains one of the cornerstones for ensuring drug safety process, mainly through signal detection and hypothesis generation [4]. This leads us to reflect on what is the "essential" substance of spontaneous reports. Spontaneous reports contain not only objective data (figures and facts, including diagnostic and corroborative tests), which can be more or less specifically or completely retrieved from medical records and investigations, but also other much less objective elements. Reporting arises from the perception of healthcare professionals or patients which, in turn, depends both on the working environment and abilities of individuals (knowledge of medicine, pharmacology, time availability, and work overload) as well as the PV systems (structure, completeness, selection, and validation of reporting; transmission of the information). The subjective individual perception of the acceptability of a drug's adverse effects vary according to severity of illnesses, availability of and access to medicines, even for recreational use of drugs. Social perception of drug adverse effects' magnitude and harm depends on economic resources, educational level, political and institutional stability, and patients and health care professionals' training and knowledge in PV. These subjective and socio-economic components of reporting play a major role in the extent to which adverse drug reactions are communicated, and the degree of their completeness, which form the basic elements of pharmacovigilance, i.e., the number of reports with good quality data. This in turn impacts how pharmacovigilance can be more or less effective in avoiding adverse effects throughout the action of regulatory bodies, or recommendation of clinical societies and guidelines.

It appears clear, therefore, that the teaching of pharmacovigilance can be focused on many aspects and with different levels of complexity and completeness in the PV content. Industry and regulatory staff usually have specific and regular training, and these courses will not be considered here [3]. This article has been written from the perspective of academia, and mainly from the perspective of a School of Medicine, and has been conceived from the experience in a non-US-UE country.

The objectives of the introduction of pharmacovigilance in academia, both in under- and postgraduate curricula, are many and all of them are important. *The teaching of Pharmacovigilance in Schools of Medicines is necessary because clinical medical expertise plays a major role in the discovery of drug-induced diseases, in signal generation and signal assessment.* Pharmacovigilance is vital for patients' safety, and the awareness of adverse drug reactions is important to help avoid undesirable drug effects. Pharmacovigilance improves the health care system's efficiency in its objectives: to avoid unnecessary complications, to reduce healthcare costs due to preventable hospitalizations and/or prolongation of hospital stays, and to enhance patient's outcomes. Pharmacovigilance contributes to the knowledge about how and when ADRs occur. However, a feature common to many countries, regardless of economic level or development of Pharmacovigilance system, is that the PV teaching (and even the teaching of clinical pharmacology) in universities is far below the minimum requirements to help sustain an effective postmarketing drug monitoring system dependent on health care professionals as active participants.

PV activities and performance also vary largely between and within countries and regions. Moreover, a drug's availability and quality are not the same in all over the world with accessibility to drug therapy influenced by economic and technology inequalities between countries, plus local regulatory differences. Populations are also different as regards their environmental, health, and literacy conditions. Health priorities and prevalent conditions vary among continents, countries, and regions.

Thus, when planning a PV University teaching program, it is necessary to identify PV priorities for each country and for each particular region: are (some or all) adverse effects neglected and people suffer from avoidable side effects? Is there a culture of health care professionals reporting? Does reporting exist at an "acceptable" level, considering the use of medicines in this specific region? If it is effective, how does it contribute to local regulatory decisions? Is publishing usual or scarce? If scarce, how many cases or cases series have been published, and what level – local, national, international?

The fundamental issue concerns whether the teaching sufficiently produces expertise in the whole range of pharmacovigilance from spontaneous reporting process to pharmacoepidemiological studies so that physicians and pharmacists are trained to recognize adverse drug reactions, to share their findings through reporting and publications, and subsequently to improve the quality of patients' pharmacological treatments, avoiding unnecessary drugs and preventing harmful effects. *This first crucial step is to gather interested and motivated professionals to maximize the impact on safety of patients and PV.*

In order to identify the main objectives for each training activity, it is necessary to build a local and meaningful list of contents in each program, taking into account local and national priorities, in order to engage audiences at their level: to "import" foreign curricula, even though they may be interesting and have been very effective in their original settings, risks not meeting the needs of professionals and students.

The basic objectives of pharmacovigilance teaching in universities should be to make students and professionals aware that ADRs are frequent overall. ADRs are also heterogeneous and can mimic any disease or manifest through a wide variety of symptoms and signs, and sometimes it is not easy to link these adverse manifestations with the known profile of the drug(s) administered to the patient. Health professionals have to internalize that most ADRs are preventable; always keeping in mind that preventability can be an evolving concept according to new findings and diagnostic methods. Students and professionals should also be knowledgeable enough to try to avoid medication errors in an efficient way and should be trained in the search of pertinent and independent drug information. They should be very motivated to search for strategies to make errors less frequent and less serious. Both physicians and pharmacists should be aware of national and international reporting systems and be able to report using the normal methods in a timely way, with good quality data, in order to become an active participant in the process of PV and in patient's safety. Scientific knowledge and clinical experience and expertise are the basis for an enhanced perception of ADRs, and this process needs to be cultivated at both the individual and community levels.

1.1 In a University Context, What Does PhV Teaching Mean?

Contents of School of Medicine curricula are mainly focused on diagnosis and therapeutics of known pathological entities. In addition to anatomy, physiology, that is, how organic systems work, and pathophysiology, how organic systems fail, and the causes for these failures – pathogenesis – are usually studied in the first years. Later, students are taught to make diagnosis of well-defined organic clinical entities, mainly the most prevalent ones, with a battery of laboratory, image, and functional tests available. Psychiatric disorders are also included in the curricula, and at the end of her or his university training, physicians are supposed to be able to identify and treat also the most prevalent mental, behavior, or mood conditions – increasingly diagnosed although much less supported by objective evidences.

Diseases can be treated through several therapeutic options: pharmacological, surgical, lifestyle advice and counseling, physical therapies (physio and kinesiotherapy), as well as psychological treatments and even more. Pharmacological therapeutics has become more and more common – the rule rather than the exception. More and more active principles are introduced in clinical practice. However, in spite of the increasing amount of drug information available, in general, curricula of medicine and pharmacy schools in universities devote few hours to the teaching of pharmacovigilance, and even of Pharmacology itself. In UK, for instance, a quite recent cross-sectional survey used to obtain data relating to the teaching of pharmacovigilance within schools of pharmacy showed that the time devoted to teaching pharmacy students about their participation in pharmacovigilance and specifically to spontaneous reporting was less than 4 h in the 4-year course in 54 % of respondents; between 4 and 8 h in 38 % of students; and only one respondent spent 20 h. About 23 % responded that their courses did not include pharmacovigilance at all [5].

Drug information – about benefits and adverse effects – must be continuously updated. New concerns and findings arise constantly, for new drugs, but also for "old" ones, and for the concomitant use of two or more active principles. *However, in texts of pharmacy and medicine, this information is "fixed" and updated – and obviously, not completely, which would be unfeasible – confined only in new editions*. Pharmaceutical industry does develop educational activities addressed to prescribers, directly through drug information to practitioners, and indirectly through academic or specialist societies, as well as by its participation in scientific meetings. The influence of pharmaceutical industry covers not only postgraduate education, but also that at an undergraduate level.

This influence of economic interests and the general social perception of medicines as essentially "good" products have led to a generalized over prescription of medicines. In addition, in many health care systems, patients are seen by different medical specialists, each of them tends to treat the illness or symptoms of the speciality, and physicians are reluctant to remove medicines prescribed by other specialists. This concept of the patient as a body composed by different pathologic

sectors is supported by the physician's under- and postgraduate training. The consequence is often overprescription, rather than a holistic view of the patient's treatment needs or even desires.

Pharmacovigilance addresses also rational prescribing. Overprescription affects all fields of medical practice, but it is an especially sensitive issue for psychiatric conditions. Sometimes, the limit between "normal" and "pathological" mood is not clear, and pharmaceutical therapy is used not in the interest of individuals' health, but in order to prioritize their functioning according to social norms. Some emotions are considered "pathological" and borders are not always objectives: When does sadness or low mood become depression? When does mourning become pathological? However, there is a cost – in terms of adverse drug reactions and both for individuals and for populations – of long-term therapies with agents for anxiety, insomnia, and mild depression. Attention deficit hyperactivity disorder (ADHD) as clinical entity should be contrasted to a social response to a stressful environment, or even to an energetic, but naughty child. If so, does it deserve always pharmacological therapy? Elderly people, particularly but not exclusively those who are in care homes, are particularly exposed to overprescription and psychiatric medication prescriptions.

When teaching pharmacovigilance, the highly hierarchical and pyramidal structure both of the teaching of medicine and the clinical practice must be acknowledged, as working well in academic settings. It is especially difficult, however, for students or young professionals to contradict or disregard established prescription models and/or advice of conservative and overworked supervisors. Thus, ideally, to work first with teaching staff and more flexible experienced professionals would be desirable, but unfortunately this is not always feasible.

1.1.1 To Whom and How to Teach Pharmacovigilance in Universities?

Under- or Postgraduate? Undergraduate teaching of pharmacovigilance should be mandatory. Students should be aware of the multiplicity of adverse drug reactions, the frequency of known adverse drug reactions, and about the fact that they can be much more if one includes consideration of medication errors. Medication errors related to drug-drug interactions, or food-drug interactions, are avoidable, but if neglected they can multiply the frequency of type A adverse reactions. Learning more about medication errors may enhance health care professionals' ability to provide safe care to their patients.

Classes of pharmacovigilance to students are usually very participative and enthusiastic. This is probably because students are not allowed to prescribe or dispensing, and therefore, they are not charged with the burden of responsibility (which, in some settings, can partially explain practitioner's reluctance to report). We have seen many times this enthusiasm frozen later, when students became

practitioners and, therefore, are supposed to be – or feel they are – the most responsible partners in patients' treatment. Thus, an essential part of PV teaching is to reinforce the subjective components of reporting, highlighting its importance in the iterative process of drugs' safe use. It is also crucial to insist on the value of medication errors already committed as starting point for improving health care system and professional education, if they are acknowledged and avoided later. Promoting discussions about legal, professional, and even emotional aspects – such as shame or feeling guilty – has great importance in promoting safe use of medicines.

Postgraduate training in pharmacovigilance is necessary because practitioners have an inadequate knowledge and understanding of the medicines they prescribe, or the interactions with other patient's prescribed or over the counter (OTC) medicines.

For physicians, there is not so much interest in learning pharmacovigilance as a set of regulatory procedures and classifications. Except for those who are decided or interested in working for pharmaceutical industry or regulatory bodies, there is no benefit in learning about this. It is not necessary in clinical practice as hospitals with pharmacovigilance departments are not the rule; indeed, they are rare in most countries.

Another important reason which can explain a practitioners' lack of interest or lack of commitment in pharmacovigilance activities is the physicians' responsibility, as discussed above. When an informative talk about pharmacovigilance is given to practitioners and product failures are mentioned, the audience usually reacts enthusiastically and contributes with lively examples and real cases. Of course, when product failures cause adverse reactions, the blame can be shifted (onto regulatory bodies, or drug purchasing procedures or others), but if failures or errors arise from physicians (because they have not taken into account drug interactions or patient's susceptibility factors), this can be felt as a potential cause of loss of prestige and even can undermine self-estimation. Then, it is necessary to give to healthcare professionals both confidence on the PV system and practical strategies to overcome what would threaten their willingness to report.

Both hospital and community pharmacists are not exempt from difficulties when they want to apply drug safety advise in their professional fields. Community pharmacists sometimes would face the uncomfortable role of contradicting medical prescribing – and then they'd risk to lose the sale and the client – and hospital pharmacists not always can fluently interact with medical staff.

Design An adaptive design – both for contents and educational strategies – favors learning and students' participation.

Audience Homogeneous or, on the contrary, mixed audience both have advantages and disadvantages. Homogeneous audiences allow a more uniform selection of topics, which will be different for physicians, pharmacists, dentists, or nurses, for instance. Heterogeneous audiences (for instance, community or/and hospital pharmacists and physicians) are extremely interesting in terms of exchange of different views, and a rich source of experiences to be exploited. When students are

professionals from a different educational level (i.e., nurses, paramedics), it would be preferable to create another section, with the same contents, but treated in a more accessible language and with explanations according to the audience's previous training.

- To build a customized curriculum for your targeted audience. Imported curricula risk not meeting local needs.
- Contents must be flexible and activities and design of the course should be adaptive to students' needs and perceptions.
- To work on examples provided by students/participants, as starting point for one or more specific topics.
- To teach your students/participants to actively search for drug safety information and promote consultation to pharmacovigilance centers.
- To promote reporting and fluent communication with National Pharmacovigilance Centers
- To work both on objective and subjective components of PV reporting

1.2 Conclusion

Medicine has developed and progressed amazingly in the last seven or eight decades. Pharmacotherapy has played and continues to play a central role in this development. However, in the same way that industrial and economic development can reach a level in which further effects can be more deleterious than beneficial, the vast spreading use of pharmacological therapeutics should be regarded not only as an undeniable progress, but also as a real, or at least a potential, harm for the health of populations and individuals. Now perhaps it is time to ask if new therapeutics – and the use that health professionals are taught to do with drugs – can effectively keep sustaining this development. And what is the real extent of the harm produced by adverse effects, serious and nonserious, on people, especially – but not exclusively – the most vulnerable, elderly, children, severely ill patients.

The title of this article refers to "teaching." However, nobody can assume that one can "teach" pharmacovigilance. Every class, every discussion, even informal, is a lively, exciting challenge and exchange of reasons to find out more and more about effects of medicine in patients and healthy people. Because of the nature of the increasing and evolving available scientific knowledge, pharmacovigilance should be studied and learned, indeed dare we say PV taught, both throughout the "entire lifecycle of the product" and "all the entire cycle of our professional lives." In order to make this sustainable, the motivation should persist, and such persistence is only possible if individuals are convinced of the value of his or her contribution to the science of PV.

Let us conclude with words of Ronald Meyboom: "Real-life medical/pharmaceutical practice is *the* source of the data and information needed in pharmacovigilance. The quality of pharmacovigilance – in terms of speed, reliability and

relevance – depends upon the data that are reported or otherwise provided by practitioners. Obviously education and communication are major tools for intensifying and further improving pharmacovigilance".

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Chapter 2
Lost in Regulation

Pia Caduff-Janosa

The aim of regulation in drug safety is to state as clearly as possible and to enforce the legal responsibility of the involved parties (regulators, marketing authorization holders and health care professionals where applicable), and to provide guidance on how the respective duties should be complied with. The guidelines issued have as a significant impact on the outcome as the law itself, as they determine the stakeholders' compliance and performance.

We have seen PV regulation develop from virtual nonexistence[1] into a well-intended but overwhelming collection of documents defining every possible detail of every imaginable contingency. The intent is to ensure the seamless safety surveillance of medicinal products from preclinical testing throughout their lifecycle in order to preserve patients from harm, but what we lack up to the present day is evidence that such extensive, in certain aspects even obsessive regulation is in fact resulting in safer medicines, safer use of medicines, and ultimately, safer patients.

[1] Pharmaceutical regulation up to the middle of the twentieth century focused mainly on manufacturing and sales issues, documentation of efficacy, as is standard nowadays, was not required. A medicine was considered unsafe if contaminated with known toxic agents, but the concept that an active ingredient itself could cause damage to certain patients was not current.

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2.1 All Well, Thanks to Thalidomide?

Thalidomide was and still is a tragedy for over 10,000 children born with congenital malformations and their families. In Europe, it also represents failure all along the line[2]: the granting of marketing authorization; the delayed recognition of the cause of the sudden increase of observed phocomelia; the hesitant approach of the regulatory authorities to investigate the problem and take action; and the failure to recognize the causal relationship between drug and ADR and to communicate openly with victims, health care providers, and the public.

The thalidomide tragedy was a wakeup call that led to a much needed strengthening of the existing regulation and significant improvement in the approval process for new medicines. Several other factors might have contributed to more sensitivity to the safety of medicines. Contrary to many adverse drug reactions, congenital abnormalities are immediately visible harms, which can be considered as possibly attributable to medicines intake affecting a vulnerable population, in this case, newborn babies. This might have contributed to an increase in awareness not only in professional circles but also in the general population that the use of medicines is not free of risk and therefore to a demand for better surveillance. It was, after all, the media coverage that pressured authorities into action.

Rapid scientific and technological progress has helped towards a more reliable investigation of efficacy, safety, and quality, providing better data to decide whether or not to grant a marketing authorization for a product, and the WHO Programme for International Drug Monitoring, the worldwide pharmacovigilance network founded in 1968,[3] has provided the means for rapid identification of areas of concern by collecting, pooling, and evaluating ADR reports from all sources. Industry safety databases have also become more comprehensive over time albeit limited to each company's portfolio. Such databases hold comprehensive pre- and postmarketing safety data but are not accessible to external parties.

All well after thalidomide? Far from it: 50 years later we are still adding to the long list of medicines causing serious harm to high numbers of patients before any regulatory action is taken.

2.2 Does the Current Regulation Work?

Searching for evidence that the current regulatory requirements and practices have indeed led to safer use of medicines and less or less severe drug-induced injury brings one quickly down to earth: these questions have not been answered yet.

[2] The US Food and Drug Administration (US FDA) did not approve thalidomide due to safety concerns, which leads to the conclusion that data pointing at a safety issue were available at the time.

[3] The program started in 1968 with 10 countries willing to share their reports on adverse reactions to medicines and counts 121 full members and 29 associate member as per September 17th 2015. For further information see http://www.who-umc.org/DynPage.aspx?id=98080&mn1=7347&mn2=7252&mn3=7322&mn4=7324

The impact of regulation on drug development was looked at in 2007 by Marchetti and Shellens [1], and within the FDA's Sentinel Initiative (http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm) a pilot study was conducted to look at what research had been performed so far to evaluate the impact of FDA's regulatory actions. The researchers focused on the methods used to evaluate impact and not on outcomes, thus not answering the question whether the regulatory actions had any impact at all.

In 2012 Nkeng et al. [2] reviewed Risk Minimization Interventions (RMIs) published from 2000 to 2009 in relation to the publication of regulatory guidance on risk management. The study, limited to the ICH region, showed that only the USA registered a substantial increase in the number of RMIs during the postguidance period, but again the actual impact of these RMIs on patients' outcomes was not addressed in this study.

Bouvy et al. [3] explored if the cost-effectiveness of PSURs of biologicals in Europe can be established and concluded that this kind of analysis can and should be performed but again provided no evidence for safer medicines under the current regulatory practice.

Pacurariu et al. [4] have described the signals submitted to PRAC in the first 18 months (July 2012 to December 2013) after this body was established while also looking at the efficiency of this new process. Eighteen months is probably too short to see the impact the PRAC recommendations have actually had on patient safety, if any. Therefore, although we have experienced in the past the impact of absent regulation, there is so far no evidence that the current regulation leads to better outcomes. If we want regulation to significantly improve patient safety, we need to know if what we are currently doing is effective. If it is not, we must stop wasting time and resources and need to think of better ways to achieve our goals.

2.3 Harmonization: Global Business = Global Safety?

Legislation is national but business is global. This calls for harmonization of regulatory requirements, at least from industry's point of view. International companies need to comply with regulation in all the countries in which their products are marketed and in which they conduct clinical trials. Different requirements lead to an increase in workload, duplication of work, and in a significant investment both in time and resources to assure compliance. The *International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) is a body of representatives of the regulatory agencies and industry associations of Europe, Japan, and the USA and has been working towards common standards and requirements for efficacy, safety, and documentation format since 1990. This body represents 17 countries and approximately 15% of the world population; WHO, Canada, and EFTA (European Free trade Association) hold observer status. ICH Guidelines have also been adopted by regulators of some non-ICH countries. De facto Europe, the USA, and Japan are indirectly driving regulation also outside their own jurisdiction.

Comparable content, common formats, and timelines help to exchange information, which is fundamental for drug safety.

It is recognized that the ICH Guidelines are scientifically sound and fulfill their purpose of establishing common standards in the environment they originate from; however, they have been developed by and reflect primarily the views of industry and regulators of highly industrialized countries excluding those of low and middle income countries. As these ICH guidelines are regarded by the influential ICH countries as the gold standard, there is pressure to implement them worldwide. Expanding ICH standards into non-ICH regions might be a way of "globalizing" pharmacovigilance by facilitating exchange of information worldwide, but countries that have been excluded from the decision making process and do not see their concerns and needs addressed by these guidelines might be reluctant to adopt them.

Many of the countries outside the ICH region have drug regulation systems comparable to those in Europe and the USA. Others have regulatory systems that are still growing and maturing. Some countries struggle with political instability, wars, and natural disasters that put an additional burden on already stretched resources in the public administration, adding to the difficulty of establishing well-functioning pharmacovigilance systems. Under such circumstances, investing resources into harmonizing regulatory requirements with ICH countries can hardly be seen as a priority. The ICH Guidelines themselves, as well as they may meet the needs of the environment that has driven them, are not necessarily the appropriate model for low and middle income countries. This is especially the case where there is no local pharmaceutical industry that can be closely monitored and medicines are provided either through vertical programs or are imported from markets equally insufficiently regulated. Moreover, the underlying diseases, health care structures, and budgets, as well as the drugs used, might need different considerations. Obvious examples of important geographical differences apart from what drugs are available and how they are made available are the state of nutrition and the phenotypes of different populations.

While some non-ICH regions prefer to go their own way, others have opted to adopt recommendations and Guidelines from ICH countries. The Guideline on good pharmacovigilance practices (GVP) for Arab countries (532 pages!) [5] is an example of adoption of the EU GVP in a different region. Yes, the EU GVP guidelines are a comprehensive and monumental opus, but does that per se make them useful in a different setting? Shouldn't there be more room (and courage) for the best possible local adaptation of sound general principles?

In the interest of global pharmacovigilance, we need to develop common standards that are applicable and acceptable worldwide. This is only possible if low and middle income countries are included as active and equal partners in such discussions and decisions. We must find and allow room for local adaptation of common requirements.

2.4 Regulatory Guidance: Help or Obstacle?

Regulation per se is neither bad nor an unnecessary burden, on the contrary. Products are put on the market for profit, not for philanthropy even though the vision and mission statements in the industrial world might want us to believe differently.

Where high profit can be made, the temptation to take shortcuts in quality, efficacy, and safety is huge and if the market for pharmaceuticals were not so profitable, counterfeiting and illegal trade of medicines would be much less of a problem too. Unfortunately we cannot rely blindly on the industry's (whether pharmaceutical or other) ethics and regulations contribute to contain damage, but they can be and are circumvented, despite the efforts and engagement of the many employees driven by high ethical standards. Temafloxacin sales were pushed even when the MAH and the US FDA were already discussing the withdrawal of the drug because of life-threatening ADRs[4] [6], and Volkswagen with their rigging of emissions tests by software in its diesel cars that has come to light in these days is just the latest of many examples of corporate skulduggery. Regulation is necessary, but the question is: are we moving in the right direction?

While legal requirements within the ICH region are on the whole comparable, the amount and kind of guidance provided for complying with these is strikingly different. The US FDA *Guidance for Industry* documents on Good Pharmacovigilance practices and Pharmacovigilance planning, together approximately 50 pages, provide practical advice on content and methodology. The reader is informed that the documents contain nonbinding recommendations, thus leaving room for pragmatic solutions. In section IV B of the *Guidance on Good PV Practices* [7] (Characteristics of a Good Case Report in the US FDA Guidance for Industry), the most important elements of a good quality ICSR are presented clearly. This is what the regulator obviously expects to receive and this is what should also be looked at when a regulator inspects a MAH to assess their compliance with good PV practices.

The US FDA approach shows common sense, after all the pharmaceutical industry is a very diverse world. The monitoring of the newest biologic agent presents different challenges than the surveillance of a product with a safety profile so well established that the product is considered safe enough to be sold at petrol stations and grocery shops.

In contrast to the frugality of the US guidance, the European Guidelines on Good Pharmacovigilance Practices (GVP) encompass 16 modules, 12 with various lengths (9–90 pages), and several addenda are so far finalized and published [8]. GVP describe frames, timelines, and formats in detail, but the attention given to the medical content of safety reports to be submitted to the authority is by contrast minimal. The stoical reader will therefore find in detail how to report but little help on the medical/scientific information essential to investigate issues of concerns and which might help formulate a useful hypothesis. This might be seen as trust in the good judgement of the

[4] Temafloxacin was licensed in Europe and Latin America at the end of 1991. Shortly after approval by the US FDA in February 1992 serious, and in some cases fatal ADRs describing a multiorgan disease involving the hematological, hepatic and renal systems were reported with alarming frequency. After several meetings with the US FDA, the MAH agreed to withdraw the drug On June 5th 1992. Between February and June the sales representatives were not only not informed about the discussions with the regulators but pushed to continue selling the product, according to J. O' Donnell in his book *Drug Injury. Liability, Analysis and Prevention*, 1st ed 2001. The withdrawal was followed by several claims of wrongful death and personal injury filed in the USA and not settled until 1997.

MAH, but it results in a focus on format instead of content with negative consequences for pharmacovigilance activities. The daunting volume and dry, technical and in part legalistic language make GVP hardly a user-friendly manual, not even for electronic wizards or longstanding pharmacovigilance enthusiasts. However, I fully agree with IR Edwards, when he points out in his editorial *Good Pharmacovigilance Practice and the Curate's Egg* written for Drug Safety in 2012 [9], "there is some very good guidance and information here." In fact GVP covers every theoretical possibility or question that might arise in the safety surveillance of medicines and provides every possible answer on how to fulfill regulatory duties – in the correct format of course. The intention is good and the effort put into compiling it is impressive: it is the lack of weighting, of room for pragmatic approaches, and of focus on scientific content and its sheer volume that makes it a well meant big monster: interesting to look at from distance but better kept under lock and key. Better guidance on essential scientific content condensed in a much shorter and more pragmatic document as its US counterpart could turn the monster into a faithful companion.

Efforts have been made to reduce workload at both ends, the regulators and the MAHs. Transferring the responsibility for literature review from the MAH to the European Authority is an important step to avoid duplication of work and will contribute to less duplicate reports in the databases, always provided that this approach works in practice. On the other hand, according to GVP, even all expected nonserious ADRs must now be reported to the authority as ICSRs and the balance between workload and beneficial impact of these requirements is doubtful.

If the regulators want to receive the relevant information for their work, they must ensure that the guidance they provide for reporters, no matter if HCPs or industry, is focused, practical and user-friendly.

2.5 Sacrificing Content for Format

Regulatory authorities have the duty to enforce what legislation dictates and some players need a little bit more "encouragement" than others to comply with legal requirements. Inspections are one way of stimulating the regulatory compliance of a marketing authorization holder. Failure to comply leads to sanctions that can go as far as the withdrawal of a manufacturing license. Major findings at inspection must be watertight, especially in countries where regulatory decisions are legally binding and a company can challenge a regulator's decision in court.

Timelines and formats both of ICSRs or periodic reports are easy to monitor and admonish in case of fault: a timeline is either kept or not, there is not much room for disagreement. If this is listed as a finding of noncompliance, it will be accepted. Whether a scientific evaluation is sound or not is more difficult to assess and criticize and therefore more open to discussion and prone to challenge. If this is at the core of major inspection findings leading to sanctions, it might pave the way to a long and costly legal dispute. To be on the safe side the attention of the inspectors focuses on form and not content and the MAHs act accordingly: fill in the right form

and submit on time, too bad if the information provided is limited to minimal reporting criteria or little more, and does not contain the information relevant for an appropriate clinical assessment.

Risk minimizing measures are often taken based on data from spontaneous ADR reports [10]. Insisting on receiving ICSRs of high quality should therefore be a top priority for regulators. If the focus of regulatory requirements was more on content than format, and if the guidance provided reflected this, it would be easier for inspectors to challenge reports of poor quality and this would act as an incentive for MAH to invest more in better reporting. Strict timelines can be a hindrance to quality of reports as once a report is filed, the pressure to complete it with additional information lessens and the necessity to forward one or more follow-up reports to the authority complicates the workflow and adds to the workload on both sides.

The current focus invariably leads to the submission of individual case safety reports listing the minimal information required to make them valid from a regulatory perspective (reporter, patient, medicinal product, ADR) but little or no information that enables causality assessment. At the Regulatory Authority, receiving reports saying "*On an unknown date, a female patient under treatment with drug X in unknown dosage, developed ADR Y. Medical history, concomitant medication, action taken and outcome are unknown*" is by no means an exception, and such submissions are the daily nightmare of any assessor asked to evaluate if there is a reasonable possibility that drug X can cause ADR Y. What we need are spontaneous reports of high quality, with a detailed description of the events, a complete chronology, the relevant medical history and information on concomitant treatment, how was the differential diagnosis carried out, action taken with the suspect drug, and outcome of the reported ADRs. Providing also time to recovery and treatment of the ADRs reported adds to the knowledge required to give provide important and much sought after information on expected course and outcome. Getting this information is difficult: HCPs are busy people with little time to spare for activities that put a burden they might perceive as unreasonable. Many HCPs do not understand the importance of reporting ADRs and the benefit they and their patient can get out of well-documented reports. A legal obligation to report is not enough: we must make sure that HCPs fully understand the value of reporting and get value back for the time they invest in pharmacovigilance. Prompt feed back to primary reporters with information that is relevant for clinical practice such as causality assessment of the reported ADR-drug association and information from the ADR databases as well as from the scientific literature motivates the medical community to contribute to safer medicines. Providing user-friendly coordination with already existing electronic records will further ease the burden of busy professionals.

Regulators have the duty to provide sound and useful information on the safety of medicines. Patients suffering from an ADR (and their HCPs) are not primarily interested in hearing from a regulator if the ADR of their concern is listed in the product information leaflet or not; they want to know what they can expect in terms of course, severity, treatment, and recovery. Well-documented, clinically focused reports can significantly add to this kind of knowledge, and every possible effort should be made to get them.

One might argue that low-quality reports should not be dismissed too quickly as they do have a role in contributing to disproportional reporting in safety databases and therefore help to highlight potential risks when mining large datasets, but we need to be aware that such reports are utterly useless when it comes to the actual scientific evaluation of the identified issue. If the only information available is that a patient suffered and ADR under treatment a causality assessment is not possible, nor can the combination be characterized in terms of risk factors or populations at risk. This gives MAHs that are not overly motivated to look into potential safety issues, a welcome reason to dismiss spontaneous reports of low quality as unassessable when concerns are being signaled by other parties. The fact that a significant number of such unassessable reports are submitted by MAHs to the authorities and that they are responsible for their content is conveniently overlooked.

We should not forget that collecting poor-quality reports, entering them in a database and transmitting them to the authority require effort, time, and resources that are not available for other, more demanding, and more important safety work. This is not going to change until regulators start putting more emphasis on content than on format. However, such a shift of focus will only lead to a real improvement if it is taken up during PV inspections and enforced.

2.6 Don't Ask for More Than You Can Handle

Marketing authorization holders are mandated to reports ADRs while participation in the safety surveillance of medicines remains voluntary for health care professionals in most instances. Even where they are obliged by law to report ADRs, this requirement is very difficult to enforce. If an authority wants to prosecute a HCP for not reporting, it has to prove in the first place that the HCP in question did in fact suspect that the condition the patient was suffering from might have been an ADR and has not reported it. Now, how are we ever going to prove what went on (or not) in the mind of somebody else? And even if this suspicion has been documented in medical records, which regulator has the capacity to screen all medical records in their jurisdiction? When professionals publish case reports on ADRs in scientific journals but no such case can be identified in the national database, the logical conclusion is that the reporting requirement has not been met; nevertheless, confronting the fallible HCPs will hardly improve reporting culture but probably achieve the contrary by creating resentment and possibly even ridicule. The legal requirement for HCP to reports ADRs does not by itself improve compliance[5]; it can be used as a medium to raise and maintain awareness of drug safety among HCP but not as

[5] In 2002 Switzerland introduced the legal requirement for HCP to reports ADRs and this was broadly communicated to the medical community. The number of reports from HCPs increased rapidly over a short time. When the authority stopped actively promoting ADR reporting on a large scale, the number of reports stabilized more or less, while reports from industry kept increasing significantly. See https://www.swissmedic.ch/ueber/00134/00441/00445/00568/index.html?lang=en

coercion. A legal provision that cannot be enforced is a toothless tiger: it is not taken seriously if it is well recognized that there will be no adverse consequences in case of noncompliance.

As basis for the marketing authorization for a medicinal product, pharmaceutical companies are rightly required to submit all available data on efficacy, safety, and quality. This documentation has become so extensive that electronic submission must be considered a blessing not only by reviewers but also by any logistics team. It is more than reasonable to ask for as much information as possible on a new drug before granting marketing authorization, provided that this information can also be thoroughly evaluated within an appropriate timeline. What is difficult for a regulatory agency in a high income country can become quickly impossible if Western requirements are uncritically adopted in countries where resources are far too scarce to process all the documentation submitted. Under the pressure of limited patent time, it is in the interest of a company to obtain approval as soon as possible and accordingly there is a lot of pressure on regulators. There is also pressure from the public: a regulatory agency is very quickly accused of dragging its feet by patients who are ill and hoping that the new drug will provide cure or at least significant relief.

Drug regulatory authorities are funded partly by taxpayers and partly by fees for services paid by industry. The former is a problem because the same politicians who decide on legislation are too often not willing to allocate the state budget needed for the work the implementation of this same legislation requires and the latter is condemned by those who think that a regulator must be completely independent from industry. This leads in any case to too limited resources for the workload and the depth of data evaluation required. This forces the regulators into a compromise between what is necessary and what is realistic, leaving all parties dissatisfied.

The same applies for postmarketing surveillance. The marketing authorization is granted, individual case safety reports, periodic reports, pharmacovigilance, and risk management plans (and their results!) must be submitted within defined timelines. Again, the rationale for these requirements is perfectly sound: the companies should continuously and reliably monitor the safety of their products and report to the authority. Once again format and timelines are given for ICSRs, periodic reports, PV Plans, and RMPs. The question still remains: are these documents being evaluated appropriately or only cursorily and then archived? Compiling these reports ties up immense resources and if the evaluation at the other end does not or cannot go much further than reading the executive summary or enter unassessed ICSRs into their database, it is pertinent to ask, if regulators should not ask for less but more focused information, appropriately tailored to the products and concentrate on this. This would still leave the option open to ask for more if needed. Do we really need every nonserious ADR reported as ICSR for every product on the market? A more focused, evidence-based approach would free up resources to invest in the scientific work that should constitute good PV practice.

Regulatory requirements should be based on evidence of effectiveness and cost-effectiveness. Requirements that prove effective should be enforced and adequate resources made available, if we want to reduce medicine-related harm to patients.

2.7 Acceptable Risks?

Even optimal regulation cannot eliminate every risk. One question that arises here is *how much risk are we prepared to take?* followed by *who decides on how much risk is acceptable?* The public's voice has been included in some regulatory proceedings,[6] but is this enough? Patients need to be able to make informed decisions. This means that the available information on benefit and risk of drugs must be communicated openly and in an understandable way. As the information must be objective and the MAH will hardly be considered free of bias, preparing and delivering it will be up to the authority.

Everybody has high expectations when it comes to therapeutics: they must be highly efficacious, completely safe, available as soon as discovered, affordable, and possibly funded by insurance or other parties. The competent authority must make sure all this is provided and function like clockwork. All this comes at a price. We must decide what we want and be prepared to pay for it.

2.8 The Regulation of the Future

We should work towards a regulation that is evidence based and cost-efficient, practical, simple, and transparent by

- Openly sharing relevant information in the regulatory environment
  - The first registration of a drug and all the information related to it could be made available to all other regulators, who in their turn could peer-review and add to it. This would reduce duplication of work, lead to leaner and more rapid regulatory processes, adapted to local needs and resources, and encourage a better and more equal collaboration between highly industrialized and low and middle income countries.
- Getting rid of overflowing bureaucracy and allow for flexibility and common sense.
  - Only data that can and will be thoroughly evaluated at the authority should be submitted. This will free up resources for more thorough scientific investigations of safety issues and the timely communication of the results.
- Ensuring that regulatory requirements are evidence based and cost-efficient
  - More efforts need to be put into investigating and documenting the impact of regulatory requirements on the benefit-risk balance for patients as well as the

[6] The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency is composed of representatives of the Member States, scientific experts and one representative of healthcare professionals and of patients' organizations respectively. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp

health care system. A documented positive impact will motivate all stakeholders to strongly engage in pharmacovigilance and to comply with requirements they can perceive as useful and important and not as an additional burden.

And last but not least, all harmonization initiatives should aim at global exchange and integration of knowledge instead of imposing Western standards in regions that need alternative solutions.

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Chapter 3
What Is the Future of Pharmacovigilance *and How Can We Make It as Good as Possible?*

Get the ADR Phenotype "Right"

Bruce Carleton

Pharmacovigilance is a scientific discipline that is underrecognized in its importance for improving understanding of drug effects in humans. It excels as a vehicle for detecting safety concerns particularly those early in the post-market phase after prescription drug approval. This is the time in the life cycle of a drug when manufacturers are required by regulatory agencies to provide adverse drug reaction (ADR) reports and the time when clinicians are gaining experience with new agents and are more likely to report ADRs [20]. The reporting of cases of drug-induced harm and subsequent analysis of such data is a critical part of population health surveillance, given the frequency of the use of drug therapy as a medical intervention.

The limitations of pharmacovigilance activities are well understood and include faint signals for many rare but serious ADRs. As well, many causal probabilities to ADR signals exist. For example, concomitantly used medications and active disease processes can make the ability to say definitively that an observed reaction is caused by a specific drug much more difficult. However, such possible confounders are not always apparent at the time pharmacovigilance processes are under way or known to pharmacovigilance scientists and may therefore be missed. A significant limitation is the quality of the ADR case report information. Lack of critical information in submitted reports remains a serious concern in pharmacovigilance science. Collecting high-quality data for more ADR reports is just part of a positive future for this science. But to fully appreciate the power and potential of pharmacovigilance as a scientific discipline, we need to go beyond the case report and epidemiological analysis of population risk.

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3.1 Quantifying Drug-Related Harm for Patients

The future of pharmacovigilance is tied to not just finding drug-related problems (in essence, reporting ADRs) but identifying solution strategies to avoid drug harm. With solution strategies comes wider acceptance of the importance of the discipline of pharmacovigilance. Most clinicians are not particularly interested in drug-related harm because the most serious risks are infrequent and treatment decisions are already taken seriously, with some thought about the potential for harm to occur. This means that there is a level of acceptance of the risk of drug harm by clinicians before prescribing begins. Knowing that an ADR has occurred in a given patient then is not generally unexpected. However, by quantifying risk versus benefit in increasingly objective ways (e.g., ADR risk prediction modeling in specific patients), clinicians can better understand an individual patient's propensity for drug harm. This is also what patients want – better defined risk information, relevant to them specifically – before they decide to take a drug that was prescribed. Patient-specific drug risk prediction helps to define which patients are at increased risk, an important first step in finding solutions to drug-induced harm. Pharmacovigilance science, as it stands, is therefore the first critical step of drug safety solutions. Moving the central focus of pharmacovigilance from signal detection to solution finding is the future for this scientific discipline. A side benefit of this approach is that medication adherence will likely be enhanced in those patients for whom the risk of ADRs is of significant concern when the level of risk is more objectively defined.

*This drug safety **solution-finding** approach assures the future of pharmacovigilance by demonstrating to those who most need to understand its virtues and the opportunities it affords – patients, clinicians, and regulators – that it can improve the safe use of drugs in patients, not just illustrate what harms can occur from specific drugs.*

3.2 Communicating Drug Risk

Drug risk communication is focused on population risk. "Dear Health Professional" letters often encompass statements such as "In worldwide clinical trials of drug X involving 16,450 patients, reports of reaction Y have been received for 14 patients." As a clinician, such a Dear Health Professional letter is filed in the round bin under my desk. Why? Because an incidence of 0.09 % means I will likely never see this reaction in my clinical practice. It is not meaningful to clinicians to see very small numbers that reflect *population* risk and not an *individual patient's* risk. Clinicians don't treat populations of patients but instead individual patients one at a time. They need risk information that compliments this individualized approach to health care. Patients ideally need the same thing – an individual assessment of *their* risk of an adverse drug reaction – not just population estimates of risk. When

examining population risk estimates, we tend to think of what the "average" patient might experience or imagine ourselves being the average patient. But how average we are depends on things we may not know about or are beyond our control, like our genetic makeup. How, then, can we communicate the risk of drug harm to individual patients in the most meaningful way? To answer this question, we first need to understand how differently patients respond to the same drug at the same dose.

3.3 Heterogeneity of Patient Response

Heterogeneity of patient response to drug therapy is well known, but not well understood despite years of pharmacovigilance detective work. Risk factors for drug harm are almost always known. Some are obvious – for example, most ADRs are concentration (dose) dependent – but for many drugs, differential risk of ADRs between patients is not well defined. Objectively quantifying and cataloging drug response heterogeneity such that clinicians can compare and contrast therapeutic choices would help tremendously in capturing the enthusiasm of clinicians in building better pharmacovigilance systems. *Pharmacovigilance needs to give clinicians what they need.* But cataloging responses can be difficult, particularly if patient outcomes are not objectively measured in the same way or with tools of unknown validity.

The lack of critical data in drug safety reports is an ever-present problem in pharmacovigilance. Clinicians are of particular value in drug safety reporting because they are generally in the best position to observe and describe patient response. But clinicians have other health-care priorities with busy schedules and little spare time. Properly quantifying drug response requires time and energy to note concomitant drug therapy, doses of all agents, comorbid conditions – all of which can and do influence therapeutic response – as well as many other factors. It is important to remember that clinicians are also rarely experts in pharmacovigilance nor see ADR reporting as a primary role.

3.4 Patient-Focused Risk Communication

Clinicians are patient focused and therefore require a patient-focused management strategy or solution for ADRs. Risk communication from pharmacovigilance professionals must increasingly fill this need if the future is to remain bright. If pharmacovigilance can provide *patient-specific risk information*, then reporting and *quality* of reporting will ensue with very little effort. Clinicians and patients will see the high value of ADR reporting when they see this information being brought back to them, formulated in a way they can use or benefit from it. For example, showing which patients are at increased risk and not just that a given drug has an

ADR risk. Clinicians, when completing ADR reports, will then begin to ask themselves, "what information do pharmacovigilance professionals need such that more patient-specific risk information reports can be generated?" instead of providing what they think pharmacovigilance experts need. There is a significant difference between these two approaches to providing drug safety information. The latter – clinicians providing ADR information based on what they think pharmacovigilance centers need – happens because they are completing the reports on the basis of what they believe will be done with it. If, for example, they imagine reports grouped by generic drug name and a broad reaction descriptor, then this is the specific information they will provide. ADR report-based literature generally focuses on ADR risk descriptions in this fashion.

The future of pharmacovigilance is based on clinicians getting what they need to make more informed treatment decisions for the patients they care for. The best advocates for pharmacovigilance are those that are served well by it.

3.5 Quality of ADR Data

Quality of the drug harm data used in epidemiological analyses is often poor and dependent on detailed cases provided mostly by "volunteer" clinicians or patients whose primary mandate is not to find solutions to these problems but only to report them. They generally see their pharmacovigilance mandate as *identifying* cases of drug harm. They can often reject the mandate to report a reaction by convincing themselves that the case is not clearly drug related and therefore not really reportable. Pharmacovigilance professionals often ask for all potential drug reaction reports precisely to prevent this filtering by health-care professionals who do not have the pharmacological background to make a proper causality assessment.

The future of pharmacovigilance depends on finding new ways to integrate clinician "volunteers" in this scientific discipline such that solutions to drug harm can be found.

The very next steps the discipline of pharmacovigilance must face are to identify how drug-induced harm should be best managed, how high-risk groups of patients can increasingly be identified before drug therapy commences, and perhaps most importantly, what therapeutic options should be considered when drug harm is likely to result in a tragic outcome. This "drug-safety-solutions-strategy" approach is best managed by pharmacovigilance professionals who are without question the best professionals to help characterize ADRs and build this solution strategy. That said, clinicians can help through the submission of better-characterized case reports which will come from them when they see more value in their reporting of ADRs. The value they see in ADR reporting comes when it helps the patients they serve. This is why finding solutions to drug safety problems needs to become the new mantra in the science of pharmacovigilance.

3.6 Active Surveillance

One important contribution of the epidemiological science of drug harm is that safety signals can be found needing regulatory or clinical action. But to ascertain the specific role of the drug to the development of an ADR (e.g., versus a concomitant disease), more than a compilation of ADR case reports is required. Detailed (and time-consuming) clinical characterization of the adverse event and temporal relationships in each case must be accomplished. Such "deep phenotyping" requires a specific type of pharmacovigilance. Active surveillance can be used to develop better-defined cases once an epidemiological signal is found, and this surveillance approach can help overcome epidemiological confounding.

Active surveillance is simply a method of pharmacovigilance but advanced by the use of trained surveillors who have standard case definitions by which to record critical data related to the ADR. As well, data are collected in real time as reactions occur or are uncovered during quality assurance initiatives, and the data can be collected over time, and treatment and management strategies to deal with the ADR are utilized. *ADR reporting is not just a point estimate for harm but an examination of the drug-induced harm over its entire course in the patient.* We need to understand harm – in whom, when it is likely to occur in treatment, and what makes patients who experience it different from those who do not. This requires that pharmacovigilance scientists collect comprehensive data on each ADR case. Active surveillance is not about collecting large amounts of data on patient drug experience, but instead collecting the right type of data and thereby creating well-phenotyped cohorts of patients from which further analyses and investigations can begin. For example, from such well-phenotyped data, pharmacogenomic determinants of drug-induced harm can be determined. This then leads to understanding genetic predisposition as well as the mechanistic basis of the ADR. This can lead to risk avoidance strategies in clinical care (e.g., not using a drug if the risk of serious harm is high) or even new therapeutic approaches to avoid ADRs or prevent them with concomitant agents to protect against harm.

We need a method to improve the quality of pharmacovigilance data. Active surveillance can help. Much of current epidemiological methods are to overcome the data quality problem with larger datasets. *"Small data" – data which are well constructed around a specific question – are likely better than "big data" in getting us to an understanding of what determinants are important in improving the safe use of drugs.*

3.7 Utilizing Pharmacogenomic Methods in Pharmacovigilance

Pharmacogenomic methods can also be employed to find genetic causes of drug harm, create risk prediction models to inform patients, and overall avoid harm in patients for whom therapeutic alternatives exist. Only expert-conducted pharmacovigilance can provide the appropriate background data surrounding the adverse

event upon which to build the genetic analyses and risk-of-drug-reaction prediction models. Some examples are the following.

Codeine, a weak analgesic, is commonly used for the treatment of mild pain. Interindividual variability in codeine analgesia is in large part related to functional polymorphisms in the CYP2D6, with resultant morphine formation ranging from 0 to 75 % of total codeine metabolism [5]. There are currently over 150 allelic variants and subvariants of varying functional activity identified for CYP2D6 (CYP2D6 allele nomenclature committee webpage: http://www.cypalleles.ki.se/cyp2d6.htm [4]). Traditionally, CYP2D6 enzymatic activity has been determined by the urinary metabolic ratio of a specific CYP2D6 substrate to its *O*-demethylated metabolite. Subsequently, genotyping methods have classified the population into four phenotypic groups: poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM), and ultra-rapid metabolizer (UM) [11]. Presently, *CYP2D6* genotype cannot fully predict phenotype. Concomitant use of a CYP2D6 inhibitor that may mimic a poor metabolizer phenotype leads to discordance between the genotype-to-phenotype predictions [11]. The majority of codeine-related deaths have concomitant drugs detected on the toxicological screen, making it difficult to determine if the death is attributed to codeine alone or multidrug use [9]. Understanding the combined role of genetic factors and drug-drug interactions contributing to these mortalities is likely to provide valuable information for the interpretation of circumstances around death, may help toxicologists and coroners decipher the cause of death, and may prevent future codeine-related fatalities from occurring.

Cisplatin is an effective chemotherapeutic agent used for a variety of solid organ malignancies in children and adults. Ten to twenty percent of all cancer patients receive cisplatin [17]. However, its use is limited by the high incidence of adverse drug reactions, including irreversible ototoxicity, peripheral neuropathy, and nephrotoxicity [2, 12, 21]. Cisplatin-induced hearing loss is an especially pervasive problem as it affects 40–60 % of pediatric patients and hearing loss at an early developmental age and can hamper the speech, cognitive, and social development of a child [6]. Strikingly, cisplatin-induced hearing loss shows significant interindividual variation; some patients are susceptible at any dose, while others do not experience toxicity at very high doses. Such wide variability implies a genetic basis underlying the ADR, and some genetic findings have been published [13, 15], but more work remains to be done to understand how these identified variants influence both cisplatin toxicity and its effectiveness as a chemotherapeutic agent.

Anthracyclines are highly effective and commonly used chemotherapeutic agents to treat adult and childhood leukemia and various solid tumors. Sixty percent of all childhood malignancies and more than 50 % of breast cancer patients each year receive anthracyclines [3, 14]. Their clinical utility is primarily limited by an individually variable, cumulative dose-dependent cardiac toxicity, manifesting as asymptomatic cardiac dysfunction in up to 57 % of treated patients and restrictive or dilated cardiomyopathy resulting in congestive heart failure in 16–20 % of treated patients [7, 8, 10, 18, 19]. The development of a predictive clinical and genetic risk model would aid in the screening, prevention, monitoring, and management of this serious adverse reaction. At least 21 genes associated with anthracycline-induced

cardiotoxicity have been identified [1]. Knowledge of these genes would improve our understanding of the mechanistic basis of the pathogenetic mechanisms for anthracycline-induced cardiotoxicity and could significantly improve our ability to predict in whom cardiotoxicity will occur.

Despite substantial evidence supporting a pharmacogenetic approach to warfarin therapy in adults, evidence on the importance of genetics in warfarin therapy in children is limited. The contribution of *CYP2C9/VKORC1/CYP4F2* genotypes and variation in other genes involved in vitamin K and coagulation pathways to warfarin dose and related outcomes in children have recently been published [16]. Associations between *CYP2C9/VKORC1/CYP4F2* genotypes and therapeutic dose, time to therapeutic international normalized ratio (INR), time to over-anticoagulation, and incidence of adverse drug reactions have been found [16]. Evidence to date shows an increased sensitivity to warfarin in *VKORC1* and *CYP2C9* variant allele carriers, emphasizing the diagnostic significance of predictive genotyping.

3.8 Linking Pharmacovigilance with Pharmacogenomics

The work of pharmacogenomics science depends entirely on the work of pharmacovigilance science. Without proper phenotyping of a patients' ADR, careful, detailed characterization of the adverse drug reaction (also known as "deep" phenotyping), identifying genetic variants of relevance to clinicians, is unlikely to occur. Drug biotransformation is a complex process of multiple pathways and in some cases saturable ones, whereby other pharmacokinetic pathways are used in part or in full. This makes the future of pharmacovigilance very bright. The decoding of the human genome holds great promise, but the use of genomic data to decode human drug response relies entirely on the quality of the drug use and outcome data that underlies such associations. A number of things can alter gene expression (e.g., diet, age, which would be captured with rigorous pharmacovigilance), but these are likely to have milder effects on drug response compared to genetic mutations. The value of pharmacogenomic information can only be found if rigorous pharmacovigilance precedes it.

3.9 New Drug Development or Drug Repurposing

One principal reason that pharmacovigilance science has not had the impact in patient care that it could have is the lack of a specific focus on finding solutions to drug-induced harm. If the mechanistic basis of ADRs can be found, then drugs developed that preserve efficacy and reduce toxicity are at least hypothetically possible to produce by avoiding these mechanistic pathways. As well, existing drugs that, for example, target key pathways of drug toxicity may be able to be successfully used to prevent toxicity of existing agents that are effective and produce positive drug outcomes but significant harm in some.

3.10 Assuring Pharmacovigilance's Positive Future

What is needed for the positive future of pharmacovigilance science is to move from considering it an independent science into one that is only really valuable if it is a part of achieving the most important outcome – a better way to predict and prevent ADRs in susceptible patients.

One model to accomplish this is to link the work of pharmacovigilance with the work of pharmacogenomics (Fig. 3.1). This model has four distinct phases:

1. The *discovery* of genetic variants that put patients at risk of specific ADRs or protect them from drug-related harm
2. The *replication* of these discoveries to ensure generalizability of findings and *validation* of why the identified variants mechanistically lead to an ADR or reduce its chance of occurring
3. The *translation* of findings into clinical practice
4. The creation of a sustainability plan to allow the process to work in perpetuity

Commercialization of the research allows the findings to be brought into widespread use. The profits from which are then fed back into the model to support the next pharmacovigilance work that leads to the next genetic discoveries, and so on.

The training of highly qualified personnel is at the center of this model, whereby personnel are trained in all relevant domains of the wheel to ensure drug safety solutions are developed. This is distinct from accomplishing just one task, such as developing pharmacovigilance activities that stand alone. Importantly, the model begins with patient- and clinician-recognized ADRs of interest and returns back to

Fig. 3.1 The Canadian Pharmacogenomics Network for Drug Safety wheel model for developing solutions to drug safety problems

them better ways to predict and prevent the ADRs they are most concerned about. This circular approach helps ensure that patient and clinician interests are addressed – an important determinant to ensuring uptake of the resulting research into clinical care.

3.11 Concluding Thoughts

Get the phenotype "right" for ADRs. This requires far more than meeting minimum ADR reporting requirements but a fundamental rethinking of the reason for pharmacovigilance in the first instance. Is it to record and report ADRs or find solutions to drug-induced harm? The latter has staying power for pharmacovigilance science – clinicians and institutions want solutions, most importantly, so do patients.

If dedicated pharmacovigilance professionals are employed to do the important work of properly phenotyping adverse drug reactions, we can find solutions to drug safety problems through new genomic technologies that can help us characterize patients based on risk and develop predictive models of drug harm. Armed with such genomic data, the mechanistic basis of these ADRs can be found, and new therapeutic approaches can be explored to minimize harm through drug development or drug repurposing.

The future of pharmacovigilance is bright as long as we meet the needs of the patients, clinicians, and institutions that we serve.

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Chapter 4
Some Other Ideas About the Future of Pharmacovigilance

Alfonso Carvajal, Teresa Falomir, and Carmelo Aguirre

It is perceived that, during this century, pharmacovigilance has evolved to a more complex discipline: new technological developments, a refinement in its methods, new tasks and, overall, new legislations have been the most remarkable landmarks. A big corpus of legislation has been implemented in the last few years, particularly those coming from the main regulatory agencies——the Food and Drug Administration and the European Medicines Agency. Particularly remarkable have been the 16 volumes of legislation released by the European Medicines Agency, intended to regulate these activities. While legislation tries to control activities, we do not know the exact amount of normative control that is necessary to improve these activities; in fact, we do not really know if a new legislation is able by itself to improve these activities. What is certain is that the workload in the pharmacovigilance centres has been considerably increased along these last years; a substantial part of this workload is devoted to paperwork.

On the other hand, agencies are claiming for independence and transparency. Independence is one of the most used words in the headquarters of big agencies. However, in addition to the official national pharmacovigilance systems, they are in parallel and sometimes interconnected, the corresponding systems set up by each pharmaceutical company. Through these systems, pharmaceutical companies collect safety information upon their products and are able to conduct pharmacoepidemiological studies. It is notoriously known that studies conducted by the industry systematically favour the industry itself.

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In order to improve pharmacovigilance activities for the coming years—regardless of other technological or methodological improvements—we suggest the following proposals:

1. Global regulation for a global market. For a global community which has access to learn through the Internet the new developments in medicine, it is nonsense a local or regional (i.e. European) regulation. For what matters to us, and as a general rule, it is not for the best that in a country or zone, a particular medicine is to be withdrawn and in other countries to remain on the market or just to insert different safety information, as it currently happens, in the summary of product characteristics. In addition, a global regulation might account for, though not necessarily, more independence from local powers and, overall, for more efficiency in terms of time and money.
2. To diminish bureaucracy. There is duplicity of legislation, bodies and resources; for instance, there exist national, European (EudraVigilance) and international (VigiBase) databases. There exists a general perception that in the digital era, there is an increase in bureaucracy. Since the possibility to store data is unlimited, more and more data are gathered, and, in accordance, more and more data are requested from the citizens. An intelligent and ethical sharing of data among administrations should be desirable.
3. A world unique body to control, and coordinate, drug safety (safety of the patients)—for instance, WHO-Uppsala Monitoring Centre. This point has in fact to do with the first one. However, it emphasizes the already happy existence of an international reference of authority in this field, that is, the WHO-UMC.
4. True independence. Pharmacovigilance activities are carried out by independent centres and independent investigators. As for studies, an independent study has been defined as that 'conducted—as far as possible—free from biases and commercial, financial and personal influences'. The best way to achieve that goal is for those studies to be conducted by a third party, an independent group: independent from the industry and independent from the government. No more studies are conducted by the industry itself.
5. Avoid complacency. Complacency is one of the sins mentioned by Inman to explain underreporting; accordingly, only safe drugs are allowed on the market. The existence of risk management and risk minimization plans has the risk themselves to favour complacency; in a way, these plans could be a reason to avoid stringent surveillance or deferral. On occasions, these plans are more focused on protecting medications than in protecting patients.
6. Prevention. From passive collection of ADRs—which is quite necessary to generate new signals—to a more proactive anticipation to prevent the already known ADRs to occur. It is obvious that the likelihood of an ADR occurrence increases as the number of medications in the treatments increase; similarly, most of the hospital admissions in elderly patients due to ADRs are tied to a handful of well-known medications. We all have the ethical imperative to avoid them. In this latter manner, pharmacovigilance crosses the border, becoming a specialized

clinical activity; there is room for this discipline to expand: it would go from the rear to the clinical ground, closer to the patients.

Our *momentum* in the world is that of autonomy; this word comes from the Greek *auto* (self) and *-nomos* (rule). Individuals and peoples are claiming for autonomy, a more direct involvement—a say—in all affairs that concern them. It is definitely the time of patients. As for pharmacovigilance, it has to move from its current headquarters to the street, from the regulators to the patients: it has to be conducted for the sake of the patients, for the sake of the persons. Our proposals are for these objectives and for this time.

Chapter 5
Best Safety Practices Now and in the Future

Brian Edwards

Since July 2012, much EU pharmacovigilance regulation has been published so an outsider might rationally conclude that it would be easy to define what 'best safety practices are' now. However, what constitutes the global 'best practice' and whether we have achieved a consensus depends on your point of view within the system both hierarchically and geographically. As of 2012, it seems the harm from medicines in the EU has serious public health implications as the European Medicines Agency (EMA) repeatedly stated the following to justify revision of the pharmacovigilance (PV) legislation [1]:

- 5 % of all hospital admissions are for adverse drug reactions (ADRs).
- 5 % of all hospital patients suffer an ADR.
- ADRs are the fifth most common cause of hospital death.
- An estimated 197,000 deaths occur each year in EU attributed to ADRs.
- EU societal cost of ADRs amounts to 79 billion euros per year.

It is uncertain, and maybe it is too early to judge, whether and how the pharmacovigilance EU legislation in 2012 will impact these figures although the EMA plans to perform an impact assessment.

The public health situation in the USA, however, shows continuing unacceptable levels of harm from medicines most notably opioids and warfarin [2–5]. For example, in February 2014, the US Office of the Inspector General reported that a third of patients were harmed by a treatment adverse event in the first 35 days of their stay in a skilled nursing facility, a third of which were related to medication [6]. Even product quality in the USA cannot be assured. The USA is recovering from a scandal whereby compounding pharmacies were producing and commercialising poor quality medicines which caused an outbreak of meningitis from contaminated

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methylprednisolone injected epidurally, sadly, often for reasons which were poorly evidenced based. The FDA has subsequently inspected many such pharmacies but has received pushback from about 12 compounders stating that they are not subject to FDA GMP requirements and instead are subject to oversight of their state pharmacy boards. In general, compounded drugs are exempt from GMP requirements if the products are for a specific patient with a prescription or are produced in limited quantities by a pharmacist. But this means variable quality standards for medicines for patients in the USA dependent on origin [7, 8]. How have patients themselves been performing? Studies have consistently shown that 20–30 % of medication prescriptions are never filled and that approximately 50 % of medications for chronic diseases are not taken as prescribed [9]. There is further evidence of global systematic dysfunction [10, 11].

The economic consequence of harm from medicines is considerable with estimated added costs to US payers of $2.2 billion from 2010 to 2014 linked to adverse events from anti-inflammatory drugs [12]. However, the extent of systematic dysfunction in post-marketing safety is aggravated by the year-on-year increase in the estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) which currently is around $2,558 million [13]. The steady rise in the year-on-year costs for developing a new medicine means that for some therapeutics areas, new medicines are no longer affordable.

So given these rather gloomy statistics and that no territory has had safety practices stable enough to evolve impact evaluations, can we honestly define what ‘best safety activities’ actually are?

5.1 What Is the Current State of Play About Best Safety Practices?

Given that ‘safety’ refers to how humans safely perform within the system, there is no consensus between the various stakeholders in medicines about what evidence to collect to determine whether a system is safe. As a result, not surprisingly, the global society is not in agreement how risk from medicines should be managed. There are fundamental unanswered questions such as:

Should we seek an absolute reduction of harm regardless of cost or a relative cost-effective and risk-based reduction?
What are the society’s expectations for safe human performance?
What level of harm is acceptable from medicines in general and from certain types in particular?

For example, Donaldson in his review of reported deaths in the NHS concluded that 3 % were attributed to medication [14]. Is such a reporting frequency acceptable or not? What level of benefit is acceptable?

Although the argument is used that healthcare systems vary, so benefit-risk of different medicines will vary too; overall, there is great concern that cost containment

may prevail over safety. This regulatory dysfunction is best illustrated by conflicting legislation in countries such as France and Italy where the off-label use of certain medicines is encouraged by governments because they are cheaper alternatives when compared to medicines which are authorised [15]. This is despite the evidence that off-label use in some circumstances increases the risk of harm [16]. In other countries even though there appears to be a licensing system, such as in India, weak enforcement has meant that many thousands of fixed-dose combination products have been marketed without evidence of benefit where companies have successfully gamed the system [17].

All of these are unanswered questions, and varied regulatory decision-making has arisen partially because there is no consensus on safety and as a consequence differing opinions about the public health responsibilities of regulators. In other safety critical areas of society such as chemicals and nuclear energy, society has internationally agreed to guiding safety principles [18]. This has not happened with medicines resulting in major disagreements across the world about what are acceptable benefits and risks and indeed what is acceptable product quality even for clinical trials [19–22]. This misunderstanding partly results from focusing solely on the pharmaceutical and pharmacological properties of the medicine itself as the main reason for harm from medicines.

Perhaps within certain groups of stakeholders, there is some consensus. For example, what does the industry want from safety? Currently, 'safety' is often equated with 'pharmacovigilance' regulations which have been derived from guidelines developed by ICH (now called the International Council on Harmonisation). There is no unifying wish list as the industry is so heterogeneous, and indeed there are parts of it, such as wholesalers and distributors, that receive less attention from regulatory enforcement than others (although Good Distribution Practice has been introduced in the EU, such good practice has not been globally agreed).

Point 21 of the Declaration of Helsinki states that 'Medical research involving human subjects must conform to generally accepted scientific principles' but what does 'generally accepted' mean and what are those 'principles'? The most ready interpretation would be the recommendations that arose from the CIOMS reports. Although some of these recommendations were adapted into ICH guidelines, some very sensible recommendations from CIOMS V and VI have not been widely adopted. A good example of what has not been adopted in the CIOMS recommendations is to use binary causality classification for SAEs in clinical trials because there is no evidence that more complicated classifications add any scientific value by improving case quality or medical evaluation.

The ICH guidelines have been implemented by regulators very differently in a de-harmonised way. This was observed over 15 years ago, but de-harmonisation has been allowed to drift and deteriorate [23, 24]. This means varying interpretation of what needs to be reported, differing definitions of everyday pharmacovigilance terms and no coherent agreement about what constitutes a good quality spontaneous case report let alone periodic report. However, what is widely unknown in the pharmaceutical sector is that there is a global body with a political mandate for regulating medicines: the World Health Organization. Article 2 of the WHO Constitution

mandates the WHO ‘to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products’. Unfortunately, the way this mandate has been translated into a global regulatory system so that the opinion of WHO is respected by all stakeholders has not been worked out. There has been no consensus about what ‘standards’ mean especially without evidence to show what is the best. Thus, without effective controls in the system or guiding principles and lack of industry support, de-harmonisation will worsen as more territories develop regulatory systems for pharmacovigilance. The consequences of de-harmonisation are not widely appreciated with its resulting increased costs, drain on resources and confusion without any net gain for determining the benefit-risk of products [25]. In the absence of evidence to support benefits from the difference in regulatory requirements, one can only assume such inefficiency, and waste has a detrimental impact on safety. Regrettably, what advantage there might be in having different regulatory requirements has been lost because there has been so little scientific evaluation to see whether there may have been public health benefits from these differences.

Despite the importance of ICH as the foundation for many regulations, the discrepancies in regulation between countries should not surprise us, as the prime purpose of ICH was not primarily for ‘safety’ but ‘to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines’. ICH ‘Safety Guidelines’ refers to the preclinical testing, not to safe use of medicines. Post-marketing safety was a spin-off and development activity primarily linked to new chemical entities and initial registration. From this derives the popular view that ‘safety’ equates with pharmacovigilance and detecting harm – or does it? There are likely to be varying views about this across stakeholders which has not been assessed.

Early PV was linked to the development of clinical pharmacology and based on principles of preparing a good adverse reaction case arising from the examination of an individual patient, knowledge of the pharmacology and toxicology of the medicines concerned and then blended with very simple epidemiological principles and an emphasis on public health and marketed products. Therefore, PV commenced with the main priority being the detection of serious and unexpected adverse reactions in individuals primarily through analysis of spontaneous reports. This is often called looking for a ‘needle in haystack’ giving the impression of a rather introverted act of preoccupation with rarities. This detracts from the predominant purpose of PV which should be to demonstrate the benefit/risk profile of a medicine that it remains appropriate and acceptable to all stakeholders, that patient susceptibilities and product peculiarities are identified and that actions are taken to maintain risk at an acceptable level. Much activity, in many companies, concerning PV is linked to establishing a system to show ‘unexpectedness’ or ‘nothing unexpected’ is happening and that the information that the company receives is as usual and that humans within the system are doing what is considered normal as described in standard operating procedures (SOPs). Thus, for many in the industry, PV is far removed

from its traditional clinical pharmacological origins. The main preoccupation in pharmacovigilance groups for much of the industry concerns processes whose main purpose is to reassure all stakeholders (patients, regulators, investors) that there is nothing to worry about. This is usually referred to as 'compliance', and indeed the regulatory emphasis is on compliance based on the assumption that if both industry and regulators comply, 'safety' is automatically guaranteed 100 % of the time. Both regulators and the industry have occasionally failed to comply dramatically [26].

Following these apparent compliance failures, the EU has had successive rounds of regulatory revisions trying to find an elusive 'perfect system'. Although compliance acts a surrogate for 'safety', for many regulatory outcomes the value for safety, as regards healthcare impact, remains unevaluated. This is not surprising in that the system is focussed on measuring 'harm' not safety.

Without guiding safety principles, how the system can confidently demonstrate such 'safety' is not a topic which has been debated. Scientific discussion and priorities have been distorted by bureaucratic regulations such as the overwhelming pressure to report as many 'expeditable cases' as possible by 15 days, concentrating on case numbers rather than quality. What little evidence there is evaluating public health benefit of the current approach is not reassuring given the confusion in the USA about serious adverse event (SAE) reporting and inconsistent adherence to 15-day reporting to the FDA [27, 28]. There is not even an agreement between ICH regulators about the best ways to handle the same dataset [29].

Although the EU may appear to have the most comprehensive PV system, the requirements to comply are now more complicated than ever. Even though they are linked to marketing authorisation status, they are not evidence based and are variably and arbitrarily interpreted by all concerned. Also, there is an incomplete capture of these decisions so that the system is slow to learn. Part of the reason for this arises from how legislators have applied the precautionary principle which acts as the basis for much other EU regulation being derived from Principle 15, 1992 Rio Declaration [30]. This states that 'where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing *cost-effective measures* to prevent environmental degradation'. Thus, based on the precautionary principle, regulations should ideally be proportionate, non-discriminatory, consistent and adaptive to scientific developments.

Unfortunately, PV regulations in the EU, unlike the USA, have been written without due regard for cost-effectiveness across the system and the burden placed on stakeholders. Since its inception, pharmacovigilance has naturally evolved into a multidisciplinary science, and yet, the importance of its effective implementation remains under-recognised by many in the society particularly as a public health and medical discipline. Even though many regulations have been written, how do we know that they have been implemented with adequate quality and that all relevant individuals are competent? PV is meant to be performed primarily for the benefit of patients. Although EMA and some regulatory agencies have been involving patient representatives in advisory committees, how involved are patients elsewhere in decision-making within the system, such as helping a company determine what a signal is and what is a risk that matters to patients?

The lack of attention to cost impact of new regulations, as required in the precautionary principle, results in under resourcing so not even regulators keep to timelines with, for example, late PSUR assessment reports and a 'signal' overload with a burgeoning agenda for the Pharmacovigilance Risk Assessment Committee (PRAC) which shows no sign of abating. The PV technology based on EudraVigilance is not fully operational leaving a state of 'inefficiency limbo'. Many risk management plans (without extra risk minimisation measures) have bloated to become a bureaucratic burden with little published evidence that healthcare systems act upon them and the patients' benefit. Off-label use is seen as a 'risk' by pharmaceutical regulators but a 'benefit' for patients and payers if the medicine has sufficient evidence of effectiveness. The disconnect of risk management as agreed with MAHs from healthcare is if anything getting worse as treatment pathways get more complicated so that it is naïve to believe that a single solution at the EU level will indeed be a solution. Even if there is a nationally recommended treatment regimen, this will be variably adopted depending on financial pressures on each hospital modifying their formulary policies. In the USA, the Officer of the Inspector General produced a damning report about the inefficient implementation of the Risk Evaluation and Mitigation Strategies (REMS) programme in 2013 [31]. Since then, the US FDA has made substantial organisational changes the effect of which remains to be seen. Artificial silos have, however, been created by separate regulatory systems between medicines, devices, cosmetics and borderline products as well as clinical safety. Not all relevant stakeholders and players responsible for safe medicines, such as healthcare professionals and patients, are covered by any single regulatory system, and many do not see PV regulations (and PV itself) as being of any relevance whatsoever to their daily lives.

Much regulatory focus is on new medicines many of which will have increased requirements compared to their predecessors potentially making it much harder to get a 'safer' medicine authorised unless the safety benefit is overwhelming. And yet patients suffer the most harm from established medicines (warfarin, insulins).

The increased requirements refer to 'risk management'. However, for many developed countries, broadly speaking, you may (or may not) have two risk management systems. The general impression is that healthcare primarily manages risk for older medicines (approved pre-1995) through normal clinical practice (which can be very variable across the world and nonsystematic as illustrated by the harm from warfarin), whereas the current regulatory system focuses on new medicines (although admittedly PRAC has taken action of older medicines). However, this is a very simplistic division, and how healthcare and regulatory risk management systems interact (or do not) is a big issue which is very variable between countries and within a country. It may also be very variable according to the medicines in question. Unfortunately, the risk management plans that are written are for regulatory purposes without end-user consultation. These plans are often unfocussed on those hazards which really matter, and they try and encompass much which would be routinely carried out anyway such as provision of educational materials to prescribers on how to use a new medicine. Imprecise terms such as 'cardiac disorder' and 'thrombosis' are medically meaningless. Another example is the new biological

immunomodulators, whereby there is a 'cut and paste' approach to risks such as off-label use, infections and malignancy without more precise definitions and further differentiation over the lifecycle of these products to tease out differential risks. In addition, all three ICH regions have implemented ICH risk management guidelines differently making it impossible to judge 'who is right' [32]. This means that in these plans, risks are often vague, poorly defined, the actual 'hazard' is not mentioned, relevance for patients is uncertain and there is a muddle between 'risks' and 'signals'. The concept of a 'safety accident' (i.e. an episode of serious preventable patient harm which is an agreed 'never event') is not mentioned. Thus, we have a fragmented system for managing risk of medicines with no consensus or guiding principles about how all countries should manage the risk of medicines.

Although PV inspections were a major driver for improvement when they started, they can only drive change so far. Inspectors are constrained by territorial regulations as to what they can say. Inspections now risk becoming a predictable exercise focusing on checking only whether processes are in place rather than whether the processes produce an end product of adequate quality. Inspectors chase every last adverse clinical event even if it is not a possible adverse effect of a medicine and is only information. The striking difference between EU and US FDA PV inspections that have different areas of emphasis and different approaches only adds to the muddle in a global organisation. Such inspections are no substitute for independent investigation of the safety system involved, which has never occurred [33, 34].

We need to acknowledge that there are many within the system striving hard to improve it. For example, there have been important initiatives such as PROTECT and UMBRA to define and describe benefit-risk methodologies with interesting recommendations. Are we to assume ICH intends to implement these ideas within Sects. 2.5.1 and 2.5.6 of ICH M4E(R2) [35]? We will only know after a consultation process is over. Presumably as has occurred with much other pharmaceutical training, the free market will be relied upon to deliver. There have been no discussions publicised about how benefit-risk decision-making will be systematically implemented.

As part of the EMA work programme 2014, a commitment has been announced to: 'Develop a programme for studying public health impact including monitoring the effectiveness of targeted risk minimisation measures. Design methodologies for drug utilisation studies, to estimate potential public health impact of adverse drug reactions' [36]. PRAC itself has concluded that 'Currently, there are no broadly accepted methods for measuring how pharmacovigilance activities are translated into health outcomes' [37]. This partly arises for not having adequate healthcare metrics for assessing safety [38–40]. The only way to be sure of the impact of new well-intended regulations is to document their effects by gathering reliable empirical evidence that can inform future research. This does not happen at present, and PRAC agrees that 'further method identification and development for impact studies will be needed'.

In other sectors, competency frameworks aligned to system roles and responsibilities are critical to assure safety [41]. Such a competency framework does not exist for pharmaceuticals. Although some companies may implement programmes,

there is no system-wide approach to training. So anyone can be a 'consultant' in PV and anybody is. There are no agreed competencies for PV auditors and inspectors, so they have variable understanding of the scientific purpose of PV. This absence of an agreed approach to who is qualified in PV and who is not is most apparent during 'drug safety crises' when there are multiple 'expert' opinions but rarely that of a 'PV expert' (whoever they are!). Similarly, although there are recommendations, there is no agreed universal adoption of a competency framework for clinical research or agreed training programme (it is the responsibility of the sponsor to ensure all in the team area trained) [42]. This means anybody can do 'clinical research' and anybody does. Although WHO-ISoP has published a comprehensive PV curriculum, there is no mechanism to make this more than 'advisory' [43]. Even competencies and a curriculum for the important role of the qualified person for pharmacovigilance (QPPV) have not been proposed. The result is variable implementation, poor understanding of the role outside the EU and therefore the risk that the QPPV role is not taken seriously by the management of any company or regulators, globally.

5.2 So What Should Be the Best Safety Practices for the Future?

Progress towards agreeing about the best safety practice is hindered by the lack of a shared mental state between all global stakeholder system about what safety means and to what the primary public health aims of PV should be. Of course the pharmacological features of a medicine are important, but ultimately safety is dependent on human performance embracing all the evidence without a blinkered view. This is not just pharmaceutical and pharmacological evidence but also evidence from organisational sciences about how humans apply and act upon that evidence especially when faced with uncertainty, ambiguity and ignorance. In addition, society ('the public') wants reassurance that there is nothing to worry about so that we must be able to demonstrate transparently that the entire system from manufacturing site to bedside is performing as expected and validated safety metrics have been communicated to the public. The absence of agreed metrics of safety means we cannot reassure and that the continuing suspicion and mistrust in the system is understandable and likely to continue. Firstly, we have to deal with the systematic state of denial about the need for a global system to ensure safe use of medicines and stop operating under an illusion that such a system exists, that regulations are the only solution and debate is discouraged. We need to accept that the level of mistrust in the current system is justified given the level of harm. Given the failure to apply organisational science systematically, there is a patchy and inconsistent safety culture, aggravating continuing mistrust and suspicion. Transparency is currently fixated on data release although poor transparency is as much due to poor system design and safety culture. We should be concerned that continuing to ignore these realities means we will be operating in a state of wilful ignorance which will only continue to erode trust [44, 45].

No system change is possible globally without leadership and assertive global political will. This was attempted in 1999 following the Institute of Medicine report, To Err is Human, but it ended up with stakeholders finding solutions in their own way not systematically [46]. Perhaps a good place to start would be products for which the system is particularly unfit for purpose (such as advanced therapies) or medicines of great public health importance which are struggling in the system (such as antibiotics for MRSA or multiresistant TB). The public health mandate of the WHO towards safety of medicines now needs to be systematised applying what we know about organisational science.

The aims of the 2012 EU pharmacovigilance legislation are admirable although they have not been agreed system-wide in the EU, let alone globally. However, they are a good starting point for seeking consensus amongst all stakeholders by developing guiding safety principles:

- Clear roles and responsibilities
- Robust and rapid EU decision-making
- Engage patients and healthcare professionals
- Science based – integrate benefit and risk
- Risk based/proportionate
- Increased proactivity/planning
- Reduced duplication/redundancy
- Increase transparency and provide better information on medicines

The main area for hope is the recognition that effective systems require quality management which is a concept well-established under the International Organization for Standardization (ISO). In effect, this refers to recognising that a safe process must also be an effective process which is fit for purpose. Although quality management is recognised in GMP, it is not yet globally accepted that this should be a routine for PV (and that this applies across the system to regulatory agencies and healthcare and not just the industry). Many other safety conscious sectors in the society have more creatively developed the ISO principles applying evidence from organisational science. Although this has occurred patchily in the pharmaceutical sector, systematically this has not occurred. It is still poorly recognised within the industry that the safety of a medicine is as much dependent on what controls exist within the system to ensure safe human performance as the pharmacological properties itself. Safety engineering about how systems science can be used to design a safely functioning system has yet to be practically applied to PV systems [47, 48]. Given that human factors are typically responsible for the majority of safety system failures, our current PV systems lag way behind in applying principles of human factors engineering. Error management is poorly developed; there are no agreed safety metrics.

Increased attention is being placed on competency-based education as a means for optimising the preparation of health professionals [41, 49]. Thus, as a matter of urgency, the training and education of PV (and indeed all activities within the system which impact patients) need to integrate organisational science into the current pharmacological and pharmaceutical content because this is ‘how you do it’

[50–53]. These are not ‘soft skills’; these are *the* ‘skills’ to make you competent to perform safely. This includes principles of a safety culture based on reporting, learning and just cultures as described by James Reason [54]. In effect, organisational science will teach us how to work in a complex system putting the human at the forefront of system design, PV training and education. In particular, we must embrace all relevant scientific evidence about operating in complex systems including that from organisational science that can help us better implement decision-making, situational awareness, leadership, communication and error management and manage personalities and behaviour. The punitive approach whenever an error occurs (the cycle of shame, blame and train), instilling a terror of deviation, needs to stop with processes developed on principles of fairness, justice, reporting and learning. We need to improve our systems, processes and feedback mechanisms, in essence, build in redundancies and forcing functions that prevent humans from making unsafe choices. We must be able to hold each other accountable for safe choices, by creating a culture of safety which encourages speaking up, promotes transparent and safe decision-making, sanctions reckless behaviours and rewards safe choices and actions.

One debilitating feature affecting how the system manages safety is replication of data. This encompasses replication of reported cases in the variety of safety databases, duplication of data that conflicts in the clinical database and the safety database and replication of information held by co-development partners, CROs or licensees [55]. We must approach data management holistically. The distinction between clinical trial data and safety data is artificial, and far too many processes are designed to resolve data conflict that is wholly unnecessary. Advances in technology, such as the real-time monitoring of electronic data capture and use of mobile technology, have provided both solutions and new challenges that now have to be resolved.

Before we start with a modernised system approach to safety of medicines, we need to vigorously promote the definition of PV building on the current inadequate definition. PV is a sociopolitical activity which, although founded in pharmacological and pharmaceutical science, now involves all who have vested interest in safe use of medicines. Not only does PV concern collecting information about suspected ADRs, but it also concerns managing the unexpected within the system and instilling vigilance as a process requirement within a quality system. PV is a multidisciplinary discipline, blending organisational, communication, pharmacological and pharmaceutical sciences. Thus, social scientists need to be more involved especially when it comes to ‘communication’. Pharmacovigilance along with other organisational factors is inbuilt into the system to support and monitor safety which itself refers to how the system controls human performance through safety constraints. Vigilance assesses the effectiveness of such constraints. The recent explosion of interest of patient centricity is an opportunity to involve patients in all levels of the system. They must play a central part in driving change in areas such as in signal detection by helping determine what is and is not serious and relevant for them, assessing benefit-risk and advising on practical solutions to enhance proper use of medicines. Patient reporting is more than just encouraging reporting of suspected

ADRs, but also it is about encouraging them and their families to speak up and keep asking questions until they are satisfied with how the system is responding. Although there has been progress, it has not been systematic or uniform and certainly has not moved fast enough. Therefore, I have prepared the following working definition of PV which helps define the link to safety as described in guiding principles:

Pharmacovigilance (PV) is defined as a multidisciplinary science consisting of systematic activities and processes relating to the detection, assessment, understanding and prevention of adverse effects or any other problem related to medical healthcare products and their handling throughout their lifecycle, thus mitigating risk and maximising benefits for patients. These activities include those required to monitor and assess a quality system embedded in a just and fair culture that facilitates reporting, communication and organisational learning to demonstrate that the system is performing according to guiding safety principles agreed by all stakeholders.

This definition needs to be kept under review with guiding principles created to implement an effective system as the basis for ensuring safe use of medicines. Ideally, an impartial society such as ISoP could act as the guardian of such guiding principles. It is time for ISoP to rise to this challenge.

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Chapter 6
Is There a Benefit from the Medical Literature Monitoring Service of the EMA?

Willibert Franzen

Besides others, literature monitoring is one of the key pharmacovigilance activities performed by the respective MAHs for their products or related product classes to have an early understanding of the newest scientific knowledge or about experiences in the use of their compounds in a real-life setting. For a globally acting organisation, these sources bear several challenges starting with the different languages but also the interpretation of the therapeutic environment where the information come from. Further – with regard to legal obligations – the next challenge is to provide timely information and updates to all respective players in pharmacovigilance like competent authorities or ethics boards. This led global pharmaceutical companies to build a concise and highly efficient system to ensure all such information is appropriately identified, collected, assessed and reported.

In 2010, the European Commission started their review of the pharmacovigilance legislation as it was predefined when initially the Directive 2001/83/EC came into force. The review targeted the goal to increase the efficiency of the pharmacovigilance system in the EU but also to reduce bureaucratic burden. Explicitly, it is said in the justification for the consolidation of Regulation (EC) No 726/2004 that the medical literature monitoring by the EMA will "enhance the efficiency of reporting and will provide a simplification for the pharmaceutical industry".

Before looking into the implementation of the monitoring process itself, it appears that the initial intention of the review and its outcome has lost connection with the existing regulations because today, we, as concerned members of the pharmacovigilance system, have to consider a legal framework which currently consists of the basic requirements set out in the EU legislation (Regulation (EC) No 726/2004, consolidated version June 2013), the GVP Module VI, the EMA guide for medical literature monitoring EMA/161530/2014, the user manual for the literature monitoring service EMA/274835/2015 (Rev. 2), the reference for databases

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which are subject to this project EMA/141813/2015, the explanatory guidance EMA/119265/2015 for the inclusion/exclusion criteria of results from the literature research for adding them into the database, the guide EMA/262834/2015 for the duplicate management and the EMA/403865/2015 guide to define the search strategies for each single compound on the list for the monitoring service.

Before the new legislation, there was a dedicated Chap. 4.3.2 in Volume 9A concerning reports published in the worldwide literature.

As of 1 September 2015, the EMA has rolled out the production version of the literature monitoring tool. The first set of substances included in the review was published in July – covering a number of 300 defined chemical substances and about 100 herbal medicines.

When checking the substances included in the search strategy, it was surprising to see compounds like ascorbic acid, calcium carbonate, folic acid, glycerol, oxygen or zinc oxide. It is an irritating situation to see these substances in the regular review – for example, in the PubMed database for 2015, there is no single hit for calcium carbonate and a reported adverse event.

Also, the components listed in the section of the herbal substances have one special characteristic – a high number of them belong to the group of homoeopathic medicines where it seems difficult to really search or identify adverse reactions coming from the basic concept of homoeopathy.

Anyway, since 1 of September 2015, the EMA has now started the service and is uploading the retrieval results to the EudraVigilance website. But the information received there as information for the concerned MAH does not, in the first step, include the entire case description as presented in the respective literature article. There is only limited information available providing some basic facts about its source and some key elements of the reported adverse event and the concerned patient. Only after this first upload the processing of the case by the EMA (or the contracted provider) starts in the background, and it is not visible when the complete information is available in EudraVigilance.

What does this mean to the concerned MAH – who has to fulfil reporting obligations around the globe?

Considering the timelines to be kept, all MAHs face the burden of a time window between 5 and 7 calendar days for processing and assessing a serious case, to leave enough time to prepare for reporting – which is today still a mixture between electronic reporting and paperwork. For an MAH to download and use the literature monitoring provided from the EMA, it cannot wait for the final case arriving in EudraVigilance – as the time it takes is not predictable. So in the end, these MAHs keep their routine literature searches running and have in addition to implement further checks for the content of the reports generated by EMA in comparison to the cases they already forwarded.

Another issue is that the information from the literature report may already have been received by the MAH as part of an ICSR. The MAHs have to follow up each ICSR with EMA and the reporter to harmonise the information received – and to

come to one common version of the assessment of the literature case with the EMA – because otherwise there will be conflicting information on the same case between databases like the FDA or the MHLW and the EMA EudraVigilance database. Up to now there is no process or concept on how to get this common assessment agreed upon. There is a definitive need to have this in place as it may be easily explained by the following examples:

- A number of reported terms. Each company has a strategy on how to identify relevant information from a report. Often due to MAH coding conventions, additional ADR terms need to be added. This will not happen when EMA is processing the case.
- The same is relevant for coding of the term itself. Although MedDRA is the common dictionary to be used, different coding conventions exist between the companies and the EMA – and the information will end up in different sections of cumulative reports or signal detection strategies.
- There might be conflicting information between the ICSR and the literature case. Usually, the MAH is obliged to follow up on received case reports to increase the data quality and to ensure an accurate understanding of the situation. In the Q&A paper of the EMA on how ICSRs and literature cases are linked and handled, it is not laid down on how to proceed when follow-up information gives evidence that the ADR was related to a different condition, which was not understood at the time when the literature report was published.

Currently, the MAH has to further understand that for all literature reports generated from sources outside the EU, it has to follow additional reporting requirements to local competent authorities in the EU like in Spain, Hungary or Germany. This will persist as an additional workload until the final validation of the EudraVigilance database has been successfully achieved. As this reporting is usually controlled by programmed workflows, reasonable financial efforts to adapt and customise the applications in use as well as the required resources for testing, validation etc. are borne by the MAHs. The same will occur vice versa when the EudraVigilance database is fully established.

Another aspect with regard to the literature search strategy of the EMA is that EMA looks only for defined substances and identifiable valid patients and sources. All those cases, where it was reported about the use of a class of products like antibiotics or anti-androgens or where the article refers to “a group of patients”, will again fall back in the responsibility of the MAH. It seems to be the attitude of the EMA that these cases are of no or less relevance – although some of them are placed into a workflow for validation – but as practice shows, this kind of information will always stay ambiguous, and the MAH is responsible for its interpretation and then includes it in its strategies for reporting and assessment. Yet again, the understanding of the EMA in this situation is not the same as the expectation of other authorities which have to be served by the responsible MAH.

6.1 Conclusion

At this stage, I would like to come back to the initial thoughts about the EMA literature monitoring service and the targeted vision as to what this tool should be able to achieve – "enhance the efficiency of reporting and provide a simplification for the pharmaceutical industry".

It is not easy to detect the enhancements created by this initiative. For single companies, there might be a simplification of work, but looking into the list of products like the chemical entities concerned – even if they are marketed by generic manufactures – most of them have relations and obligations outside the EU and need therefore to follow their established processes.

So, yes, there is an effect – in reduction of duplicate reports received at the EudraVigilance database – but does this justify the current system? Wasn't there an easier and more efficient method available to keep control of these duplicates at times of cloud computing and the dream of big data, especially where all these case have one common attribute – the source of the article.

And another question needs to be raised: Is it adequate that the MAHs are paying fees to maintain this system? The EU parliament should also have a look into this – and they should investigate what was the real benefit to the pharmaceutical industry after a phase of 1 year of service.

While in the past, the legislative bodies of the EU defined requirements for MAHs to report information to the respective authorities – which initially created the problem of multiple duplicates in the EudraVigilance database with regard to literature reporting – a clearer definition of conditions and responsibilities for reporting and a harmonisation process on international level, like ICH to align strategies, would be much more effective.

At the time being, we see the bureaucratic burden increasing in a lot of different areas – at a time when the EU commission has a dedicated office for the reduction of bureaucracy. In order to follow legal requirements, the industry has to provide the resources to cope with these requirements. Then they find themselves in discussions about the increased costs of their goods or – in the case of pharmaceutical products – in the discussion of the cost burden put on health systems.

With regard to the literature monitoring process and requirements, why can't we find a standardisation at a global level under the lead of the ICH – as it has been done successfully in other fields like GCP or risk assessment?

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Chapter 7
The Unified Drug Safety-Clinical Database

Giovanni Furlan and Barry Burnstead

7.1 Main Sources of Individual Case Safety Reports

Effective pharmacovigilance requires ease of access to all sources of pertinent safety data. For drugs under development or recently launched, the clinical trial database represents a vital source of safety information. However, the responsibility for the clinical safety database typically lies outside of the control of the safety department. Similarly, for a recently launched drug, noninterventional prospective studies are another source of important safety data, and also the data regarding these studies typically lies outside of the safety department. Access to clinical trial and observational safety data varies between organisations, but it is evident that direct and open access for pharmacovigilance is atypical despite this data being essential for drug safety to continuously assess the safety profile of a drug.

Safety operations focus on individual case safety reports originating from post-marketing, clinical trials, noninterventional prospective studies and organised data collection systems in general (i.e. including patient support or market research programmes). The ratio of case reports originating from these data sets will vary widely depending on the life-cycle stage of the product, on how innovative it is and on its safety profile. In fact, if a product has a safety concern, it is more likely that observational studies (both retrospective and prospective) will be conducted to better characterise the risk. The comprehensive data repository for all trial-related data is the clinical database, whereas for observational prospective studies, the database might be the same as for clinical trials, but more often it is a separate one. However, both clinical trial and observational prospective studies not only share

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similar methodologies for collecting data but they also have comparable (even if not identical) individual case safety report reporting requirements. Traditionally study data is collected on paper case record forms and entered in the study database. For clinical trials, serious adverse event information is also entered into the drug safety database, whilst for observational studies, both serious and non-serious adverse reactions (ADRs) may need to be entered in both databases, resulting in duplicate records. Therefore, reconciliation of study records is considered a vital activity to ensure consistency in all forms of regulatory reporting. This activity has been accepted as an expensive necessity, and the risk of inconsistent reporting must be managed.

7.2 Reporting from Different Databases

Traditionally, clinical operations and drug safety departments have independently elected to collect somewhat different sets of safety data from studies. This has resulted in duplicate processing being the norm and contrasting databases have evolved. Typically, duplicate processing has been recognised and addressed for clinical trials [2], but not for observational studies. Serious adverse events occurring in clinical trials and adverse reactions from noninterventional organised data collection systems of any programme are processed in the safety database, which is focused on ICH E2B [3], the standard for individual case safety reports, on ICH E2F [4] and on ICH E2C [5], that include the standards for the preparation of summary tabulations. ICH E2C requires that summary tabulations of serious adverse events from clinical trials and serious adverse reactions from noninterventional studies are included in the Periodic Benefit-Risk Evaluation Report. Current regulations require expedited submission of serious adverse reactions originating from clinical trials in XML format, whereas for prospective interventional studies, not only serious adverse reactions [1] need to be submitted but also non-serious ones. However, the information on those same events is presented in study reports and will be sourced from the study database which conforms to different standards than the drug safety database. In addition, safety data from clinical trials often lie in a separate database from observational study safety data, and the data has different standards and structures.

Independent evolution has perhaps been misleading because each database has been designed and updated to meet different requirements, which are complex and stringent for clinical trials and pharmacovigilance and less demanding for observational studies. However, the need to submit good quality safety data originating from observational studies has been recognised [20], and initiatives such as those from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) are raising the data quality expectations in observational studies. Despite the standards for drug safety, clinical and observational studies being different, in certain cases regulations require access to multiple databases to produce aggregate reports such as for Developmental Safety Update Reports (DSURs), prepared according to ICH E2F standards [4]. The drug safety department typically has the

responsibility for the preparation of this document, but the serious adverse events stored in the drug safety database are not the only type of adverse events that a drug safety department requires to prepare a DSUR. The list of subjects who dropped out of a study due to an adverse event spans both the serious and non-serious adverse events, and safety findings can originate from adverse events of both categories. Consequently, this data needs to be retrieved from the clinical database. Furthermore, ICH E2F requires a focus on signs and symptoms of significant toxicities such as QT interval prolongation, hepatotoxicity, hypersensitivity and immunogenicity. If only the safety database is relied upon to perform assessments of these adverse events, the first signs of toxicity might be overlooked. Whereas, the non-serious adverse events or laboratory data would highlight any safety issue not yet detectable in the drug safety database alone. In addition, the DSUR requires a discussion of safety findings from noninterventional studies, and these safety findings can originate both from adverse reactions (which should be included in the drug safety database) and from adverse events, typically not included in the safety database.

In fact signal detection and evaluation, one of the most important drug safety activities, requires access to safety data residing in all databases. Whilst signal detection is typically performed on spontaneous data (even if signals can originate from clinical trials and observational studies), signal assessment [6] requires not only the analysis of the serious adverse events from clinical trials and of the adverse reactions from observational studies (which are normally in the drug safety database) but also of non-serious adverse events and reactions from clinical trials and adverse events from observational studies, which can be found in the clinical study databases. Consequently, a drug safety department needs to be fully aware of the content of the relevant study database and, more in general, of the adverse events originating from any organised data collection system. However, their partial overlap with the drug safety database can generate confusion since serious adverse events from clinical trials are contained in both the clinical trial and safety databases. Similarly, adverse reactions from observational studies are also contained in both the study and in the safety database, thus generating confusion. One must also remain aware that overlapping duplicate data have been subject to quite different validation exercises.

7.3 Inefficiencies and Regulatory Risks of Having Multiple Databases

Today, any critical assessment of the drug safety and clinical systems would question the value of duplicate processing of safety information. It is not only data processing that is performed twice but also medical coding, dictionary management, maintenance of code lists and setting-up, validating and maintaining separate databases. Essentially, the same data is validated twice, and, at the end of all this, the duplicate records need to be reconciled. If contradictory information permeates the two systems, the consequences can be inconsistencies in formal reports that could result in major or critical non-compliance.

One of the greatest risks of having separate pharmacovigilance and study databases probably lies in the obligation that pharmaceutical companies have to perform adverse event causality assessment. In fact, a Suspected Unexpected Serious Adverse Reaction (SUSAR) originating from a clinical trial needs to be expeditely reported to an authority if either the company or the investigator [7, 8] (depending upon local regulations) deems it related to the investigational medicinal product. For adverse reactions from observational studies (and for organised data collection systems in general), not only serious adverse reactions need to be submitted to regulatory authorities but also non-serious adverse events assessed as related to the investigational medicinal product by either the investigator or by the company [1]. If the not-related adverse events are only transmitted to the clinical department (as typically happens), the risk is that causality assessment will not be performed in time to permit the submission of a case within the regulatory timeframe (should a case not previously assessed as related by the investigator or be assessed as related by the company) or that it will be performed by someone who is not aware of all the risks of the investigational medicinal product and of their characteristics since this expertise typically lies within the drug safety department. Missed or delayed causality assessments can result in negative inspection findings [9], whilst contradictory information in different databases and systematic or gross mistakes in adverse event causality assessment can cause loss of confidence in data quality and ultimately precipitate an inspection. Hence, ongoing reconciliation between the study and drug safety databases becomes a necessary burden.

The analysis and assessment of the drug safety profile requires access to both the safety and clinical databases, but this is complicated by the use of different medical coding dictionaries and database standards. Even when the same dictionary is used, each operation might be using a quite different version at any point in time. MedDRA [10] usage is an example of differing dictionary version usage. This situation is manageable, but no excuse exists for different internal code lists being applied to common data items. This duplication carries an inherent operational cost and impedes rapid response by the pharmaceutical industry to regulatory issues. Such inefficiencies are not welcomed by an industry which is experiencing resource constraints characterised by reduced profit margins and decreasing R&D productivity despite increasing costs. The luxury of independent systems will ultimately be challenged [11].

7.4 Unifying Data Acquisition

One of the key differences in data processing between clinical trials as compared to adverse event reporting to drug safety lies in data acquisition. Technological progress [12] greatly increased the speed with which clinical trial data is collected and has introduced instantaneous data validation or logic checks that can ensure this data is of higher quality. Electronic data capture (EDC) [13] and electronic patient diaries (eDiaries) are the most used collection tools employed nowadays for clinical trial data acquisition, whilst other prospective organised data collection systems more frequently rely upon

paper reporting. EDC is a much more efficient way for collecting data and relies upon the Internet to reach all clinical trial sites. Its success has depended upon limiting the requirements at each investigator site by avoiding adding additional hardware at the investigator's site to support software. Only minor applications are installed locally on existing site PCs since the core functionality resides on the central server. An array of case report forms are presented as electronic forms allowing data to be processed without recording results on paper forms. In addition to data processing, EDC provides a two-way communication tool between sponsor and site that is fully traceable.

EDC significantly contributes to make study safety operations more efficient, but drug safety might have concerns over serious adverse reaction reporting timeframes. In the majority of EDC studies, either the clinical data management operation or the study monitor is the first to be aware of an adverse event, whilst the responsibility for submitting SUSARs to competent authorities and ethic committees typically lies within drug safety. If the communication between the clinical and drug safety department is not seamless, there is the real risk of non-compliance due to delayed submission caused by the loss of precious time. This might occur as the regulatory clock starts when the first sponsor representative, typically an employee in the clinical department, becomes aware of a SUSAR whilst those in drug safety might be blissfully unaware. To overcome this potential issue, automated email alerts are employed to notify drug safety of a new adverse event. This solution could also overcome any similar issues related to regulatory reporting of adverse reactions from observational studies.

Another concern that still prohibits organisations from implementing EDC for studies other than clinical trials is the difference in the quantity and quality of information available for adverse events originating from clinical trials as compared to those originating from spontaneous reports, observational studies or patient support programmes. However, it should be noted that adverse reactions qualifying for submission to regulatory authorities need to comply with the same E2B standards (that include the minimum needed information for an individual case safety report) regardless of their source. Furthermore, to comply with the obligation to perform a causality assessment, an additional minimum set of information (such as patient's concomitant conditions or concomitant medications) needs to be collected. Therefore, the only difference between the collection of safety data from clinical trials and other organised data collection systems lies in the number of fields that the investigator needs to complete. This can be easily accommodated by customising the EDC or eDiary user interface.

Despite EDC being more efficient, most safety operations retain their separate processing procedures based on paper adverse event report forms that are faxed/emailed in. In contrast, the safety organisations that have embraced the new EDC technology have removed their dependency on faxing or email by consolidating data acquisition into one process. They receive all information from clinical trials via EDC by creating SAE screens, including fields to accommodate narratives. This reduces the burden on the investigator to comply with two procedures and eliminates data conflict. Furthermore, SAE data is subject to programmed data quality checks, thereby delivering better quality information to the safety database than previously. The amalgamation of each data acquisition process into one location addresses the source of data inconsistencies and eliminates reconciliation. This can

be referred to as single sourcing [14], and it could also be applied to observational studies. For these types of studies, the benefits of unifying data acquisition would be comparable to those for clinical trials since the risk of drug safety not receiving adverse reactions in time for regulatory submission would cease to exist. Furthermore, since it would be easier for drug safety to make a causality assessment for all adverse events (and it would be more likely that causality is assessed by a drug safety person who knows the safety profile of the drug in depth instead of being assessed by a nonspecialised person within the clinical department), the risk of gross mistakes in performing this exercise would be greatly mitigated.

Once EDC has been implemented, separate databases can be retained to meet independent reporting requirements even if the databases have information in common. However, there is no reason for which there cannot be a single aggregate database jointly shared by the clinical and drug safety departments. In this scenario, different end users could have access to predefined data sets, the ones they need for their tasks. For example, drug safety would have access to the data sets pertaining to all adverse events and to summary reports on laboratory and clinical data, but not to data sets pertaining to the efficacy of each single patient. In this way users would feel they are looking at "their database" despite the data not being permanently stored in an ad hoc format, but remaining in the unified database. It is evident that merging data acquisition is the first step towards combining the two databases.

7.5 Unification of Clinical and Drug Safety Standard Interface

The clinical and safety databases have evolved separately, and this has led to contrastingly different standards. The Clinical Data Interchange Standards Consortium (CDISC) is a non-profit organisation that defines the data standards for clinical trials and addresses the requirements for data submission to the FDA as part of a new drug application which includes electronic submission data tabulations and analysis data sets. The corresponding standards are defined in two models – Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) [15]. The SDTM data is presented as SAS or XML files, whilst the ADaM data sets are provided for the FDA statisticians to either repeat or perform further statistical analyses. They are presented as statistical analysis software (SAS) data sets and are accompanied by case report tabulations that in the electronic format are supplied as define XML files [16]. These standards have become the Centre for Drug Evaluation and Research (CDER) and Centre for Biologics Evaluation and Research (CBER) preferred format for data submission.

However, the focus is on the single-source capture of safety data which relates specifically to the Clinical Data Acquisition Standards Harmonisation (CDASH) [17] (that is applied to all adverse events within a clinical database) and on ICH E2B [3], the standard for electronic submission of adverse reaction information to regulatory authorities. These are the two standards, previously mentioned, that have been separately developed for the clinical trial and drug safety databases. The CDISC CDASH-E2B project team has mapped these two standards [2]. The analysis of the

differences between CDASH and E2B (version R2 [18]) has shown that they are purely a matter of convention and are not driven by clinical research and drug safety having different scientific requirements. For example, new CDASH domains have been proposed such as "death" and "parental information" solely for SAE case reporting since these fields are required by E2B but not by CDASH. CDASH employs lettering for individual labels which intuitively describe the data contained within (e.g. AESDTH refers to a serious adverse event resulting in death). In contrast, E2B labelling is alphanumeric with no relationship to the data type: CDASH field AESDTH is labelled as A.1.5.2 according to E2B (R2). Another difference between the two standards is that CDASH does not embrace context information to the extent that E2B does. However EDC has the advantage that dates of reporting and updating event information are extracted from the EDC system as each entry has a date-time stamp. E2B instead requires the individual case safety report first awareness date to be entered by a company representative. It has to be recognised that E2B standard [3] is changing and has more detailed requirements than before. Therefore, the mapping exercise with CDASH needs to be redone. A further step could be the unification of the CDASH/E2B standard. This unified standard would not only make it easier to develop the unified database interface, but would avoid maintaining two different standards and to redo the mapping every time one of these standards changes. Unluckily, no work for unifying the CDASH/E2B standard has yet been done.

Even without going so far as developing a unified CDASH/E2B standard, the mapping of these two data conventions is the foundation for capturing adverse event information for both clinical and drug safety needs, and since it resolves the discrepancies between the clinical and drug safety standards, it makes the use of EDC more attractive for safety operations. The mapping can be used as a basis for software vendors to develop functionalities that can capture data according to a standard that meets the needs of clinical and drug safety. It starts with creating fields large enough to accommodate case narratives and introducing alerts for SAEs/ADRs and would extend to include SAE/ADR capture in its workflow. Both SAEs and ADRs are being mentioned since there is no reason why the benefits of single-source data capture cannot be extended to observational studies. The only difference between capturing the data for an observational study as compared to a clinical trial would be that for an observational study, there would normally be less detailed information, and therefore the interface fields that need to be used and completed for an observational study would need to be defined in advance, prior to beginning the study.

Thanks to SAE/ADR capture, the workload of case pharmacovigilance processing teams would decrease since data entry for clinical trial and noninterventional study individual case reports would no longer be necessary. Benefits would also include aggregate reports such as Periodic Benefit-Risk Evaluation Reports (PBRERs), Risk Management Plans [19] (RMPs) and DSURs that require spontaneous post-marketing, clinical trial and noninterventional data for their preparation. Streamlining the data management frees up key resources to concentrate on the only scope of safety operations: protecting patient safety. The ultimate aim for clinical and drug safety departments is to collect and analyse safety data efficiently in order to understand the safety profile of the drug, detect early signals and minimise risks. The unified safety database would free up resources to achieve this aim.

7.6 The Single Safety Data Repository

Current efforts to develop common clinical and drug safety standards are aimed at achieving common data collection procedures and assisting software vendors to develop a unified process. The unification of the process could embrace not only clinical trial and spontaneous safety data but also noninterventional organised data collection systems. The objective is to streamline safety data processing and lay the foundation for merging all adverse event information into a single repository. Drug safety has the opportunity to embrace existing technology solutions to maximise efficiency and effectiveness. Common data acquisition technology that has emerged in the clinical trial arena can ultimately lead to the merger of all data into a single storage environment and thereby achieve cost reductions whilst streamlining the business process. Once sponsors have successfully merged the acquisition functions of the clinical and drug safety operations, then the single database concept could be the natural progression. The idea is not only to have a single interface for database interface for clinical and drug safety departments but also to have one single repository from which all the needed single and aggregate reports can be extracted for the needs of both the drug safety and the clinical department.

Single sourcing and unified repository for all safety data require the rethinking of the workflow (see Fig. 7.1). For drug safety departments, the roles assigned for case processing would only need some refinement: for example, there might be the need to dedicate additional resources to causality assessment within case triage, especially for adverse events originating from observational studies (which today are one of the areas most at risk of non-compliance and inspection findings). Today this task is commonly performed by the department in charge of these studies, and drug safety only becomes aware of the cases already assessed as related by either the

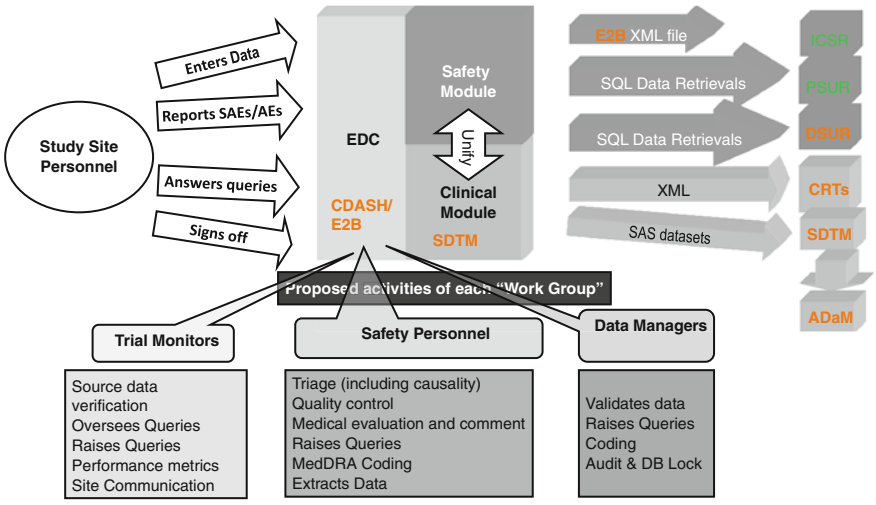

Fig. 7.1 Unified clinical/safety database workflow

investigator or, much more uncommonly, by the company. However, fewer resources would be needed by drug safety to enter, and ultimately verify data, since these tasks would be performed by study site personnel.

Technology offers improvements not only from compliance perspective but also from an operational one. Following EDC implementation, the individual case safety report triage step, still performed on paper by some organisations, would become completely electronic. The responsibility of drug safety officers in performing quality control (including data coding) would not change, and drug safety physicians would continue to evaluate a case by reviewing the data, as is already current practice. The advantage would be that both the safety officer and the drug safety physician would be capable of raising queries within the EDC system, send them to the investigator and receive and process the response electronically. More importantly, both drug safety and clinical personnel would be able to review the queries that have been raised by both departments and the answers that have been received, thereby avoiding replication of queries raised to a site. In addition, the clinical monitor's source data verification procedure would be fully accessible to drug safety auditors. Site communication is enhanced with the adoption of EDC since safety bulletins and instructions can be mailed at all sites and the whole process would be traceable with read/receipt logs, thereby reassuring that vital safety information has been communicated to all investigators. Since both drug safety and clinical department share the same system, drug safety would be more involved in the preparation and management of the safety bulletins that now are typically managed by the clinical department even if the safety department is, by definition, the main responsible of the safety profile of a drug. Finally, the more technically challenging activities such as data extraction for aggregate reports would fall to a safety database administrator. It is perhaps this role that would be challenged the most by having to understand the clinical database and systems. Of course roles and responsibilities will vary from organisation to organisation, and the levels of technical competency will influence the level of EDC responsibility that will be assigned. However the main change driven by the unified database would probably be a cultural one, since drug safety and clinical departments, which now operate separately, will need to be much more integrated (see proposed activities in Fig. 7.1).

Ideally EDC systems should be configured to accommodate safety operatives but this is not always so. All EDC vendors need to engage safety professions to advise them on all safety requirements to enable comprehensive data capture. The safety database administrator role is pivotal since they will be expected to familiarise themselves with the clinical data systems at the most technical level. The EDC system and all common work groups are depicted in the diagram above. A common pathway for data acquisition can lead to an environment that will provide all the necessary forms and data extractions in a range of formats familiar to the operatives of the independent systems.

Fundamental changes to working procedures are typically met with scepticism; therefore anticipating issues is the formula for successful process improvement. In Table 7.1, some benefits and drawbacks as perceived by both clinical research and drug safety operations together or alone are listed.

Table 7.1 Unified safety database benefits and drawbacks

	Shared by safety and clinical	Safety only	Clinical only
Benefits	Data cleaning shared	No need to key in data for clinical trial serious adverse events	Level of data processing and cleaning safety data reduced because safety will need to perform these tasks first
	Harmonized safety information accessed at one data source	No need to key in data for non-interventional prospective studies adverse reactions	
	Reduced risk of failing to perform adverse event causality assessment	No risk of late receipt of an adverse reaction from an organized data collection system that needs regulatory submission	
	Reduced cost for database set-up, validation, maintenance	More efficient preparation of aggregate reports thanks to easier and quicker access to all safety data	
	No need for adverse event reconciliation	Gain effective communication tool to reach all site personnel	
	Consistent coding		
	No duplication of coding		
	Queries to Investigators visible to both departments thereby avoiding repetition		
Drawbacks	Perceived loss of data ownership	Selected drug safety personnel must become familiar with clinical data management technology, standards, data and outputs	Clinical data management team has to accommodate non optimal long text fields to make them compliant with E2B requirements
	Operations will need to be restructured. Must motivate personnel in both departments to embrace combined standards in the long terms	Current EDC products are designed to meet clinical data management requirements and new functionalities are required to satisfy drug safety needs. Safety needs to work with vendors to deliver the new functionalities	
	Closer cooperation between clinical and safety departments		

7.7 Conclusions

The need for pharmacovigilance professionals to access all types of safety data is widely recognised. It is self-evident that having independent processes to manage clinical trials, noninterventional organised data collection systems and spontaneous safety data is inefficient, costly and risky resulting in non-compliance. A single system for capturing all information from the study sites reassures the sponsors of data consistency and facilitates pharmacovigilance access to all data. It is also the foundation for establishing a single data repository that would offer a convenient single source for the preparation of aggregate reports and continuous access to all study data for signal detection, validation and evaluation of activities. As both financial and regulatory pressures grow, comprehensive access to all data is essential. The unified safety database concept is the ultimate solution that can deliver total data access and make it easier to protect patient safety and free up resources for achieving this goal. The dilemma is whether the pharmaceutical industry should wait for software vendors to grasp the concept and create a solution or if the industry should take the lead by specifying the fundamental features of a unified database.

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Chapter 8
Behind the Scenes: 'Silent Factors' Influencing Pharmacovigilance Practice and Decisions

Ulrich Hagemann

8.1 Executive Summary

Apart from data originating from formal studies – experimental or observational – a number of not science-related factors have influence on pharmacovigilance practice, on decision-making and on effectiveness of risk mitigation measures. Such factors touch the relevance of basic research in natural sciences; the 'environment' in which pharmacotherapy and pharmacovigilance is practised; the characteristics of national drug markets, drug supply, access to medical care and social security systems; and last but not least economic forces entering and conquering our health systems. In this article observations and trends in regulatory management and healthcare systems leading to failures in pharmacovigilance activities are delineated and commented upon.

Sociopolitical, sociocultural and ethical elements should be linked more closely with current pharmacovigilance so that a holistic approach emerges.

8.2 Introduction

Assessment of benefit and harm in pharmacovigilance and decisions on risk mitigation, of whichever type, are widely based on scientific data derived from formal studies of various types. What is written on the banner of pharmacovigilance gurus is that these data should be valid, leading to robust decisions by regulators or marketing authorization holders (MAHs), and frequently they are not allowed to be put into question. Fine, but if you look behind the scenes and into more shadowy corners of

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the pharmacovigilance house, you will find a lot of different, unsaid, not considered or neglected factors which influence assessment, decision-making and outcomes in pharmacovigilance. This text does not deal with sophisticated methods, tools, biases, etc. in various scientific pharmacovigilance-related disciplines, e.g. in pharmacoepidemiology, but addresses in this context 'soft' items or 'silent factors'.[1]

8.3 Progress in Science and Pharmacovigilance

Box 8.1
Progress in biomedical research leads to better therapeutics and options for treatments. Outdated medicinal products kept on the market expose patients to less effectiveness and avoidable risks and burden social budgets with unnecessary costs.

New pharmacological data and findings are frequently put into authorised data sheets but leaving it to the physicians to read and understand the information and to follow recommendations. This practice may cause medication errors.

New diagnostic tools open better insights into morphological conditions and into biochemical pathways and processes. If such tools are not used to confirm exact and correct diagnoses of adverse drug-related reactions (ADRs), signal detection and management can be made substantially difficult.

Funding of epidemiological studies remains a major problem. An approach to have available a robust financial basis for the conduct of epidemiological studies could be to build a fund fed from money of the three major players who should have the utmost genuine interest in finding answers to drug-related issues: the pharmaceutical industry, the health insurance companies and the government.

8.3.1 Basic Research in Natural and Biosciences: From Old to New Drugs

A medicinal product entering the market after being authorised through a competent authority stands at the end of a long chain of research in various biosciences. There are innumerable undisclosed researchers in the prehistory of a medicinal product, and without their intelligence, knowledge, inquisitiveness experience and good fortune, there is no or only little progress imaginable. What would we have in hand without the discovery of DNA and knowledge about its complex structure and

[1] The relevance and shortcomings of communication in pharmacovigilance including the complexity and extent of bureaucracy are not addressed in this article. These topics have been dealt with comprehensively in a theme edition of *Drug Safety* in 2012 [1–3].

function? What would we do without the still incomplete knowledge about biochemical or metabolic pathways in higher organisms? And how would we start a pharmacological treatment without all the other physical-technical equipment and tools in various medical disciplines?

To illustrate the relevance and the contribution of bioscientists to a safe use of drugs and thereby to pharmacovigilance, antiulcer treatments might be a good example amongst many others. Decades ago anti-acids like aluminium or magnesium compounds for the treatment of acid-related gastrointestinal disorders have been used widely as cheap and moderately effective medicinal products. The knowledge about their ability to neutralise hydrochloric acid came from basic chemistry and was combined with the finding in biochemistry that hydrochloric acid is secreted into the stomach. After the detection of H_2-receptors in gastric parietal cells, histamine antagonists as potent inhibitors of gastric acid release have been developed and introduced into therapy of these diseases. They were widely used as well and caused numerous and various side effects. Further basic biochemical research revealed the more sophisticated mechanism and pathway of acid release, i.e. the proton pump. The development of the proton-pump inhibitors offered a much more effective treatment of peptic ulcers and gastro-oesophageal reflux disease with less risks and harm. Nowadays they constitute a standard therapy, and they are widely used even as OTC products.

However, as a science-based consequence, anti-acids and H_2-inhibitors have not been taken from the market despite of their unfavourable benefit-to-harm balance compared to proton inhibitors. As a result this means that patients taking H_2-inhibitors are exposed to a preventable risk, and health systems are burdened with the costs for outdated medicinal products. Should we have in place a mechanism and tools to remove medicinal products from the market generally when evidence based better therapeutic options are widely available?

8.3.2 Implementing New Scientific Evidence to Medical Practice

Results from basic biomedical research are telling us a lot about differences and variations in individuals and their pathways in metabolism. We know about slow and rapid metabolisers; we know about the arsenal of CYP 450 enzymes and subtypes leading to drug interactions; we know about specific alleles predisposing some patients for serious adverse reactions or conversely to high efficacy. And as soon as we know about such pharmacological details, in pharmacovigilance we frequently follow an extremely simple approach to protect patients from harm resulting from biological variants: putting the available information in the product information!

Does this effectively protect patients from harm? Will a physician first explore all possible circumstances and conditions which may have an influence on efficacy or safety before prescribing a specific medicinal product? Can we assume that physicians are familiar with related possible risks and their magnitude, and can we request that they will perform a number of tests to confirm or exclude a specific metabolic or genetic precondition? Probably and realistically not, and that means as a consequence that regulators and MAHs deposit responsibility to follow the

instructions in the product information to physicians not acknowledging what happens in reality. That is disappointing and disturbing and quite probably leads to medication errors. Moreover, both regulators and MAHs cannot assess at a later stage whether a specific pharmacovigilance decision was effective or not.

8.3.3 Diagnosing and Assessing Adverse Drug Reactions

New diagnostic tools in human medicine open better insights into morphological conditions and into biochemical pathways and processes. It's no longer only the 'old fashioned' x-ray investigation still used frequently; high technology imaging and other diagnostic tools like immunoassays, radionuclide markers, etc. with high sensitivity and specificity have found their way into everyday medicine.

Availability of modern diagnostic tools increases the relevance and requirements for making a correct diagnosis in case of a suspected drug-related adverse reaction (ADR). The appearance and cause of medical events and symptoms are frequently not clear and definite; they can be very similar despite different underlying causes. Proper differential diagnosis using best available tools helps to find the true diagnosis and plays an important role when assessing single case reports on ADRs or case series. But such an approach is rarely well documented if at all. In observational studies from various sources, we frequently have diagnoses of ADRs and outcomes 'as documented' in the patients' health records or databases, e.g. claims databases, but reliable confirmation of the diagnosis is lacking.

Incomplete or unconfirmed diagnoses of medical events reported as single cases are, and have been, a substantial problem, e.g. in signal detection and consequently in signal management and decision-making. What is needed to ascertain a deep vein thrombosis, a pulmonary embolism, a specific type of hepatitis, a vision disorder, or a mental disorder? And how can such blurred diagnoses be brought into the context with one (or more) medicinal products? At least within signal management procedures based on spontaneous reports, the medical assessor should have full access to patient records. Normally it will be extremely difficult to perform ex post additional investigations to substantiate the ADR. Reporters should be advised to document their diagnostic steps as completely as possible. Also, under-pressure healthcare professionals are more likely to make medication errors and also fail to make diagnoses of iatrogenic injury. Root cause analysis should be considered as a tool to elucidate the basic reasons for medication errors and related ADRs.

8.3.4 Funding Epidemiological Studies

A major problem was and still is funding of epidemiological studies particularly those in which a specific issue (drug utilisation, risk, effectiveness, comparative benefit and harm) is investigated. The problem is aggravated in cases in which the item of interest relates to a huge number of generics, substance groups or therapeutic

classes (e.g. NSAIDs and cardiovascular risks, the epoetins and tumour progression or stroke, ACE inhibitors during breastfeeding, etc.).

An approach to have available a robust financial basis for the conduct of epidemiological studies without major and unacceptable delay could be to build a fund fed from money of the three major players in the supply system of pharmaceuticals: the pharmaceutical industry, the health insurance companies and the government. These are the players who should have the utmost genuine interest in finding answers to drug-related issues: the industry has an interest in keeping a licence or to avoid a disaster and carries main responsibility for their products, insurance companies are the collective payers for medicinal products and should minimise costs for treatments of drug-related harms, and government would comply with its overall political responsibility to run an optimal and beneficial drug supply system. In case a post authorization study (PAS) on a specific risk- or effectiveness-related issue is needed, the study would be performed on a protocol agreed by an official scientific body. Study sites or data sources, investigators, epidemiologists and statisticians would be recruited by consensus. Research networks like ENCePP could give support. The costs for requested PASs or those of high relevance for patients would be financed from the fund, and long-lasting debates about financing could be avoided.

8.4 The Environment in Which Patients Are Treated and How Pharmacovigilance Is Affected

Box 8.2

The huge abundance of medicinal products in developed countries has a couple of undesirable consequences like waste of resources, imbalance in drug markets, medicalisation of lives, etc. *We should think about a concept to assess the needs for pharmaceuticals tailored to an optimal supply of medicinal products in healthcare systems.*

Premature drug licensing of insufficiently investigated or developed medicinal products has consequences for pharmacovigilance in a wider sense and means a fundamental change in drug safety philosophy, i.e. giving a licence first and look on safety and effectiveness later. This change may cause major disturbances incl. in risk communication and of trust into authorities and industry. We should rethink current practice of early and premature licensing and develop a modified safety architecture.

It is paramount to know whether people have access to medical care and to which extent. In regard to pharmacovigilance, we frequently suffer from uncertainties about drug exposure to estimate the magnitude of a risk, an important element in benefit-to-harm assessment. This situation points to the necessity to develop and establish, more than currently, drug utilisation research.

Drug delivery shortages can have serious consequences for patients like the risk of non-adherence, decreased efficacy and effectiveness of drugs and causing harm. There should be a legal obligation for marketing authorization holders to provide enough production or storage capacities to avoid drug delivery shortages.

Pharmacovigilance without a proper co-operation between partners in healthcare systems will not be successful and finally not in the interest of patients. An effective co-operation between healthcare professionals, caregivers and the individual patient should be warranted.

8.4.1 Characteristics of National Drug Markets

General practitioners usually fall back on a limited number of medicinal products or active ingredients they are familiar with. Medical specialists usually prescribe a different and smaller repertoire of medicinal products. However, in developed countries we are faced with a huge abundance of medicinal products, new and old ones, thousands of generics and complementary drugs. What use can a general practitioner make of a choice out of hundreds of licensed beta-blockers, ACE inhibitors, fluoroquinolones, NSAIDS, analgesics, etc.?

Such abundance has a couple of undesirable consequences and promotes unfavourable developments:

- A complexity of drug markets which is not understood by general practitioners or which they are not even aware of
- An unimaginable waste of resources: material, intellectual; administrative, financial, environmental and of human resources
- Using drug licences (duplicates, triplicates) as trading goods that can be sold and bought by MAHs
- An enormous imbalance of availability of medicinal products in developed countries compared to, e.g. primary healthcare in developing countries
- A general not reflective understanding of pharmacotherapy as the most effective, rational and 'cheapest' instrument to treat patients ('a pill for every ill')
- Negligence of non-pharmacological approaches to prevention or treatment where acceptable and appropriate
- A medicalisation of lives
- A weakening of patients' personal responsibility

Decades ago we had a rational concept of supply of pharmaceuticals – to have in place a limited and manageable spectrum of effective and safe medicinal products for primary care (which may be different from the WHO 'Essential Drug List' developed for different purposes). Should the involved parties think about a new approach to assess the needs for pharmaceuticals, tailored to an optimal supply of medicinal products in a given healthcare system and then its implementation?

8.4.2 *Premature Drug Licensing of Insufficiently Investigated or Developed Medicinal Products*

The vast majority of general practitioners, medical specialists, other healthcare professionals and particularly patients are never asked for an opinion on where is an urgent need for an effective pharmacological tool and what they think about medicinal products that should be investigated, developed and marketed with high priority. Decisions on drug development are primarily made by pharmaceutical companies. The driving criterion has been frequently, and still is, an expected high profit after launch of an innovative, new, 'me-too' or lifestyle medicinal product into medical practice.

Cancer diseases, dementia, multiple sclerosis, mental diseases, epilepsy, diabetes or cardiovascular diseases – as examples – are diseases that need effective therapeutic options, and they are associated with a morally demanding connotation. But if people with or without one of these diseases would be asked more specifically whether medicinal products should be introduced into medical practice as soon as possible and at an early premature stage of research and development, the majority would possibly respond 'yes'. National drug agencies are in a dilemma: their role is to make medicinal products available to physicians and patients based on good evidence for efficacy and safety but also to meet patients' expectations on availability of new medicinal products at the earliest possible time.

This melange of aspects can be summarised as follows:

- Pharmacological research produces innovative therapeutic options for the treatment of a specific disease.
- The active compound has the potential to generate high sales which is of interest for the pharmaceutical company.
- Agencies may have still concerns on the basis of available scientific evidence about an insufficiently substantiated benefit-to-harm balance.
- Interested parties and patients put pressure on agencies to grant a drug licence early and without any delay even if the medicinal product is not fully investigated.

This had in the past, and still has, consequences for drug monitoring and for pharmacovigilance in a wider sense. Since a couple of years, regulators and industry have developed procedures and rules to grant early licences and thereafter to monitor drug safety and effectiveness. This meant a fundamental change in drug safety philosophy, i.e. giving up the principle to grant licences only for sufficiently investigated and developed medicinal products. Instead a bunch of unanswered questions on efficacy, effectiveness, quality and safety are written down in Risk Management Plans (RMP). This concept seems to be followed more frequently than ever and possibly too frequently. Pointedly formulated this means: give the licence first and look on safety and effectiveness later, and companies thereby have their foot in the door of the market. In some cases this approach might be acceptable in the interests of patients and depending on what is known about the disease resp. the indication, the

active ingredient or the medicinal product. In some cases[2] an early and premature licensing has caused major disturbances, e.g. in regard to a need to conduct extensive epidemiological studies and the interpretation of observational study results. Such a change in philosophy also has effects on making regulatory decisions incl. later modifications over time and in risk communication, the latter affecting patients' understanding of drug safety. In turn this affects the good standing of regulatory authorities and industry negatively.

In conclusion, we should rethink current practice of early and premature licensing and develop a modified safety architecture. A rough approach could be to build a concept in which patients' needs, current medical science and research capacities are the primary pillars. A triangle of three categories of medicinal products, i.e. (a) used in orphan diseases[3] or which are eligible for a compassionate use, (b) generics and (c) new chemical entities, including chemical modifications of known substances ('me-too'), with available therapeutic options or established standard therapy should be the 'coordinates'. For the first two groups, rules and procedures are established since long and do not need substantial change. Medicinal products of the latter group would be subject of discussion in a panel with representatives of patients, medical sciences, regulatory agencies and pharmaceutical industry. The panel would define for which active ingredient or dosage form a comprehensive spectrum of research and development should be performed prior to granting a licence in order to establish a positive benefit-to-harm relationship acceptable for patients and based on current scientific knowledge. The panel should consider specific requirements in different regions, and the recommendations may vary accordingly.

8.4.3 Access to Medical Care

It is paramount to know whether people in a specific country or region have access to medical care and to which extent. Lacking access to medical care in developing countries is well known and remains a huge challenge for global health. However, even in developed countries, we can observe an increasing disparity between people with high and low income or those depending from welfare systems. In consequence a fraction of patients have full access to medical care and can afford the total spectrum of pharmacological treatments. Another fraction has limited or even no access to medical care or treatment which alone constitutes a violation of equal rights. The patients belonging to the latter fraction possibly consider not to see a doctor or healthcare provider if they have health troubles, or they cannot pay for a medication because the costs would exceed their small budget, or they may

[2] Examples are glitazones and cardiac risks (2010); somatropin: cancer risk in children born small for gestational age (SGA; 2005); epoetins: thromboembolic events and tumour proliferation (2004).

[3] NB: In practice, defining small subgroups, e.g. of a relatively frequent disease entity, possibly based on genomic screening (*cf*. Chap. 1), has constituted the status of an orphan drug in the past.

consider to stretch the duration of application or to take 'drug holidays' for cost reasons.

In regard to pharmacovigilance, we are frequently faced with major uncertainties about drug exposure, and frequently the proportion of non-adherent patients is unknown and not considered. To know exposure and to estimate the magnitude of an identified risk are important elements in benefit-to-harm assessment. This situation points to the necessity to develop and establish, more than currently, drug utilisation research and to connect this field of research to pharmacovigilance as an integral and science-based element.

8.4.4 Drug Delivery Shortages

Relatively new challenges are drug delivery shortages even in developed countries. This relates to vitally important medicinal products (originator or generic medicinal products; gene technology products; recombinant biologics, e.g. monoclonals and biosimilars; specific application forms, e.g. inhalators or special syringes). Obviously no type of medicinal product can be excluded from possible delivery shortages. Reasons for this, and seen so far, are production failures or contamination in cell cultures, miscalculations in production capacities, closing of production sites abroad or inland. There is currently no obligation for pharmaceutical companies to guarantee supply availability at any time for medicinal products for which they hold licences. Additionally globalisation of drug markets and building up production sites somewhere on the globe for economic reasons support the occurrence of drug delivery shortages.

Drug delivery shortages can have serious consequences for patients in the sense that an indicated and necessary treatment cannot be continued, an optimal treatment in emergency situations cannot be provided and patients being familiar with their current medication must switch to therapeutic alternatives either from the same substance group or another. There have been cases in which a change in dosage regimens of a vital treatment was introduced by the European Medicine Agency ('rationing') to bridge the delivery shortage.[4,5] All these options carry a risk of non-adherence and decreased efficacy and effectiveness of drugs. Despite there are only few data from drug utilisation studies and from studies investigating the risks associated with such changes in treatments it takes not much fantasy to imagine that patients may experience harm when switching from one medicinal product to another – for reasons outside their own responsibility and decision. It seems appropriate and necessary that pharmacovigilance should address such problems following drug delivery shortages and to help work on solutions.

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[4] www.ema.europa.eu: Myozyme™ (alglucosidase alfa); EMEA press release (EMEA/13509/2009, January 16, 2009).

[5] www.ema.europa.eu: Cerezyme™ (imiglucerase), Fabrazyme™ (agalsidase beta); EMEA press release (EMEA/389995/2009,June 25, 2009).

Should there be a legal obligation for marketing authorization holders to provide enough production or storage capacities to avoid drug delivery shortages? Should there be a list of 'essential medicinal products' or substances for which such a guarantee is warranted? We should post this on our agenda.

8.4.5 Integrated System of Partners in Healthcare Systems

Pharmacovigilance without a proper co-operation between partners in healthcare systems will not be successful and finally not in the interest of patients. As long as diversified structures in a healthcare system exist, maintaining different professional groups and their sometimes egoistic interests, we will fail to arrive at an effective supply of pharmaceuticals, medical and pharmaceutical care in the interest of patients. This means in practice that medical professionals being experts in diagnosis and treatment should open up to a partner-like relationship with pharmacists who should not restrict their self-concept to be drug experts only. Similarly, an effective co-operation with nurses and caregivers should be warranted, at whatever level and setting. Finally the individual patient must be taken seriously as a subject that has health complaints seeking for help and being a self-governing human being with own interests and the fundamental right to health: comprising mental, psychical and social wellbeing.

8.5 Economic Factors

Box 8.3

Various concepts have been developed to resolve the problems associated with reimbursement of expenses for medicinal products within social security systems. All concepts have consequences for patients, and pharmacovigilance has not yet paid enough attention to the complex interactions between pricing, reimbursement, Health Technology Assessment (HTA), good medical care and patients' needs.

Drug advertising towards the public is a concern. Particularly in the audiovisual media, an enormous imbalance becomes apparent between the content of an advertisement and the known characteristics of the medicinal product. The alternative is to forbid drug advertising in favour of officially certified and understandable drug information.

Local community hospitals are acquired by private healthcare companies with shareholders in the background. These new models for financing hospitals have effects on treatment outcomes and risks, and insofar pharmacovigilance is touched. However, the effects are largely out of range of influence of MAHs or regulators.

8.5.1 Reimbursement and Pricing Systems: HTA, Fixed Prices and Budgeting

The expenses for medicinal products within a social security system are hotly contested between suppliers: the pharmaceutical industry, the payers and the health insurance companies. The first wants to realise an optimal profit, the latter two are committed to keep the system, stable and alive, and based on the insureds' fees.

Various concepts have been developed to resolve the problems associated with these conflicting interests. One is to define fixed prices for medicinal products sometime post-licensing usually for those which are well established in therapy and which are used in standard medical care. This relates mainly to generics but not exclusively.

More sophisticated approaches have been developed for assessing the therapeutic value of new medicinal products after a licence has been granted.[6] In this context, institutes now established in some countries[7] and doing Health Technology Assessments (HTA) have, and will have, their heyday. Their task is to give an evidence-based opinion on whether a new licensed medicinal product has a high, moderate or no added therapeutic value compared to standard treatment. Which therapeutic option is defined as 'standard treatment' differs in countries and has been matter of controversial discussion. Subsequently and depending from the outcome of the HTA, upon prices and reimbursement is decided. In case a high or moderate added value has been confirmed based on a generalised conclusion from available data, the medicinal product can be prescribed and is reimbursed whatever the price is. If no added value is confirmed, the medicinal product can be prescribed but is not, or not entirely, reimbursed and must be paid for by the patient – that is sometimes not affordable.

Another concept in use is to build a budget for each physician per quarter which he is not allowed to exceed when prescribing medicinal products. If he exceeds his budget, a penalty could be imposed to him or, much more relevant for patients, the latter don't get the medication they need at the end of the quarter because the prescriber refuses a prescription. We have only little insight on what that means in regard to best medical care.

All these concepts have consequences for patients, some may be good or acceptable others not. Pharmacovigilance has not yet paid enough attention to the complex interactions between pricing, reimbursement, HTA, good medical care and patients' needs.

8.5.2 Drug Advertising

For a long time, drug advertising towards the public has been a concern. It is allowed for 'over-the-counter' (OTC) products in many countries mainly to increase sales (and probably not public health). Particularly, in the early phase, after the

[6] The term 'new' is unspecific. It is used here in the meaning of 'new active ingredient not used in pharmacotherapy so far' or 'active ingredient not yet used in the licensed indication'.

[7] Established in Austria, Canada, EUnetHTA, France, Germany, UK, USA.

switch from ‘prescription only medicine’ (POM) to OTC status, MAHs put a lot of money and efforts to capture as much market shares as possible. In audiovisual media an enormous imbalance becomes apparent between the make-up, e.g. of a video, and the authorised description of the characteristics of the medicinal product. Frequently you are confronted with advertising statements or messages you never had in mind when making a decision in favour of a switch from POM to the OTC status.

There is only one conclusion possible: to forbid drug advertising completely in favour of officially certified, understandable and freely accessible drug information. What works in regard to tobacco should work for medicinal products as well, and nobody needs polished drug advertisement.

8.5.3 Role of Owners of Hospital Trusts

At least in developed countries since a couple of years, a substantial change in the hospital landscape has taken place. Local community hospitals have been acquired by private healthcare companies with shareholders in the background resulting in relevant changes for supply of basic health services. There might be some debatable reasons for this in regard to optimising the quality of specific medical interventions such as surgeries, etc.

However, these private healthcare companies try to make profit and want to fulfil the expectations of shareholders. In reality, economic aspects and aspects of cost effectiveness are introduced into medical practice. For example, and more relevant, medicinal products administered in the hospital are not allowed to be prescribed by general practitioners for aftercare because of cost reasons or budgeting. So either patients are switched to other medicinal products or the medication is stopped earlier than actually necessary or at all. All these options are associated with effects on treatment outcomes and risks, with consequences for pharmacovigilance activities. However, the effects are largely out of range of influence of MAHs or regulators.

8.6 Summary

The purpose of this text is to list and address a few aspects, problems and factors in the neighbourhood of pharmacovigilance concepts and activities. Some items are related to science, others are more sociopolitical. There are probably more issues than described that fall into the same broad category, but the purpose here has been to raise these broader issues for more active consideration.

The relevance of basic research in natural sciences, some affecting the integrity and personal welfare of many of us, is outlined. The ‘environment’ in which pharmacotherapy and pharmacovigilance are practised, such as the characteristics of

national drug markets, drug supply, access to medical care and social security systems, is spotlighted. And last not least, economic forces entering and conquering, in a way, to our health systems are viewed critically.

8.7 Conclusions

Pharmacovigilance is not just a stand-alone area of science built on a 'nucleus' of natural sciences and comprising various disciplines like medicine, pharmacology, epidemiology, etc. There is a trend to squeeze pharmacovigilance in a narrow bed bordered by formal procedures, strong rules, SOPs, bureaucracy and insufficient resources. All this happens in a world where economic considerations become ever more prominent, and health systems are not excluded from this trend. There are many more areas outside this nucleus worthy of consideration and put into context with current pharmacovigilance practice. Sociopolitical, sociocultural and ethical elements should be linked more closely with current pharmacovigilance so that a holistic approach emerges. These elements should be addressed at conferences and training courses. Currently there are obviously more questions than answers.

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Chapter 9
Shaking Up Culture and Communication in PV [V6]

Bruce Hugman

Pharmacovigilance has not achieved either the public profile as a health priority or the impact on patients' lives that we might have hoped; the vision of comprehensive patient safety, though much stronger since thalidomide, is still far from being realised. Great strides have been made in some regions and institutions, but the overall picture is still deeply disturbing: harm to patients is widespread [1].

Drug regulation, a major element in the overall picture of patient safety, has fallen short of expectations [2] and, often, become a sluggish, bureaucratic operation [3], with ever-burgeoning systems and ever-fatter, impenetrable, burdensome documentation developed in often remote and secretive organisations [4]. For example, too many patients have been exposed to dangerous drugs – or killed [5] – during long periods of regulatory indecision or inaction (Vioxx (rofecoxib), Mediator [6] (benfluorex hydrochloride), Avandia (rosiglitazone)); incomprehensibly irrational and costly decisions have been made (Tamiflu and the statins débacle); there is insufficient information about patients' experience of drugs in the post-marketing period (especially harms) [7, 8] and poor communication to patients and professionals of such information as there is; women remain at greater risk in general of exposure to unsafe medications and drug interactions than do men [9]; the public has become critical, if not cynical about official commitment to their interests; trust has been severely compromised in many places [10].[1]

[1] See Chapter XX, Lost in Regulation, for much more on this topic.

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There are other challenges too: pharmaceutical companies, the victims of blossoming regulatory bureaucracy, have, from time to time, shown themselves to be more interested in profit than ethics,[2] [3] and more expert in managing public relations than upholding patient welfare and safety. Only a small percentage of all trial results are published, with a hefty bias towards positive results, to the neglect of neutral or negative results [4]. It's a mixed and very worrying picture.[4]

On the other hand, there are wonderful new resources, activities, tools and communications – websites, apps, forums, videos, social media channels and community projects – across the whole medical field, many from independent organisations and collaborations,[5] some sponsored by national agencies,[6] but through the decades, at the heart of the official drug safety establishment, things have hardly changed at all in terms of culture, methods, reach and influence.

9.1 Culture and Communication

The tone, style and method of all communications reflect the values and priorities of the individuals or organisations behind them: the paternalistic tone of the physician reflects his own, unquestioned sense of expert superiority; the small fonts and extensive, dense black text of public documents (including software licences, bank terms

[2] GSK's Study 329 is amongst the most notorious examples of negative clinical trial data being corruptly represented as positive and used as the basis for massive and profitable marketing of an ineffective and dangerous drug (Paxil/paroxetine). A recent reanalysis of the original data has revealed the extent of the fraudulent claims (see: http://www.bmj.com/content/351/bmj.h4320). Johnson and Johnson's Risperdal/risperidone has also been subject to massive controversy and punitive litigation as a result of evidence of underestimated and undeclared serious side effects (see, e.g. http://www.drugdangers.com/risperdal/).

[3] Turing's decision, in September 2015, to increase the price of Daraprim by around 5,000 % was a controversial and emblematic example of the drive for profit irrespective of its impact on patients or health funding.

[4] I am going to write some very critical and negative things about the practice of pharmacovigilance. The global picture is not, of course, one of unmitigated blackness and failure, but I am not going to qualify my remarks at every stage with mentioning the achievers and the exceptions; where the hat fits, it is probably being worn. You, my reader, must judge if any aspect of what I say applies to your own circumstances in your country or whether you can pat yourself on the back for having avoided all the old pitfalls and shown the way to new and better things. The opinions are based on reading, observation and experience in many parts of their world, including Europe and far beyond.

[5] The Thai Health Promotion Foundation, for example, has been using original and creative videos for some years. One of their most famous is at https://www.youtube.com/watch?v=aHrdy6qcumg

[6] The US Centers for Disease Control and Prevention (CDC; www.cdc.gov) appears to be an agency in tune with the modern age in the variety, ingenuity and reach of its communications; Medindia (www.medinida.net) is a modern site for patients, similar to other excellent official and voluntary resources in a few other countries (e.g. www.patient.info in the UK). But these operations are not primarily concerned with regulation or pharmacovigilance.

and conditions, and, of course, patient information and ADR reporting forms) reflect the indifference of public and commercial bureaucracies to their audiences, to clarity and transparency, their deafness to criticism and their detachment from the modern world. The official expectation of compliance, with, for example, ADR reporting procedures, dreamed up in government offices without consultation, reflects a hierarchical and authoritarian set of values and expectations that are no longer widely effective or acceptable in many societies; such official behaviour can result in indifference, non-compliance, protest or even defiance.

Dobbs et al., in their useful book, *No Ordinary Disruption* [11], analyse the current trends that are going to surprise and disable commercial enterprises that are not ready for them: 'four forces colliding and transforming the global economy: the rise of emerging markets, the accelerating impact of technology on the natural forces of market competition, an aging world population, and accelerating flows of trade, capital and people'. They talk of managers having to 'reset [their intuition]', abandoning the profound instinct to defend the status quo, and needing to sponsor 'reset catalysts' to develop breakthrough methods and technologies. The message is pertinent for all organisations. Failure to make these radical changes will lead to decline and irrelevance.

Attractive, appropriate and effective communications come from individuals and organisations that know their audiences and partners intimately and are collaborating with them to provide the best solutions. Such communications, however, cannot come from remote, inward-looking, unreformed sources; the precursor to great communications of the future is, therefore, lively, focused organisations doing great work in intelligent, modern ways; a commitment to 'radical engagement' in and with society, as John Browne describes it [12].

Great communications come out of great enthusiasms and great commitments. While drug regulation and pharmacovigilance employ many individuals with these qualities, the institutions themselves inhibit creativity and experiment and tend to have a demoralising effect on the liveliest of personalities. Some of the greatest vision and energy is evident in developing countries, but, even here, stodgy and inefficient bureaucracy, imitative of Western style, embracing the latest ponderous, probably inappropriate foreign guidelines, often stunts change and progress.

9.2 What Needs to Be Done? Some Helpful Models

In this chapter, I am not going to set out a list of specific desirable future communications activities that will resolve all the problems and obstacles, not least because I am not that clever and because I am not engaged at the front line where the needs and deficiencies are so specific and palpable. What I can review are successful organisational values, ideas, principles, methods and solutions that have emerged in other fields which point to changes that might help us dig ourselves out of the hole we are undoubtedly in. Pharmacovigilance needs to reset its intuitions and practices.

I want to concentrate on thinking about how we might create an environment in which the well-known problems were grasped as urgent priorities that required novel, unusual, unexpected answers; a culture that would generate brand new solutions. If we have the right culture and priorities, and liberated and free-thinking staff, the good communications will inevitably follow. Where can we find inspiration?

Parallels and metaphors can sometimes illuminate issues with which we are complacently familiar. Here's a few to launch us on this topic in pharmacovigilance about which so much has been written to so little general effect. Throughout the text, I've inserted what I regard as key principles and values at various points in the argument.

Reflection *As long as professional and organisational culture and practice remain rooted in the past, patients will never be effectively protected from harm or satisfied with the communications they are offered.*

9.3 The Sports Arena

As I write this short essay on communication – one of the most radical engines of modern life – and its place in the future of pharmacovigilance, the 2015 Athletics World Championships are gripping crowds in Beijing and around the world. Nearly 2,000 of the fittest, most ambitious and determined individuals from over 200 countries are pushing themselves to their limits, chasing records and medals, often taking human performance to remarkable new levels. This and other comparably stunning international events (like the World Artistic Gymnastics Championships in Glasgow in October 2015) remind us of one category of the astonishing achievements of the human race: physical prowess. In some aspects, they also remind us of the beautiful marriage that is possible between competitive strength and gracefulness.

Such life-enhancing elements of human potential stand in stark counterpoise to their opposites: our capacity to be ponderous, heavy-footed, cautious, flightless and dull. These are characteristics of much of our social planning and organisation, especially of unreformed bureaucracies in the public and private sector.[7] Far from striving for excellence, competing for medals and applause on the world stage, many organisations exist behind high walls, out of public sight, and, if competing for anything, it must be for medals for the world's most impenetrable, cumbersome, oppressive, infuriating operations – often sluggish and corrupt as well. Don't be misled by glassy towers in smart capitals; they are prone to as many of the

[7] While WHO achieves many great things, especially through its small, decentralised, agile units in the field, its intrinsic weakness as a lumbering, centralised bureaucracy was starkly revealed in the disastrous handling of the early days of the 2015 Ebola epidemic. It was a failure that contributed to the ultimate death toll of more than 11,000 people.

bureaucratic foibles and absurdities as are dim, ex-colonial establishments dressed in crumbling brick and plaster.

Reflection *Athletes train to achieve excellence and compete to break records; many pharmcovigilantes huddle in isolated bureaucracies, buried in paper, striving to resist change or envisage or reach new heights.*

9.4 Agile Thinking and Action

The Manifesto for Agile Software Development [13], known as The Agile Manifesto for short, was developed in February 2001 by a pioneering group of 17 independent and independently-minded software developers. It arose out of thinking and research that had started in the 1960s and was a reaction to traditional Gantt-driven[8] project planning and 'waterfall' management[9] among other managerial disabilities.

Agile thinking, as its name implies, embraces flexible, interactive, iterative, evolving, progressive project development[10] in contrast to the relatively static and predictable tasks and milestones of Gantt-style operation.[11] It is closer to creative gymnastics or artistic improvisation than it is to building pyramids.

The insights and principles of agile management are not so much a method or rule-book but more a set of values and priorities to drive rational and effective action and behaviour. They do not imply a rejection of the old ways (see table, 'while there is value in the items on the right, we value the items on the left more'), but they do imply making very specific, discriminating choices about to how to handle any project and about the values and priorities underlying its management. Agile adaptability and constant reassessment, for example, are essential aspects of effective production in a world of constant change and upheaval. The daily 'sprint' challenges almost every element of traditional business planning and project management ('How do the realities of today, *this* day, influence and change what we were doing yesterday?') Agile values and practices are transferable to many other specialist fields, not least marketing and communications (even family life, it has been proposed [14]).[12]

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[8] Henry Gantt developed his chart in the decade before the First World War, and early applications included US military planning.

[9] 'Waterfall' management is the style typical of traditional hierarchical power structures where decisions are made at the top and are cascaded (maybe dumped) onto those below, whose duty is not to reason why but to get the specified job done.

[10] Terms like 'sprint' and 'scrum' come from this field.

[11] So central, by the way, to development aid projects; so alien to the cultures of many developing countries in which they take place.

[12] David Furniss (Will 2014 be the year telehealth comes of age?, *The Guardian*, 21 January 2014) wrote: 'I predict that 2014 will be the year of the agile worker – this means giving staff access to data and information on the move, helping them spend more time with patients and less time travelling or in the office'.

The Manifesto for Agile Software Development
We are uncovering better ways of developing software by doing it and helping others do it.
Through this work we have come to value:

Individuals and interactions over processes and tools.
Working software over comprehensive documentation.
Customer collaboration over contract negotiation.
Responding to change over following a plan.
That is, while there is value in the items on the right, we value the items on the left more.

Agility is one of the qualities that define athletes and gymnasts and, in the intellectual and behavioural sense, a core quality of the most creative and productive individuals and teams in all walks of life. It is not, however, a common quality in bureaucracies, their operatives, processes or communications. It is, by any definition of 'rare,' rare in pharmacovigilance and patient safety communications.

In our important field there are no competitive incentives or medals, no mass audiences or live cameras and few public consequences for failure, to spur anyone to exceptional effort, indeed to any effort at all.[13] (In the tough and parallel world of commerce, these kinds of complacency and inaction lead to rapid annihilation.) We've been bemoaning the underreporting of ADRs for decades: who are the medallists at the world ADR reporting championships? Who is setting the new world records, driving the sport forward?[14] For all the talk of international collaboration, which should include an element of progressive competition, few seem willing to set the pace and challenge others (or learn from others) to push back the frontiers on a global scale; few will question, let alone throw out the old ways. Patients will continue to suffer from harm, while we know so little about the causes of the great harm they suffer [15, 16].

One aspect of competitive sports is the constant search for new materials and equipment – for golf-club shafts, sprinters' footwear, swimmers' or cyclists' fabric or the hulls of yachts – anything that will give a competitive edge over older methods or technology. The primary urge is to win, and the most memorable winners are those who win with style; winners who are not just technically brilliant but also have character and depth. The winners take the glory, but the race for excellence that they win elevates and enhances standards everywhere and influences and inspires those who will never win, but who love the game.[15] There are some brilliant new tools and methods in pharmacovigilance, but there are many that belong to the dark

[13] Drug scares and crises do bring the operation of regulatory and PV bureaucracies into the glare of publicity. Such incidents are often the result of deficiencies in courage, agility and communications, not of science or intelligence.

[14] Underreporting is not just about numbers, of course, but also about relevance and importance. Poor quality reports are as serious an issue as low numbers.

ages and wouldn't survive two seconds in the bright light of a competitive public arena (oh, reporting forms, package inserts and PSURs; endless, debilitating mountains of paper; processes hijacking purposes; quarantining inconvenient data; centralised diktat; playing the game by secret, undeclared rules and protocols; muddling science and politics; etc.).

Reflection *The best software developers are engaged in a kind of improvised, live, progressive, theatrical dance; pharmacovigilantes plod under burdens like donkeys on a mountain expedition. Future, agile methods and communications will change and develop from day to day as patients, science and society change and will reach those who need them as they, too, change, learn and grow.*

9.5 Disruptive Innovation

The concept of disruptive innovation, first elucidated by the brilliant thinker, Clayton Christensen in the 1990s [17], is, in spite of some flaws and inconsistencies, at the heart of understanding how radical change happens in almost all fields of human enterprise. The essence of the theory, in the commercial world, but with applicability in principle across society, is that established and successful companies engage in 'sustaining innovation' as they improve their products and services and move upmarket (usually) to higher profits and (sometimes) greater customer satisfaction. As they concentrate on more sophisticated, costly and profitable products, they become vulnerable to popular new products and services entering at the bottom of the market; in time, these new products and services may displace the old ones and threaten the survival of traditional producers (the Blackberry is a modern victim of this process).

In terms of products, this happened in the development from huge mainframe computers to PCs to laptops and mobile devices. In terms of brands, it happened to Chrysler and Ford and many flourishing European marques when Toyota and Honda entered at the low end of the automobile and motorcycle markets all over the world. In both cases, established manufacturers of relatively expensive high-end products were blind-sided by radical, dangerous disruptive innovation. (And now, the Japanese are under threat from South Korea, India, China and Tesla as well as resurgent Western brands.) Christensen points out that the same processes have happened in steel manufacture, retail shopping, telephony and healthcare.[16] Among the most recent radical disrupters outside healthcare have been Uber (citizen taxis) and Airbnb (citizen domestic accommodation). Both have caused mighty headaches for dyed-in-the-wool regulators and operators whose taken-for-granted assumptions

[15] The NHS Wales 1000 Lives project runs an attractive campaign called Champions for Health, originally inspired by the 2012 Olympics. It doesn't have many of the real characteristics of international sport, but it has borrowed some of the colour and energy of sporting culture (http://www.1000livesplus.wales.nhs.uk/c4h).

and monopolies are being shaken; Uber and Airbnb, even with all their early-phase problems, have provoked massive popular support and prompted defection from traditional loyalties and behaviour. But those innovations have, like cyber security, left slow-footed legislators and bureaucracies in a state of confusion and shock.

Innovation and Risk

Innovation always carries some risk, to established systems, to the organisation itself or to clients/customers/users. However, a fertile, agile organisational culture combined with disciplined risk management can minimise risk and enhance opportunity. In the commercial world, the best examples can be found among venture capitalists who take big risks within their total portfolios but have strenuous mechanisms for monitoring and managing them. Advanced processes support bold but controlled planning, as described by Accenture, by using, for example, '[r]isk scenario (or simulation) analysis…a structured, forward-looking process designed, unlike traditional SWOT analysis… to discover how multiple factors combine to create both vulnerability and opportunity'.

Accenture points out how the courage for innovation often fails and organisations *renovate* but do not *innovate*. This topic, amidst the whole discipline of effective management, is a large and important one, given too little attention in organisations who define their purpose too narrowly and cautiously and believe their core knowledge and skills (in our case, pharmacovigilance and pharmacology) are sufficient. Communication is another huge speciality largely excluded by such narrow definitions.

For a very helpful article, see Accenture, The art of managing innovation risk (https://www.accenture.com/us-en/insight-outlook-art-of-managing--innovation-risk.aspx).

MinuteClinic and other brands in the USA [18] pose a major threat to the previous monopoly of traditional medical practice: immediate, high-street access to a very wide range of medical services delivered by in-store nurse practitioners at (relatively) affordable prices. Mobile Health (mHealth) in all its forms – Telemedicine, also known as Telehealth and Telecare – in India [19], Africa [20], Australia [21] and emerging in Europe [22] and Remote Patient Monitoring (RPM) are transforming access to medical care and delivery with affordable, effective and popular services for everyone, though the impact is particularly dramatic for dispersed rural populations and housebound patients, poor or not. The vision of these schemes is radical; the embrace of technology is uncompromising; the communications are fluid, vivid and direct.

[16] A further threat to their success is the complacency and arrogance of great companies and bureaucracies. The most remarkable example of that in recent years has been Volkswagen, which abandoned core business ethics and forgot that they were accountable, and would be held accountable, to users and authorities round the world. One account of the disaster here: http://www.telegraph.co.uk/finance/newsbysector/industry/11881819/Volkswagen-live-VW-issues-profit-warning-sets-aside-6.5bn.html

SMART Health India [23] is one such programme:

> …a unique low-cost, high-quality healthcare delivery system that enables both community health workers and doctors to provide state-of-the-art healthcare for common chronic diseases for a fraction of the price it would otherwise cost. It utilises advanced mobile health technologies that provide the healthcare worker with personalised clinical decision support to guide the Systematic Medical Appraisal Referral and Treatment (SMART) of individual members of the community.

Telemedicine for Patients with End-Stage Renal Disease (ESRD) in India

The introduction of at-home peritoneal dialysis (PD) in contrast to hospital-based haemodialysis (HD) is saving lives and startling amounts of money. Treatment of ESRD patients in the USA costs in the region of $170,000, while at the Lazarus Hospital in Hyderabad it is about $12,000. Vijay Govindarajan reports that 'rural patients performed well on PD and had significantly better survival rates than did their urban counterparts'[17].

Govindarajan writes: 'Lazarus Hospital uses mobile phone short messaging service (SMS), inexpensive digital cameras, and the internet to address patient accessibility issues. Those technologies — coupled with a dedicated PD team (comprising medical and paramedical staff) have enabled the hospital to develop a unique PD remote monitoring system. The innovation is in the software that provides the connectivity'.

There is resistance to such a system in the USA, even when the benefits to patient and the healthcare system are so great. He continues: 'What is the primary driver of this system-wide inefficiency and cost? Most health care providers would agree that it is physician "mindset": higher physician reimbursement for HD than PD, and concerns about accessibility in a geographically vast country contribute to historically low use of PD in the U.S.' Does this sound familiar?

At the heart of this, and several others of the innovative Indian schemes, are Accredited Social Health Activists (ASHAs), who are mature members of village communities, usually women (there are 650,000 villages in India). Across the globe, the term Community Health Worker (CHW) has been adopted to identify a wide range of participants in comparable schemes [24]. The radical impact of these initiatives relates to *decentralisation*: a substantial fraction of diagnostic and treatment services are removed from institutions (primarily urban) and from centralised professional monopoly, dispersed, and placed firmly in the middle of everyday, neighbourly life. Regulators and PV centres have not begun to react to these imperatives of dispersal and decentralisation, in spite of the presence of regional centres in some places (under threat as some of them are), especially, to the genius of local people on the ground as agents of change.

[17] Govindarajan V. Telemedicine can cut health care costs by 90 %. *Harvard Business Review*, April 23, 2012.

Sundar Subramanian et al. make the point vividly in a recent article in the *Harvard Business Review* [25]:

> In a few years, the idea of receiving medical treatment exclusively at a doctor's office or hospital will seem quaint. Wearable technologies, implanted devices, and smartphone apps allow continuous monitoring and create a ubiquitous, 24/7, digitized picture of your health that can be accessed and analyzed in real-time, anywhere. Data gathering isn't the only force moving treatment out of the doctor's office; telemedicine, home diagnostics, and retail clinics increasingly treat patients where they live and work. In the next decade, these trends will create a veritable gold rush in patient data and consumer options.

This enthusiasm for the new does not imply accepting all innovation without reservation. As far as possible, we need to be sure that new devices or new processes do not cause new problems. Agile development (especially persistent engagement with end users) helps to avoid the worst consequences; constant monitoring and impact assessment are critical processes; multiparty discussion and review may help reduce the risk of unforeseen consequences. But we must not doubt that slow evolution alone will never solve problems, especially intractable ones.

How long does it take for a reported ADR to reach its destination, be logged and assessed, compared, matched and to result in some useful outcome for patients and professionals? Well, you know: it's months rather than weeks, and sometimes years (see references v and vi). Not entirely agile.

When will pharmacovigilance feature in this brave new world of dynamic progress and innovation?

Reflection *Rapid, accessible diagnostics and treatment are dispersed in the field, onto the streets where people live, in multi-partner enterprises where the locus of meaning is in the hands of the people who need them in the furthest corners of the lands where such systems exist; pharmacovigilance remains a specialised, exclusive centralised activity, slowly and inexpertly transmitting top-down messages to other experts and to largely unknown and invisible (and indifferent) public audiences. Future sources of medicines and safety data and information will lie in dispersed communities where patients and health professionals are engaged in active and innovatively disruptive healthcare systems, supported by the best technology; effective communication will arise from the availability of comprehensive, tailored resources, perfectly matched in content and delivery channel to the immediate needs and priorities of health workers, other intermediaries and patients, in any location, at any time.*

9.6 The Wisdom of Crowds

Another remarkable innovation is CrowdMed: the website where patients with complex and unresolved diagnoses can put their case before potentially hundreds of health professionals and other patients (the site's 'detectives') for software-distilled commentary and suggestion. It appears to deliver good results in very difficult

cases.[18] [26] A patient says, 'I can't thank the founders of CrowdMed enough. After years of struggling and living in terrified uncertainty, I actually have a diagnosis and am beginning treatment.' This remarkable project reminds us of three truths, uncomfortable for the medical establishment (and bureaucracies): individual physicians (or officials) don't and can't know everything and do make mistakes; the collective experience and intelligence of crowds can deliver superior solutions across the spectrum of many human problems and dilemmas; dispersed communities of people with common interests (e.g. disease-specific organisations) will have definitions of problems, solutions, and priorities that are different from those of experts, officials and others who spend their lives proposing solutions from centralised locations remote from domestic front doors.

Reflection *CrowdMed relies on the collective genius of concerned and dispersed individuals to solve complex problems; pharmacovigilance struggles from the centre to animate crowds who are distant and largely indifferent. The future of communications in pharmacovigilance must be determined by the collective intelligence and priorities of the people who are the intended beneficiaries and by their playing a central part in the process.*

9.7 Social Care in the Netherlands

Buurtzorg[19] has revolutionised home health and social care in the Netherlands since 2006. From small beginnings, the organisation now employs over 6,000 staff, mainly nurses, in 580 self-managing teams (*no managers*), caring for more than 70,000 patients. It's a lean organisation with about fifty back-office staff and an almost flat hierarchy. The scheme's purposes were to improve care, reduce costs and help patients to achieve or regain independence and increase staff and patient satisfaction. By all those criteria, Buurtzorg has been an immense success. It is now being imitated in the USA, Japan and other places. Its genius in that it tosses into the air old concepts of fragmented delivery of care and of how workers in the field should be managed.[20] In its conceptualisation and implementation, it is focused exclusively on the *job-to-be-done*, as described in the next section.

[18] 'Of the several hundred cases that have already gone through this process, approximately 80 % of the patients we've contacted have reported their top diagnostic or solution suggestions to be accurate. In addition, over 50 % of our patients report that their CrowdMed results brought them closer to a correct diagnosis or cure – and these patients had already seen 8 doctors, been sick for 8 years, and incurred over $55,000 in medical expenses to date, on average' (https://www.crowdmed.com/faqs).

[19] See Gray et al. [27].

[20] 'How do you manage professionals? You don't!'; in, K. Monsen and J. de Blok, 'Buurtzorg Nederland', *American Journal of Nursing*, Aug. 2013 113(8):55–59.

Reflection *Buurtzorg provides superior care in a notoriously fraught and complex field by throwing aside all the traditional concepts of social care delivery and staff management; pharmacovigilance continues to do what it has always done in using historic methods of management, decision-making and delivery. The future of communications in pharmacovigilance will be participation in the delivery of comprehensive, integrated information and data, relating to a patient's entire health needs and priorities, to support one-stop consultation and decision-making at the point of need.*

9.8 The Job-To-Be-Done: Does the User Know Best?

Henry Ford is reputed to have remarked: 'If I asked customers what they wanted, they would have said a faster horse'. Were providers limited entirely by the imaginations of their customers and users; there would be little progress and no disruptive innovation at all. (Buurtzorg is a good example: patients would have been able to express the kind of social care experience they might dream of, but they would probably not have been able to conceptualise a radical, organisational solution to fulfil their hopes.) Great innovations and breakthroughs often take place far beyond the current wishes, needs or expectations of the public (electricity, telephony, cars and iPhones are four potent examples of this truth). On the other hand, a provider who does not pay attention to users' and customers' opinions about existing products or services, or their 'help wanted' signals, is very quickly likely to go out of business or lose influence and credibility entirely. (Kodak and Woolworth are two examples from that other parallel world. Pharmacovigilance hasn't exactly gone out of business, but neither has it captured the imagination of the world.)

Another of Christensen's inspired concepts is the *job-to-be-done*, that is to say identifying exactly what it is a user wants to achieve with a product or service. This often demands a radical reappraisal of established manufacturing, planning and marketing practices. The classic, oft-quoted example in the literature refers to the customer who buys or hires a 5 mm drill: the job-to-be-done is not the acquisition of a pretty 5 mm drill but *the making of 5 mm hole*. Christensen says that for manufacturers, traditional demographics (age, sex and so on) are more or less a distraction because they give you only characteristics associated with the purchase, not a causal link. Users seek a drill or a newspaper or patient information not because they are young or old, rich or poor, or male or female, nor necessarily because they want or like what is actually provided but because they have a job-to-be-done; they will take the resource most approximate to their needs. In traditional (and complacent) markets, many users are actually underserved and therefore mildly (even very) dissatisfied, certainly less than wholly satisfied (this is true of public assessment of medicines safety information[21]). When resources for the job-to-be-done are not adequate, users find workarounds or compromises or multiple methods for meeting their requirement.

[21] For example, Abubakar et al. [28].

The customer as a segmented individual is the wrong unit of analysis; it's the job-to-be-done that rules the day and that is stable through time, while the customer and the technology are ever changing. (Segmentation plays a part only in as much as individuals will have differentiated needs in relation to the application of the solutions for the common job-to-be-done: literacy, mobility or visual acuity would be three such categories.)

So what is the job-to-be-done for PV? In the words of the vision of Uppsala Monitoring Centre, 'a world where all patients and health professionals make wise therapeutic decisions in their use of medicine' [29]. That means having the best, up-to-date evidence and information about medicines or procedures, and alternatives to them, available at the point of need, in forms that are exactly tailored to the preferences and abilities of each patient and their health professional. Because the wisdom of PV is only one element in the total world of medicines information, the job-to-be-done is also one of purposeful collaboration with many other parties in ensuring that patients and professionals can have a single, authoritative, credible source of contemporary information and guidance in multiple, accessible formats. That's my formulation of the job-to-be-done, but that is not based on asking a few million patients and health professionals across the world who are the ones who really know what they want. Only when we've asked them can we be sure.

It's disruptive innovators (who may be established entities) who come along with products or services that perfectly serve the job-to-be-done and remedy the extent to which users previously felt underserved that sweep the board – for a time, at least. It happened with retail grocery, computers, cars and – one of the great disruptive innovators that has held its ground for decades – IKEA. IKEA doesn't so much sell furniture, as it sells a one-stop solution to the job-to-be-done of equipping and furnishing an empty flat or house at low cost, though it fulfils many other needs too.[22]

Disruptive innovation is less likely to come from the boardroom or the senior management meeting than it is from a free-thinking staff or outsider group, which can, in some favourable circumstances, be within an existing organisation. The greatest innovatory organisations have an open, collaborative, cross-disciplinary, liberal, risk-taking culture, in which failure is tolerated (even rewarded[23]), where ideas are treasured and pursued. Corporations and bureaucracies are too steeped in

[22] If, as IKEA's head of sustainability recently asserted, the appetite of Western consumers for home furnishings has reached its peak, the company has to envisage a radical new strategy to maintain its dominant position. See Guardian Live Event, 14 Jan 2016, http://www.theguardian.com/membership/audio/2016/jan/14/is-business-action-on-climate-change-believable-guardian-live-event

[23] 'For instance, a large advertising agency awards a quarterly Heroic Failure trophy to recognize clever, unproven ideas that may not work out in practice but nevertheless demonstrate creative risk taking. And an online payroll provider offers $400 to the winner of its Best New Mistake Award, which goes to an employee who made a mistake but learned from it—and, in doing so, helped other employees avoid similar mistakes. The idea behind both awards is to support creativity by encouraging openness about errors and rewarding those who genuinely learn from their failures' (Accenture, see credit in boxed text, p. XX).

the daily processes and tasks of their history and are too preoccupied with maintaining business as usual from day to day to disrupt anything. They are too firmly attached to data and evidence which, as Christensen points out, relate only to the past and tell you little about the present and next to nothing about the possibilities of a radically different future. An obsession with data and evidence is, in some manifestations of its influence, highly inhibiting and retrogressive.

Reflection *CrowdMed, Buurtzorg and Apple (to date) all have vivid and relevant definitions of the job-to-be-done that their users hold most dear (or realised that they held most dear when they were given the choice); everything they do is focused on helping users to achieve their job-to-be-done in the most effective way and to extend their conception of what is possible. Pharmacovigilance has no clear definition of the job-to-be-done and finds itself buried in processes that might or might not serve some vague goal of patient safety but lack entirely specific, practical and immediate focus. The real job-to-be-done in pharmacovigilance is actually very simple, but it has been elaborated, corrupted and bureaucratised to the extent that it can hardly walk, let alone fly.*

The point of adducing these examples is to show the discontinuities of innovatory solutions from established practice: disruptive innovation demands abandoning 'the way we do things round here' and challenging vested interests and habits, intellectual, professional, bureaucratic and commercial.

9.9 Where Does All This Leave Us?

If pharmacovigilance is to deliver on its promise – and it's a grand and important promise (see p. XX above) – the whole enterprise has to be transformed. It has to be moved out of smug centralised bureaucracies and dispersed among those who care about it and will benefit from its insights and revelations, supported by often simple but radical technology. The balance of power must be equalised among all those whose health and safety depend on good information and good decisions and on those who can help them maintain and regain them. It must be subject to radical disruptive thinking and action.

Above all, we must define the job-to-be-done, clearly and boldly, and then shape our activities and systems to deliver that swiftly, efficiently and, in the modern world, cost-effectively. And what is the job-to-be-done in terms of the wishes and needs of the people pharmacovigilance should serve? We need to answer that by a conscientious decision about what we regard as the reason for the existence of pharmacovigilance and through penetrative investigation of what patients and health professionals really want and need. I can make an offer (see above, p. XX), but that simply represents the same corrupting process I have been criticising throughout this article. Who on earth am I, a writer and lecturer in communications, to say what the job-to-be-done is for the patients and health professionals of the world?

9.10 What I Will Say Is This…

In the core pharmacovigilance activity of reporting ADRs and drug safety concerns in general, how are we doing? Two thoughts: first, at he time of writing, there are 11 million individual case safety reports in the WHO database, VigiBase; sounds great, eh? Well how about this: Eleven million reports divided by 40 years of collection, further divided by 120 member countries of the WHO Programme: 11,000,000/40/120 = average total of 275,000 reports per year over 40 years or 2,291 reports per country. World population: 7,300,000,000 (Sept 2015) [30]; 1 report per 20,500,000 persons in the world per year. Number of prescriptions filled in US pharmacies in one year: 4,002,661,750 (2014) [31]. How are we doing? (This is very crude aggregating and averaging, but the figures are not, in themselves, misleading.[24])

I can't prove that reporting methods are exclusively to blame for this lamentable performance (and they may not be). However, looking around the world, I can see a few reporting apps and web-based reporting sites, but I can see an enormous volume of paper forms churned out on all continents (most of them lying around neglected). Completing badly designed, complex, black and white paper forms is probably not the favourite activity of most rational, sentient and busy people in the world. It does not encourage the quality of information that would raise the system beyond mediocre. I have been saying this for twenty years in teaching, articles and books (and not just me) – with, as far as I can judge, little effect in many places and no effect at all in most. Bureaucracies continue to do what they've been doing since their beginnings with little or no attention to what is happening in the outside world, the results of research, or common sense.[25] The ADR reporting system doesn't work; it needs fixing.

9.11 Medicine and Pharmacovigilance

Historically, innovations in medicine have taken many years to become accepted into routine practice (clot-busting drugs and CAT scans in stroke care are examples), and there is still strong organisational and professional resistance to change. However, technological advances, especially home-monitoring platforms, are

[24] From very small beginnings, the annual number of reports has been on a rising graph, with great increases in recent years. The figures quoted do not reflect this improving trend over time, but the aggregate historic averages are correct. [The number of reports in VigiBase will be substantially higher by the time you read this.]

[25] The WHO's extant guidelines for setting up a PV centre, published in 2000, have, as item number two in the list of activities: 'Design a reporting form … and start collecting data by distributing it to hospital departments, family practitioners, etc.' There is no commentary or suggestion that there might be other ways of doing the job (WHO: Safety Monitoring of Medicinal Products 2000).

opening up radical new possibilities of all kinds (including cost-saving) that are irresistibly driving new ways of doing things. The patient safety movement has made great strides in recent years, too, though the gap between vision and reality is still large.

All around us, the world is changing. Fleet-footed, agile processes and technologies are occupying more and more of our attention and providing more and more benefits. We all recognise when suppliers fall short of best contemporary standards, and we are impatient with those that fail to keep abreast and deliver the goods and services we want in the ways we expect. If pharmacovigilance were ever subject to that kind of scrutiny, it would not win many medals.

How does pharmacovigilance practice measure up to what is happening elsewhere in the field of medicine and society? Does pharmacovigilance seem quaint and irrelevant or dynamic and vital? There doesn't seem to be much doubt. Who's going to rescue it?

We must.

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Chapter 10
Pharmacovigilance Indicators: Desiderata for the Future of Medicine Safety

Ambrose O. Isah and Ivor Ralph Edwards

10.1 Introduction

10.1.1 Historical Perspective

The thalidomide tragedy highlighted an unacceptable harm and potential risks of taking medicines [1]. This resulted in a global resolve that such a tragedy should never occur again, and all machinery to achieve this was put in place in the more developed countries in a rather systematic manner. This initial and prompt response ultimately resulted in the establishment of the WHO Programme for International Drug Monitoring (PIDM) schemes [2]. The initial focus was on suspected adverse drug reactions however over time the scope broadened to include other medicine-related problems. The occurrences regarding issues on medicinal safety after the thalidomide experience underscore the need for continuous watchfulness. The nomenclature has become more embracing and issues bordering on medicines safety coined "pharmacovigilance."

10.1.2 Definition and Scope of Pharmacovigilance

The operational definition of pharmacovigilance is "the science and activities relating to the detection, assessment, understanding, and prevention of adverse drug reaction and any other drug-related problems" [3]. The scope covers and is not

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limited to adverse drug reactions, medication errors, substandard spurious, falsely labeled, falsified and counterfeit medicines (SSFFCs), as well as reported cases of lack of effectiveness of medicines, misuse/abuse of medicines, and drug–drug interactions. The product concerns include medicines, conventional, alternative and traditional medicines, vaccines, biosimilar, etc.

The set-up of the fundamentals to enable operation of the established discipline of PV including definition of terms/terminologies with the development of the World Health Organization Adverse Reaction Terminology (WHO-ART), Medical Dictionary for Regulatory Activities (MedDRA), and an expansive drug safety dictionary enable a universal language [4–6]. The development of processes from the simple reporting form to submission of suspected adverse reaction case reports, causality assessment, signal detection, and confirmatory/validation procedures including the use of data mining by Bayesian probabilistic methods has enabled deductions to be made from the various pharmacovigilance activities. Furthermore, the development of technologies such as standard tools including a case management system, the VigiFlow, the continuous refinement of the search, and statistics into the versatile VigiLyze buttresses the extent of the sophistry and growth of Pharmacovigilance. There are now 124 Full Members and 29 Associate Members of the PIDM, and the global database (VigiBase) now hosts over 13 million ICSRs.

Despite this tremendous trajectory of growth in over 60 years with improved and sophisticated science and technologies, there has been until recently a gap in pharmacovigilance metrics for assessing, evaluating, and monitoring its status, growth, and impact. The burden presented to the health care system is enormous as illustrated by the findings in the USA [7] identifying adverse events to medicines as a leading cause of morbidity and mortality further buttressed by Pirmohammed et al [8] in the UK. The enormous cost of drug-related problems such as hospitalization, prolonged hospital stay, emergency department visits, and indeed the entire management cost the US over $30.1 billion annually [9].

This growing realization of the adverse social and economic impact of drug-related problems further underscores the need to provide objective indices to monitor pharmacovigilance activities and outcomes.

10.1.3 Rationale for Indicators

The rationale for the development of metrics to enable assessment, evaluation, and monitoring of the PV structures, processes, outcome, and impacts could be outlined as follows:

To serve as metrics which at a glance provide the pharmacovigilance, landscape of a given setting and provides information on the activities of the various stakeholders making input to pharmacovigilance processes. They enable the identification of weaknesses within the PV system thus allowing for appropriate intervention. They further provide the tool to monitor the changes enabling tracking of the progress, growth, and trends. While the main objective is not for comparison between

settings, the indices allow for critical observations to be made within a given setting as well as inferences to be made between settings so as to further identify crucial factors at play in the pharmacovigilance system. These knowledge aid stakeholders to measure their performance and motivate them to a desired goal.

During the early period of pharmacovigilance as alluded to above not much attention was paid to development of metrics for assessment of performance within the system. One of the earliest comprehensive attempt towards this objective was the comprehensive assessment of the European Community System of Pharmacovigilance detailed in the publication by the Fraunhofer Institute Systems and Innovative Research Karlsruhe, Germany, in collaboration with the Coordination Centre for Clinical Studies at the University Hospital of Tubingen, Germany. The Fraunhofer survey and report devoted some significant aspect of their work to suggesting some metrics to serve as critical success factors and also as performance indicators. Despite this, the use of PV indicators at a more global level was not pursued further until recently.

10.2 The Pharmacovigilance System

In order to provide indices for the assessment of PV activities in any setting, a comprehensive understanding of the pharmacovigilance system is imperative. Since inception, and to a large extent currently, the pharmacovigilance system is based on the spontaneous reporting of suspected adverse drug reactions. Initially passive and voluntary, reporting was by healthcare providers and via the pharmaceutical industry; over the years, various other methods have been put in place to encourage reporting of adverse reactions/events. Measures to stimulate reporting to active pursuit of adverse events (such as intensive monitoring, cohort event monitoring, targeted reporting) are now accepted as desirable steps to obtain information of the safety profile of medicines. Again, the reporting sources have been broadened to include not only doctors but also pharmacists, nurses/midwives, and now patients/public-consumer while still maintaining the industry as a mandatory reporter in most instances. This constellation of stakeholders, including the corporate bodies of the National Pharmacovigilance Centres, the National Regulatory Agencies and other well-established agencies such as the US FDA, the EMA, and WHO Collaborating Centre at Uppsala (UMC), constitute a holistic system interacting in an articulate manner in the handling of medicines safety issues.

The Fig. 10.1 highlights the elementary processes of identification of suspected drug-related problems, the collection, collation, and initial analysis and storage of the data. This is followed up by more focused and sophisticated reviews as the data move into and up the ladder with handling by specialized levels of expertise and technologies. The detection, causality assessment, and validation/confirmation of signals are outcome. The positioning of an elaborate management of identified risks and its prompt communication and management ensures that the entire process produces an outcome related to the primary objective of pharmacovigilance which impacts on medicine/patient safety.

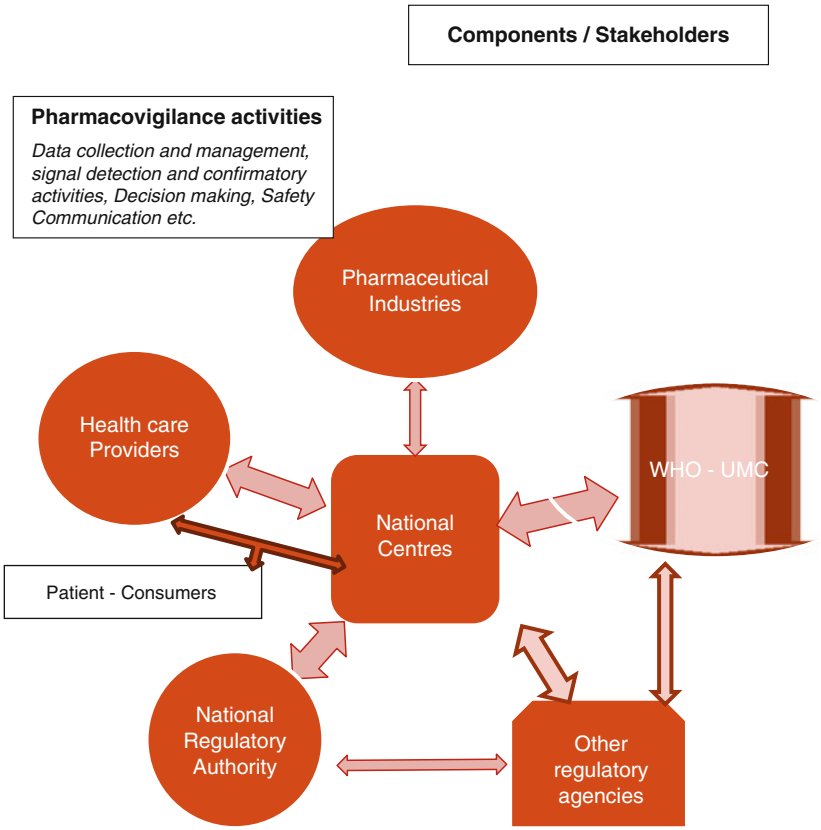

Fig. 10.1 Diagrammatic representation of the Pharmacovigilance System

10.3 The Indicators

10.3.1 Definition

An operational definition of indicators entails measures that would allow the evaluation of baseline situation and the progress made in given systems during assessment of services and interventions. Pharmacovigilance indicators are implicitly tools which provide these indices for the evaluation and assessment of the pharmacovigilance system. They measure the inputs, processes, outputs, and outcomes/impact as it relates to the system.

10.3.2 Characteristics of an Ideal Indicator Set

The problem that constantly plagues sets of indicator is the apparent lack of use by the target group or stakeholders for whom it was intended. Some of the reasons adduced for the poor or nonutilization are attributed to the complexities of the

indices. An ideal indicator set should have the attributes that will ensure its use and integration into the routine pharmacovigilance subsystem. It should be easy to measure, understand, and interpret as well as inexpensive to obtain. The indicators should not require too high a level of expertise to establish and put into use and should be reproducible irrespective of the investigator. It is important that the indicators are sensitive enough to detect PV problems needing attention and sufficiently robust to serve as an efficient monitoring tool.

10.3.3 The Process of Development of the Indicators

During the early period of pharmacovigilance as alluded to above not much attention was paid to the development of metrics for assessment of performance within the system. One of the earliest comprehensive attempts towards this objective was the comprehensive assessment of the European Community System of Pharmacovigilance detailed in the publication by the Fraunhofer Institute Systems and Innovative Research Karlsruhe, Germany, in collaboration with the Coordination Centre for Clinical Studies at the University Hospital of Tubingen, Germany [10]. The Fraunhofer survey and report devoted some significant aspects of their work to suggesting some metrics to serve as critical success factors and also as performance indicators. Despite this the use of PV indicators at a more global level was not pursued further until recently. Other efforts to establish comprehensive PV indicator sets developed in the last decade include the following:

- European Society for Quality in Health care (Office for Quality Indicators, Arhus Denmark) [11]
- Kshirsagar NM, Olsson S and Ferner RE Paper in International Journal of Risk and Safety in Medicine [12]
- The MSH-USAID Indicator-based Pharmacovigilance Assessment Tool (IPAT) [13]
- WHO Pharmacovigilance Indicators [14]

Some pharmacovigilance assessment metrics may be found in Regulatory Assessment Check Lists. These are usually of a different format and not comprehensive for pharmacovigilance facilities. Others are now found in pharmacovigilance inspection metrics, which may focus on MAHs to the exclusion of processes involving other PV stakeholders/components.

There are other plans by regional bodies such as countries under the WHO PAHO umbrella and the East African Regional Community to select some indicators considered appropriate for their needs. The French Health system has introduced a set of indicators to evaluate its PV activities in its facilities.

In the last 5 years, two set of indicators have gained prominence notably the Indicator-based Pharmacovigilance Assessment Tool (IPAT) [13] and more recently the WHO Pharmacovigilance Indicators [14]. It is also of interest that some of the metrics have been used for regulatory assessments and the IPAT have been used to study pharmacovigilance systems in some African and Asian countries [15].

In this chapter, I will further elaborate on the process of development of the WHO indicators with some mention of the IPAT. The WHO indicator set was developed from the perspective of National Pharmacovigilance Centres and focused on the need to provide a self-assessment tool within the context of PV facilities. The IPAT entails more of a system-wide approach and may require some expert guidance for application.

10.4 The WHO Pharmacovigilance Indicators

The concept of developing WHO Pharmacovigilance (WHO PV) indicators was crystallized in Accra, Ghana, during a meeting of Pharmacovigilance Experts from Africa (later coined *PVSF – Pharmacovigilance sans frontier*) in 2007 under the auspices of the WHO Geneva and the Uppsala Monitoring Centre, Uppsala, Sweden. The indicators were developed by a consensual approach involving the above-mentioned African PV experts, the National Pharmacovigilance Centres, following the policy layout and direction by the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP). This was followed by a systematic assessment of the pharmacovigilance system noting the key elements in the structure, processes, and outcomes/impact which should be evaluated. The approach followed by other WHO indicator manuals [16–18] was put in context and findings from literature notably the landscape study by Olsson et al [19] further identified key processes in PV activities, and this led to identification of candidate indicators which further populated the indicator set. Reference was also made to the Australian Therapeutic indicator schema [20]. The candidate indicators were scrutinized in-depth by national centers and the members of the PVSF in the processes of selection and categorization of the indicators. The validation of the indicators was carried out by pharmacovigilance experts.

The IPAT was similarly developed by an initial literature search to identify candidate indicators. Elaborate effort was made to avoid repetition of indicators noting their sources and providing assessment questions. There was a further need to identify areas not covered by the indicator set initially obtained and addressing it appropriately. This was followed by the Delphi method using a 15-member group. The output of the final round was reviewed by external Experts.

10.4.1 The Classification of the WHO PV Indicators

There are a total of 63 WHO indicators (Table 10.1) further classified into three types: Structural (21), Process (22), and Outcome/Impact (20). An additional 11 items concerning background information (Annex 10.1) for the setting are provided to give a clear picture of the environment where the assessment is being carried out.

Each of these types is further categorized into two: Core (total 27) and Complementary (total 36). Core indicators (C) are those considered to be highly relevant, important, and useful in characterizing pharmacovigilance, while

Table 10.1 The classification and disposition of the WHO Pharmacovigilance Indicators

	Category		
Types	Core	Complementary	Total
Structural	10	11	21
Process	9	13	22
Outcome	8	12	20
Total	27	36	63
Public health program	NA	NA	9
Background Information	NA	NA	11

Complementary indicators (T) are those additional measurements considered to be relevant and useful. They serve to further characterize the pharmacovigilance situation in the stated setting but need not be used in all instances.

In essence, there are six headings of indicators: Core Structural, Complementary Structural, Core Process, Complementary Process, Core Outcome/Impact, and Complementary Outcome/Impact. The detailed outline and list of Core indicators are shown in Annexes 10.2, 10.3, and 10.4. The Complementary indicators may be obtained from the manual [14] or using the link provided.

In view of the importance of public health programs, a few indicators are selected across the spectrum of structural, process, and outcome/impact indicators.

10.4.2 The Background Information

The background information (Annex 10.1) include those on demographics, economics, health care system, and pharmaceutical scenario, thus describing the milieu where the pharmacovigilance activities are taking place and other factors likely to impact on them. The data obtained here also serve as the denominators for the indices. The dynamics of the components incorporated in the background information must be clearly understood since this affect the pharmacovigilance landscape to a large extent. The socio-demographic parameters are constantly changing, influencing the age and gender structure of the population which in turn determine the pharmaceutical scenario – the therapeutic category and class of medicines' distribution and use, the level of health facilities, and the personnel disposition. The profile of the adverse events depends significantly on these developments.

10.4.3 The Structural Indicators

The structural indicators (Annex 10.2) assess the existence of key pharmacovigilance structures, systems, and mechanisms in the setting. They assess the elements which give visibility to pharmacovigilance – the presence and availability of basic

infrastructure required to enable pharmacovigilance operations. They also assess the available human resources whose work guarantees the operation of the PV facilities. They assess the existence of an enabling instrument in the form of a policy, legal, and regulatory framework for pharmacovigilance to operate. The provision of adequate funding to ensure sustenance of structure and function is paramount. The pharmacovigilance establishment must be seen to be financially independent and its integrity untampered with by vested interest. This is essential to maintain credibility of any output from the facility. The indicators here also assess the communication strategies in place which ensure the dissemination of processed information, its vital output. The responses required are essentially qualitative in nature, indicating presence or absence of the parameters.

10.4.4 The Process Indicators

The process indicators (Annex 10.3) assess the entire mechanisms and degree of pharmacovigilance activities. They measure directly or indirectly the extent to which the pharmacovigilance system is operating. The dynamic and interactive activities determine to a large extent its output and ultimate impact. The set of process indicators measures and informs of the tempo of pharmacovigilance activities, and the information obtained in the short or long term allows for prompt and appropriate intervention, which may be corrective to achieve the desired goal.

10.4.5 The Outcome/Impact Indicators

The outcome/impact indicators (Annex 10.4) measure the effects (results and changes) of and due to pharmacovigilance activities. They accommodate both short-term and long-term effects and the trends observed in the course of pharmacovigilance operation. They are of utmost importance since they serve as tools for advocacy to persuade policy makers, health managers, and other stakeholders regarding allocation of resources. They measure the extent of realization of the pharmacovigilance objective, which in essence is ensuring patient safety. The focus of the impact of PV is definitely on efficient and safe use of medicines.

10.4.6 The Indicators for Public Health Programs

The establishment of public health programs to address the burden of HIV/AIDS, malaria, tuberculosis, leprosy, schistosomiasis, filariasis, and intestinal helminthiasis, etc., with the supply of medicines by partners, has made significant impact

on the health status of persons in the resource-limited settings of Africa and Asia. Usually the medicines are deployed in large quantities to a large population. In this situation, the interplay of many factors determines the eventual outcome. Notably the medicines are comparably known to be more toxic, administered by low-level health personnel with meager facilities and resources for supervision and in weak PV systems.

The spectrum of indicators span across the structural, process, and outcome and are limited to nine to serve as metrics for what is obtaining in these programs (Table 10.2). The indicators enable assessment of the PV setup, operations, and focus while ensuring early detection of harm. This early warning is so paramount here since any delay can cause irreparable harm. The checklist of the WHO PV indicators has been used for self-assessment by a number of countries, and plan for a comprehensive development of a web tool and database to enable continuous monitoring is being considered.

Table 10.2 The public health program indicators

#	Assessment questions
PH1	Are pharmacovigilance activities in place within the public health program (PHP)?
PH2	Do all main treatment guidelines or protocols in use within the PHP systematically consider pharmacovigilance
PH3	Is there a standard ADR reporting form in the setting?
	PH3a: are there relevant fields in the standard ADR form to report suspected medication errors?
	PH3b: are there relevant fields in the standard ADR form to report suspected counterfeit/substandard medicines?
	PH3c: are there relevant fields in the standard ADR form to report therapeutic ineffectiveness?
	PH3d: are there fields in the standard ADR form to report suspected misuse, abuse and/or dependence on medicines?
PH4	What is the total number of ADR reports collected within the PHP in the previous year
PH5	How many ADR reports (per 1000 individuals exposed to medicines in the PHP) were reported in the previous year?
PH6	How many reports on therapeutic ineffectiveness were made in the previous year?
PH7	What percentage of completed reports were submitted to the national pharmacovigilance center in the previous year?
	PH7a: Of the reports satisfactorily completed and submitted to the national pharmacovigilance center, what is the percentage of reports committed to the WHO database?
PH8	What is the number of medicine- related hospital admissions per 1000 individuals exposed to medicines in the PHP in the previous year?
PH9	What is the number of medicine- related deaths per 1000 individuals exposed to medicines in the PHP in the previous year?

10.5 The Indicator-Based Assessment Tools (IPAT) from the MSH-USAID [13]

The indicator-based assessment tools (IPAT) set has 43 indicators (26 core and 17 supplementary). These are classified into five components which include the following:

Policy, law, and regulation; Systems, structures, and stakeholder coordination; Signal generation and data management; Risk assessment and evaluation; and Risk management and communication. They are further classified based on the product they are measuring into structural, process, and outcome indicators: Structural: measures systems and physical infrastructures; Process: measures how the pharmacovigilance system works; and Outcome: measures the final product of all the inputs into the pharmacovigilance activities.

Indicators are again classified based on importance or how essential they are to a functional pharmacovigilance system. The Core indicators are those regarded as the most essential, while the others fall into the Supplementary.

The System for Improved Access to Pharmaceuticals and Services (SIAPS) program have carried out preliminary comparative analysis of pharmacovigilance systems in some African and Asian countries [15].

10.6 General Limitation of Indicators

There are however some limitations to the use of the available indicators. The indicator set does not capture in detail the spectrum of function for the structural indicators where the qualitative response is dichotomous. For instance, the issues relating to funding does not allow for the level to be determined. This implies that a follow-up question should be provided so as to obtain a more comprehensive information. However, the weighting and quantification scoring scheme envisaged for the WHO PV indicators will address this problem.

The level of difficulty in obtaining the values for the outcome indicators are noted but in the circumstance appears unavoidable. The healthcare system should provide the necessary support so as to obtain these data. The IPAT pays less emphasis on the outcome/impact indicators.

Further details of the activities regarding the industry and the traditional medical practitioners may need to be provided to complement pharmacovigilance assessment. There may be need to appropriately position the use of these sets of indicators in the pharmacovigilance subsystem in a harmonization process so as to ensure appropriate comparative analysis of systems, exchange of data, and guidance.

10.7 Discussion (Road Map for the Way Forward)

The development of indicator sets for the monitoring and evaluation of PV systems have been introduced into this health subsystem to enable some watchfulness regarding the safety of medicinal products. The indices ensure the early detection of

any deficiency or defect in the "structural" or enabling instruments or aberrations in the relevant activities. The presence of a viable space and standard accommodation, an enabling political and legal environment provided for by law goes a long way to offering the protection required for PV outfits to carry out their sensitive activities which have far reaching consequences resulting from their decisions. The policy and legal instruments protect the decision-making process and also enables appropriate intervention in and to some extent outside the PV subhealthcare system. The indicators capture the need for the sustainability of PV systems ensuring that adequate funding is provided for its activities and that the human resources are available to render the required services. The communication strategies must be efficient to enable the system reach other stakeholders and the consumer public with appropriate information in the safe use of medicines.

The timely detection allows for intervention and rectification of untoward developments. Another useful application of the indicators is the information obtained from changes in trends from continuous monitoring process which again alerts the system to some developments which may either be positive or negative. In the former instance, the development provides information to allow for re-enforcement of the identified ongoing activities and for a replication in other settings, which may benefit from such measures. In the latter instance, there is a need to arrest the prevailing factors and where or when not identified to trace it systematically and limit or stop its influence.

The impact indicators are of tremendous value as a tool which provides valuable information regarding the safety of medicines. The signals generated in a PV system are early warnings – a wakeup call – for care regarding the use of a medicine. It is imperative that operators in the system are efficient and effective using available tools to detect the potential harm as was intended by the early workers and founding fathers of pharmacovigilance.

The other metrics in this category focus on the degree of harm caused by medicines – the morbidities and mortalities – and their monitoring allows for proper application of measures to reduce them. Again, the statistics obtained serve as useful tools for advocacy in building a case or justifying the allocation of resources to the appropriate sector for intervention to stymie the harm. When resources are allocated in adequate amounts and in a timely manner to ensure pharmacovigilance activities are effectively applied, there is a significant cost saving which for most times is not realized by health managers, policy makers, and other functionaries in government. From a futuristic perspective, it is intended that pharmacovigilance will promote the clinical care component of harmful effects of medicines in the health care system. The present operations focus on reported adverse events: the handling of these reports to determine causality or noncausality, decision-making, and communication strategies. The perception of risks and its management is pivotal to contemporary PV operations. However, this is not comprehensive or holistic from the patients' point of view who would rather wish the bad medicines are detected preregistration and not administered at inception and should an event occur, should be diagnosed immediately and appropriate treatment put in place. What are the legal implications of the occurrence? Any liabilities? On whose door step considering the chain of care.

The ability of indicators to monitor the performance of PV in this regard concerning patient safety and ensuring that the subhealth system achieves a favorable outcome will be the ultimate goal. Every indicator when well and rightfully interpreted has enormous value. A constellation of these indices measuring the existence of enabling structures and metrics measuring performance and impacts/outcomes would ensure an efficient and effective pharmacovigilance system. It is imperative that the culture of routine monitoring and evaluation be adequately integrated into the healthcare system with due consideration for the pharmacovigilance subsystem to ensure medicine and thus patient safety. The effective and efficient use of these metrics will enable the weak and fledgling systems in the LMICs to grow making reference to defined parameters, which would guide their trajectory.

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Annexures

Annex 10.1 Background information[a]

#	Assessment questions
BG1	Total population of the setting (country, region or facility)?
BG2	Sex and Age structure of the population?
	BG2a: Male:Female
	BG2b: Life expectancy
	BG2c: Dependency ratio
BG3	Total number of drug manufacturing units
BG4	Total number of pharmaceutical establishments
BG5	Total number of pharmacies and drug outlets
	BG5a: Public
	BG5b: Private
BG6	Total number of registered drugs (including all brand names)
	BG6a: prescription only
	BG6b: pharmacy sale only
	BG6b: general sale
BG7	Total number of medicines in the national list of essential medicines
BG8	What proportion of drugs are sold or obtained in the informal sector
BG9	Percentage of medicines that are counterfeit/substandard in the pharmaceutical market
BG10	Total number of hospitals and clinics
	BG10a: public
	BG10b: private
BG11	Total number of health professionals in each category
	BG11a: doctors
	BG11b: dentists
	BG11c: pharmacists
	BG11d: nurses
	BG11e: others

[a]To be obtained when assessing a setting with the WHO PV Indicators

Core WHO Pharmacovigilance Indicators

Annex 10.2 Core structural indicators

#	Assessment questions
CST1	Is there a pharmacovigilance center, department, or unit with a standard accommodation?
CST2	Is there a statutory provision (national policy, legislation) for pharmacovigilance?
CST3	Is there a drug regulatory authority or agency?
CST4	Is there any regular financial provision (e.g., statutory budget) for the pharmacovigilance center?
CST5	Does the pharmacovigilance center have human resources to carry out its function properly?
CST6	Is there a standard reporting form in the setting?
	CST6a: Are there relevant fields in the standard ADR form to report suspected medication errors?
	CST6b: Are there relevant fields in the standard ADR form to report counterfeit/substandard medicines?
	CST6c: Are there relevant fields in the standard ADR form to report therapeutic ineffectiveness?
	CST6d: Are there relevant fields in the standard ADR form to report suspected misuse, abuse and/or dependence on medicines?
	CST6e: Are there relevant fields in the standard ADR form to report suspected medication errors?
CST7	Is there a process in place for collection, recording and analysis of ADR reports?
CST8	Is pharmacovigilance incorporated into the national curriculum of the various health care professions?
	CST8a: Is pharmacovigilance incorporated into the national curriculum of medical doctors?
	CST8b: Is pharmacovigilance incorporated into the national curriculum of dentists?
	CST8c: Is pharmacovigilance incorporated into the national curriculum of pharmacists?
	CST8d: Is pharmacovigilance incorporated into the national curriculum of nurses or midwives?
	CST8e: Is pharmacovigilance incorporated into the national curriculum of others – to be specified?
CST9	Is there a newsletter, information, bulletin or website (a tool for pharmacovigilance information/dissemination)
CST10	Is there a national ADR or pharmacovigilance advisory committee or an expert committee in the setting capable of providing advice on medicine safety?

Annex 10.3 Core process indicators

#	Assessment questions
CP1	What is the total number of ADR reports received in the previous year?
	CP1a: What is the total number of ADR reports received in the previous year per 100,000 people in the population?
CP2	How many reports are (current total number) in the national/regional/local database?
CP3	What is the percentage of total annual reports acknowledged/issued feedback?
CP4	What is the percentage of total reports subjected to causality assessment in the past year?
CP5	What is the percentage of total annual reports satisfactorily completed and submitted to the national pharmacovigilance center in the previous year?
	CP5a: Of the reports satisfactorily completed and submitted to the national center, what percentage were committed to the WHO database?
CP6	What is the percentage of reports of therapeutic ineffectiveness received in the previous year?
CP7	What is the percentage of reports on medication errors received in the previous year?
CP8	What is the percentage of registered pharmaceutical companies have a functional pharmacovigilance system?
CP9	How many active surveillance activities are or were initiated, ongoing or completed in the past 5 years?

Core WHO PV Indicators (Continued)

Annex 10.4 Core outcome/impact indicators

#	Assessment questions
CO1	How many signals were generated in the past 5 years by the pharmacovigilance center?
CO2	How many regulatory actions were taken in the preceding year consequent on national pharmacovigilance activities?
	CO2a: how many product label changes (variation)
	CO2b: how many safety warnings on medicines to: CO2bi : health professionals CO2bii: the general public?
	CO2c: how many withdrawals of medicines?
	CO2d: how many other restrictions?
CO3	What is the number of medicine-related hospital admissions per 1000 admissions?
CO4	What is the number of medicine-related deaths per 1000 persons served by the hospital per year?
CO5	What is the number of medicine-related deaths per 100,000 persons in the population?
CO6	What is the average cost (US$) of treatment of medicine-related illness?
CO7	What is the average duration (days) of medicine-related extension of hospital stay?
CO8	What is the average cost (US$) of medicine-related hospitalization

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Chapter 11
Thoughts on Pharmacovigilance in the Future: There Are More Weber-Effects

Ronald H.B. Meyboom, Hubert G.M. Leufkens, and Eugène P. van Puijenbroek

Over the past few decades, pharmacovigilance, both in terms of execution, responsibilities, and decision making, has dramatically changed, i.e., from the individual vigilant doctor observing something *unexpected* in a patient and reporting this to his colleagues, to a scientifically and legally enforced *social system* [1, 2]. Today there are several ways for following up medicinal products after their introduction into medical and pharmaceutical practice, e.g., spontaneous reports, risk management plans, prospective safety studies, registries, and the like. Both the formal requirements of the science of pharmacovigilance and the legal marinade of handling drug safety by industry, authorities, and health care professionals have resulted in a critical transition of the drug safety scenery [3, 4].

Along with the establishment of the first pharmacovigilance centers and the gradual increase in the number of reports to be analyzed new methods evolved. It was not only the individual case report, including an hypothesis about a pharmacological mechanism and individual risk factors, which contributed to the signal, but also numerical information based on the analysis of such spontaneous reports became more important as well. Disproportionality analysis and time trends made their appearance, maneuvering with various statistical methods, but essentially contrasting the number of *observed* reports against an estimated number of the *expected*. But still the importance, and appreciation, of the well-documented and the comprehensive, clinically seasoned individual reporting never disappeared. The same holds

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for the attributed value of chemical structure and mechanism-based pharmacological thinking in pharmacovigilance [5, 6].

A landmark paper in the transition of pharmacovigilance towards more quantification has been the well-known analysis of Peter Weber in 1984, showing temporal patterns of adverse reaction reports in the United Kingdom regarding nonsteroidal anti-inflammatory drug (NSAID), i.e., a rise in the first few years after market introduction, followed by a decline [7]. This pattern has been repeatedly coined as the Weber effect, contrasting time trends of spontaneous reports and the dynamics of the market cycle of individual medical products, i.e., number of years since launch, exposure changes over time and reporting behavior of health care professionals, and later also that of patients and consumers.

Since Weber's original paper was published, various investigators have replicated this market effect on reporting behavior, while others did not. But apart from that, the key message that could be derived from Weber's paper was the observation that time trends of spontaneous reports are virtually never random. Any conclusion from such reporting systems should take into account the *social system* in which the reports are generated. Thereby, the concept of the Weber effect has been influential in many ways on how pharmacovigilance has been organized, legally enforced, and scientifically studied. A spontaneous report on a suspected adverse drug effect is never "alone." This in particular the case in the area of biologicals where drug action, underlying disease, and disease modification are very close [4].

11.1 Three Dimensions of Pharmacovigilance

For pharmacovigilance, "spontaneous monitoring" constitutes a backbone model, and within this context, a case report is defined as a notification from a physician concerning a patient and a suspected adverse reaction and is at the same time a clinical diagnosis, with a particular provisional suspect drug or interaction in mind. Over the years, pharmacists, nurses, and patients themselves have also contributed significantly to signaling suspicions concerning an adverse drug effect, but in the end clinical, pharmacological and epidemiological expertise is needed to frame and classify the adverse problem within the context of medical and pharmaceutical practice, science and rules of the *social system* in which pharmacovigilance operates.

Reasoning from this perspective, three major dimensions of pharmacovigilance can be distinguished.

1. *Medicine, medicines, and uncertainty: doing good to patients*

   The term medicine refers to medical practice as well as to enriching knowledge, experience, and skills. Since time immemorial, caring for patients has been connected with uncertainty and insecurity. Of very many treatments and interventions, the scientific evidence and knowledge are more or less incomplete or

inconclusive, and proof of efficacy and safety uncertain or even doubtful. While many diseases need prompt diagnosis and treatment, there is a constant struggle on how to reduce uncertainty in both. Medical decisions need skills, commitment, and responsibility and may unintendedly and unexpectedly lead to adverse outcomes. Such outcomes are inherently associated with both the art and the science of medicine.

2. *Monitoring, vigilance, and science: building the best evidence*

   The history of drug safety is full of examples where (new) medicines have sooner or later been found – unexpectedly and unpredictably – to be associated with harmful events. There is a constant need for thoughtful and systematic monitoring of medicines after they have been approved by regulatory authorities. Monitoring of spontaneous reports and systematic signal detection have been the impetus for formal scientific inquiries, enabling learning and evidence building about a suspected side effect. While vigilance and formal scientific inquiry are two sides of the same coin, both are different, in principle and in practice. Vigilance (alertness) is an integrated feature of the practice of medicine; scientific inquiry has many practice correlates, but focuses essentially on learning and knowledge gain.

3. *Regulation, industry, and legal system: ensuring public health*

   A critical feature of drug safety is the fact that roles and responsibilities of stakeholders, i.e. industry, authorities, and health care professionals, are heavily regulated in the context of a myriad of legal systems, both nationally and globally. While regulation essentially is designed to ensure public health, the way stakeholders take responsibility and fulfill their roles affects their behavior, governance, and decision making. Over the years, pharmacovigilance has left the "safe" environment of the individual doctor's ward and has become part of a *social system*, with all the inherent features of bureaucracy, control mechanisms, risk avoidance, and focus on compliance with legal procedures.

11.2 Another Weber Effect: "Iron Cage"

Traditionally physicians have always stressed, for quality of practice reasons, that pharmacovigilance should not be a sequential, but a cyclic system where systematic feedback mechanisms from the formal pharmacovigilance knowledge base into daily clinical practice results in less harmful care for patients. This means that pharmacovigilance, like any other system to enhance the quality in medicine, will blossom in an environment where all three dimensions flagged above are in a balanced fashion. For sure the practice of medicine, i.e. doing good to patients, will benefit from the best conceivable evidence building and an environment where stakeholders are enforced to comply with existing regulations and legal systems in place. Over the last decades, pharmacovigilance has become increasingly institutionalized. However, as another Weber, i.e. the German sociologist Max Weber, not "our"

Peter Weber, showed about a century ago institutions tend to become bureaucratic for the sake of efficiency, rational calculation, and control [8].

The current flow of institutionalizing pharmacovigilance has many good reasons, without any doubt. The history of pharmacovigilance has not really been a convincing account of great efficiency. This flow, however, also increasingly shows features of what Max Weber coined as an "Iron Cage" where procedures, precautionary dominance, compliance with the regulation, and legal enforcement become so commanding that solving a safety issue from a clinical, patient, or public health perspective is sometimes (even frequently) in danger. You do not need to be a believer of Weber's "Iron Cage" to witness the risks of the more or less automatic dynamics of institutionalizing an important societal activity as pharmacovigilance.

In Europe, the Fraunhofer assessment of the European community system of pharmacovigilance in 2006 has been influential in building a new legal system [9]. While we can be positive about the introduction of that new legal system in terms of setting clear objectives, tools, and regulatory guidance, we have also some concerns about the balance in the three dimensions mentioned before [3]. This is also seen in many other countries across the globe. Formal requirements for efficiency and scientific or legal reasons can go at the expense of the origins of pharmacovigilance, i.e., doing good patients and ensuring a better quality of pharmacological treatment.

Traditionally, pharmacovigilance has been envisaged as a two-way communication system, for health care practitioners and so-called pharmacovigilance "centers," learning step by step through listening to each other. If unusual and unexpected adverse experiences in patients were consistently similar and occurred without another more likely explanation, just a cluster of clinical observations constituted a substantial amount of evidence pointing to a connection: with a particular suspect exposure, medically plausible or not, and with or without a statistical backup.

The role of regional and/or national pharmacovigilance "centers" has always been very important in fueling signal detection and liaising with clinical practice. They are, and have been, also highly variable and sometimes rather unpredictable. The very fact that many of these centers have been often underresourced and undervalued – some were operating like a kiosk linked to a hospital ward or an academic pharmacy department – has caused ample concern about their sustainability and reliability when it comes to performance and credibility in times of a safety crisis.

The history of pharmacovigilance shows tremendous output and extremely useful "first signals" and tangible practice experiences generated by the early generations of these "pharmacovigilance centers" [10, 11]. In the early days of pharmacovigilance in countries around the world, drug regulation and drug monitoring were more or less simultaneously introduced. While drug approval and regulation were basically seen as a governmental activity, drug safety monitoring often also was a responsibility in which national medical associations played a role or even took initiative (e.g., Germany, The Netherlands).

11.3 The Way Forwards

It may seem doubtful whether the rather "romantic" view of pharmacovigilance past, i.e., the individual physician watching and listing carefully in candlelight to his patients in search for the unexpected, will have much of a future. As experience suggests, however, this practice may continue to be needed for highlighting drug problems that are otherwise hard to detect in an early phase. What will be of critical importance for a healthy future of pharmacovigilance is whether we can ensure a fruitful continuum between what is happening in daily medical practice and, more downstream, the myriad of formal systems of logging, recording, and reporting for various efficiency and regulatory reasons. This continuum has no "romantic" connotations, but is an essential building block for getting the best results in terms of evidence generation on drug safety and changing medical and pharmaceutical practice when needed [12, 13]. An open eye for new signals should more or less be a kind of natural starting point for those working with patients. Adverse drug reactions will present themselves as a clinical entity, driven by a variety of biological, physical, and psychological factors.

As such, pharmacovigilance should in general be part of a differential diagnosis that every physician should take into account. Thereby, we should also not forget that pharmacovigilance will depend very much on the way we will handle the resolution issue, i.e., too many pixels will blur the bigger picture (sensitivity), too few pixels will go at the expense of finding the right signal-noise ratio (specificity). The resolution issue is best served by a clear balance between the three dimensions coined before. That means also thoughtful clinical and pharmacological reasoning, the application of the best available scientific methods of signal detection, analysis, and aggregated database work. But also apart from such technical requirements, the basic concept of pharmacovigilance strongly embedded in medical practice needs continuous support. For sure, there is no way forwards for pharmacovigilance in an "Iron Cage."

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Chapter 12
Effective Treatment Matters: Revitalizing Pharmacovigilance

Emmanuel Obi Okoro

12.1 Preamble

The thalidomide disaster remains a constant reminder that medical treatments can be hazardous. Since then, however, cross-border cooperation has fostered global awareness and galvanized actions. The result is better tools for detecting adverse drug reactions (ADRs) and assessing risk–benefit of medical treatments that guide therapeutic decisions. Unfortunately, despite these advances and widespread drug safety monitoring activities, treatment qualities of many conditions of public health importance remain problematic.

For example, treatment quality of hypertension in type 2 diabetes tends to fall short of set standard, even when access is unlimited. Several reports [1–5] show that less than 20 % of such treated patients in some population groups have their blood pressure (BP) lowered to targets that optimally prevent untimely deaths and other adverse cardiovascular events in type 2 diabetes. These observations are troubling and raise concern that an intervention like lowering BP, capable of reducing untimely deaths by up to 50 %, may end up achieving far less [5–8]. The urgency of this matter is compounded by data showing that hypertension and type 2 diabetes have become leading drivers of untimely deaths and disabilities in virtually all regions of the world. Fortunately, effective medicines that prevent untimely deaths and unnecessary sufferings can be found in almost every jurisdiction.

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12.2 Problem

The problem, however, is that different individuals/groups may need different interventions to achieve the same treatment objective because of variation in disease behavior related to differences in genetic makeup and ethnic/racial background [7, 9–12]. For example, while occlusive atherosclerosis, which leads to stroke, heart attack, sudden death, etc., can complicate hypertension and type 2 diabetes, requiring additional medication types beyond those normally required to effectively lower BP, this may not be a treatment priority for many, because of the genetic variants of the disease they have [13–27]. Unfortunately, this is not how treatments are always delivered in real life.

12.3 Why Does This Happen?

Several factors contribute to this:

First, medicines are sometimes inappropriately promoted/utilized as *one treatment size fits all* with the active involvement of actors who have the duty to protect consumers.

Second, the complex power structure of hospitals could sometimes undermine oversight function that should ensure large-scale procurement of medicines which are in accordance with the best evidence of disease pattern and treatment priorities in the population being served.

Third, conflicts of interest in developing the best way to treat a condition from available options can result in the promotion of a particular medical treatment at the expense of superior alternatives suggested by evidence and circumstance.

The consequence of these observations is that many patients could end up with medicines they do not need, thereby leading to substandard care and waste of resources [25–35].

Incidentally, many scholars [32–41] have drawn attention to the corrosive effect these observations can have on the capacity of health systems to deliver evidence-based effective/efficient care to citizens. What is even more intriguing is that medical education is sometimes bent to suit the business agenda of third parties that stand to gain from clinical decisions that doctors make on how best to treat their patients in a way that could undermine public confidence in healthcare services ([36–39], see *Guardian* newspaper of June 19, 2014. www.ngrguardiannews.com). Marketing of medicines in this way can boost sales but it could also backfire.

12.4 Challenge

In the light of the foregoing, it seems important to attempt to fully understand why this happens at all, if effective solutions are to emerge. First, inventor brands increasingly face stiff competition from cheaper generics that reach the market place

Fig. 12.1 Proposed adjustment to risk–benefit consideration of medicines

without necessarily going through all mandatory phases of medicine development, many of which are capital intensive and laborious.

Second, lack of harmonization of regulatory requirements across regions means the same things are often replicated before marketing authorization is granted for the same medicinal product even in markets within the same zone of similar population groups.

Third, investment in drug research and medicine development is capital intensive and a high-risk venture. Investors understand that if their ideas fail, they could lose money, but when it succeeds, the reward can be handsome; but there is another type of failure that successful investment with enormous health benefits can be made to bear through no fault of theirs. For example, if a product that delivers a better treatment outcome is bypassed in the procurement/prescription process, this could mean resources are wasted on inferior therapies. Further, as government has primary obligation for citizens' health and welfare, it ought to indemnify investors against such losses. One way this may happen is if state actors become venture partners in developing therapies with potential benefits for large segment of their population. This way, it is compelled to strengthen oversight function over operations within health systems that can undermine the capacity of public health expenditure from optimally serving citizens. Such a strategy can promote efficiency in resource application that is capable of improving service quality and lowering cost, if the notion of risk–benefit is expanded to include price comparison of competing alternatives as a surrogate for health benefit. By so doing, the risk of poor and expensive care is minimized particularly if provider reward is tied to treatment outcome (Fig 12.1).

Investors are usually not keen in finding new treatments if the potential market is small and the profit margin is thin. But if a condition is of public health interest and affects many people, as diabetes and hypertension do, incentives may be given to investors, particularly, small biopharmaceutical companies to concentrate their efforts in developing products tailored for such markets that may even have application elsewhere in unexpected ways, while bigger ones are encouraged to reconfigure their products to make them relevant to local realities. A consumptive product/service that excludes majority of potential customers on

account of inability to pay cannot be in the best financial interest of the business.

In view of the above, the following may not seem entirely unreasonable. First, investments that deliver important treatments could be encouraged by extending their patent life beyond what currently obtains, if prices progressively come down as market expands. Second, harmonization of medicine regulatory requirements in regions of similar people may lower development cost and speed up the time new entities take in reaching patients as effective medicines. Hopefully some of such savings can reach customers as more affordable medicines.

12.5 Platform

Vital to any of these is the creation of a platform that can bring key stakeholders together, where important questions are asked. By listening to all sides, perspectives, insights, ideas, and opinions in an atmosphere of mutual trust/respect, necessary conversation can begin. This has the potential to deepen understanding of what patients truly desire and what professional care givers require to meet those needs better. With such insight, research scientists, investors, and clinicians can begin to contribute in finding solutions to the endless possibilities this creates for delivering better treatments everywhere, not just in some regions or population groups.

Sometimes, individual efforts work at cross-purpose to each other. For example, healthcare professionals and the pharmaceutical industry can come together to deliver better treatment. But this may also result in an undesirable alliance that could make it possible for vulnerable people to receive medicines they do not need, despite regulation (see Fig. 12.2 from *Vanguard* newspaper of December 8, 2012; also available at www.vanguardngr.com).

In addition, supply-side actors in the value chain of medicines, i.e., investors, research scientists, regulators, consumer protection agencies, institutional providers, professionals, etc., can assume they know what is best for end users/beneficiaries, when this may not be the case. No system, no matter how benevolent, can effectively meet the needs of those it serves, if it has no way of engaging them to find out firsthand what their real priorities are. Exchange of ideas, perspectives, and concerns can enhance trust and consensus around which solutions that benefit all are likely to emerge. Unfortunately, the current system in operation is one that is capable of generating enough blame to go round, especially when things go wrong. One consequence of this is that each can pursue its agenda, even if the method employed means devastating consequences for others in the value chain. For example, investors may perceive rightly or wrongly that the present scheme of things is not fair enough to the enormous risk they

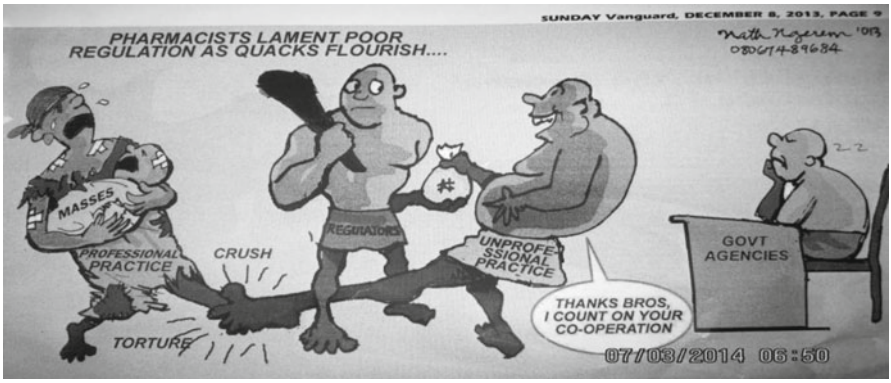

Fig. 12.2 State of medicine consumer protection (Courtesy of Sunday Vanguard Newspaper of 08 December, 2012, www.vanguardngr.com)

undertake to bring valuable medical treatments to healthcare systems especially when things do not work out as envisaged. In such an investment climate, it is not entirely difficult to envisage how consumers can end up with medicines they do not need which promote substandard care or how important new information with safety implications can be concealed. On the other hand, consumers may feel entitled to effective treatments as a part of their social contract with national governments, despite other equally important priorities demanding attention from the limited resources of governments and the consumptive nature of healthcare services. In such seemingly conflicting circumstances, the arbiter role of regulators could come under intense pressure to play to the gallery especially when things go wrong, as they are bound to in any human endeavor. Sadly, doing so can inadvertently send the wrong signal that medicines can be entirely risk-free for everyone. This is a public perception that can backfire and undermine public confidence in the capacity of health systems to serve them well. There is, therefore, in my view, a need for the public to be fully educated to the point of accepting the reality that some risk will always exist each time medicines are taken by the sick to get better; much the same way, the flying public has come to accept the inherent risk of air travel as part of the enormous benefits this brings.

12.6 Public Hearing

Beyond this, medicines are best tailored to local requirement, if all of humanity is to benefit maximally. Consequently, pharmacovigilance needs to constantly adapt to the changing health needs of the population it serves, if it is to remain relevant.

The momentum generated so far has created an undying optimism that safety monitoring of medicines as an integral part of health systems will always strive to minimize the risks associated with medical treatments. Sadly, the state of knowledge is such that despite the best of intentions, the risk of medicine-related harm cannot be totally eliminated for everyone and for every medicine at all times. This is a reality we may have to live with, at least for now, if the tremendous health benefits that come with modern medicines are to continue. Unfortunately, it is not entirely clear whether this is how the public perceive our message. This can drive an unrealistic expectation of what *pharmacovigilance* is about.

Maybe the time has come for the aspect of pharmacovigilance that is dedicated to better treatment outcome to be emphasized more than the present situation where we may be inadvertently reinforcing a public perception that every medicine can be safe for everyone at all times, once it is approved for widespread use. This we know is certainly not the case.

In this regard, it seems important to restate that medicines, much like so many other essential things in life such as sex, fire, water, petrol, cars, airplanes, etc. though potentially hazardous and sometimes deadly, can deliver tremendous benefits when used properly. Specifically, no medicinal product is known to be always safe or harmful; much of the outcome depends on how it is used rather than its intrinsic toxicity. To that extent, it can be said that very few medicines, if any, are taken simply because of their harmlessness, but more for the expected health benefits when wisely utilized.

Therefore, promoting wise use of medicines can deliver superior outcome and also protect investments. In particular, consumer protection mechanisms, especially those independent of treatment facilities and regulatory authorities, can enhance better utilization of medicines by engendering a culture of accountability for *treatment outcome* and *value for money* of prescribed medical care.

Having said this, it is my contention that where serious uncertainties exist about the safety of a medicine in relation to its overall place in the delivery of effective treatment for a condition of public health importance, it may well be in the interest of stakeholders to hold public hearings. This can involve independent scientists, bioethicists, and market authorization holders, regulators, NGOs, media, and citizens. This way the general public is better informed, and ownership of the issues involved is transferred to society in a way that also guides individual choices and generates evidence-based policy. This could cascade down to the level of treatment facilities beginning with a strategy to deal with identified medicine-related problems and a pharmacovigilance round table that can bring key stakeholders together as captured in Figs. 12.3 and 12.4.

In this, it is possible that ongoing studies linking genetic ancestry with disease behavior could result in useful information relevant to treatment choices that individualizes care.

But until this becomes a clinical reality, effective treatment is not entirely impossible if we try without giving up, even if doing so may seem difficult initially [40, 41].

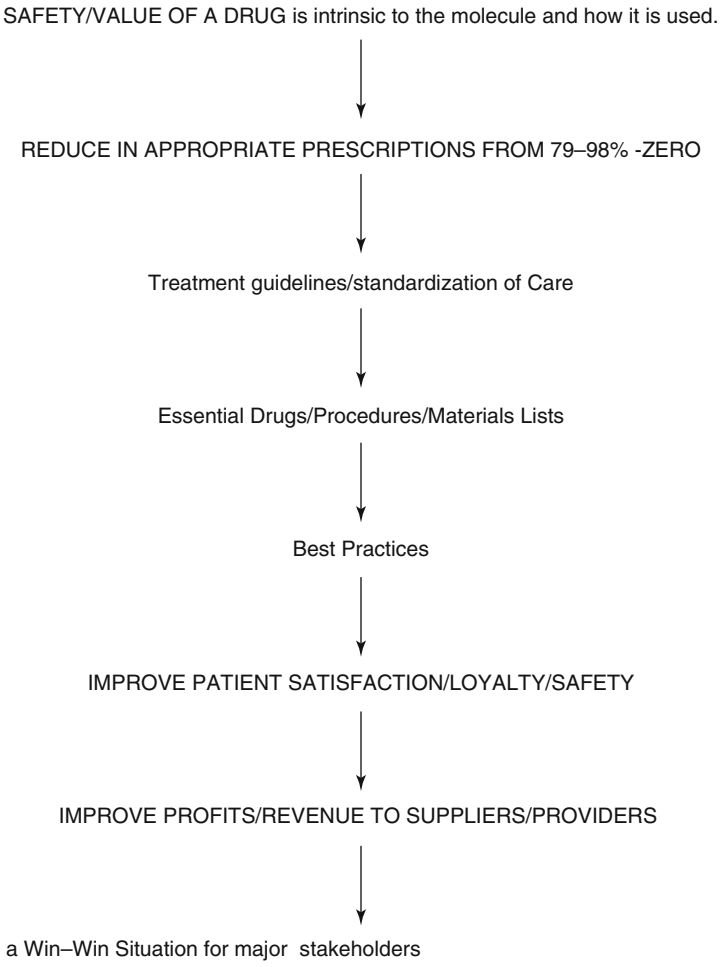

Fig. 12.3 Summary of pharmacovigilance strategy adopted in one university hospital (see Okoro, EO, 2005 references [42, 43])

In summary, a mechanism that brings key actors in the health sector to the same table can create a synergy that makes investments work better for society without necessarily being a financial disaster. The multilateral nature of transnational agencies that promote global health, in my view, puts them in the best position to drive the process. And this can begin with future ISoP conference/meeting by having a section dedicated to patient interest group where ordinary people, consumers, their representative, the media, and members, market authorization holders (MAHs), and providers can come together to have a free/open session where issues relevant to them can be raised and listened to.

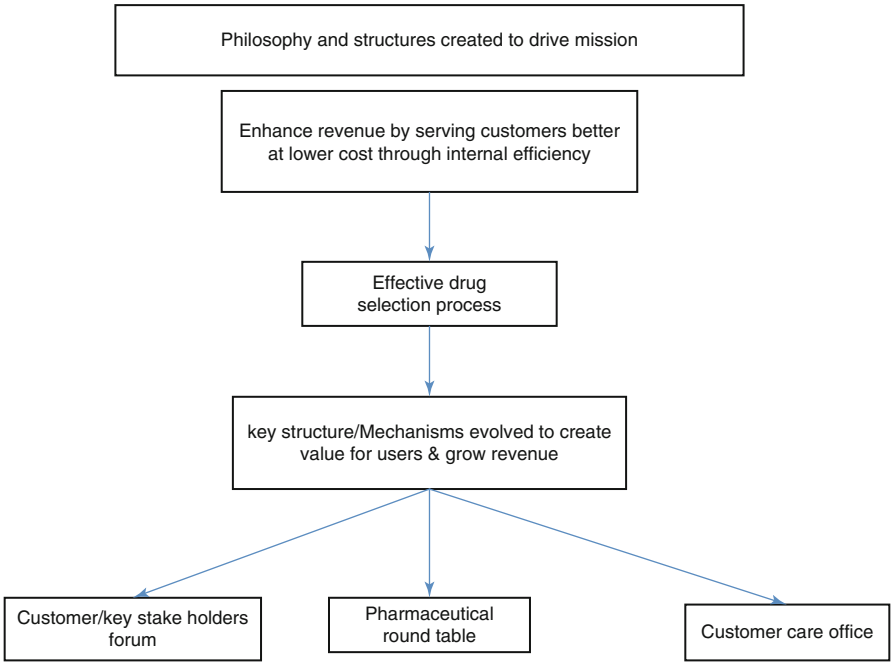

Fig. 12.4 Structures/processes that drove the strategy defined in Fig. 12.3

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Chapter 13
Broadening the Scope of Pharmacovigilance

Eugène P. van Puijenbroek and Linda Harmark

13.1 Summary

Over the past years the scope of pharmacovigilance widened, allowing for better adjusted information on adverse drug reactions (ADRs) to the needs of both regulators, clinicians and patients.

For treatment and managing the ADRs, not only is information on their clinical aspects important, but also information characterizing our attitude and behaviour towards ADRs. For healthcare professionals as well as patients this information is vital for optimizing treatment. Unfortunately, many of the methods used in pharmavigilance are still focused on the detection of unknown serious and often rare events but not on extending our knowledge of the known, more common but often burdensome ADRs encountered by patients. To do this, pharmacovigilance should make a shift from the focus on finding new, previously unknown associations and elucidating the frequency of events to the analysis of the content and meaning of ADRs for both healthcare professionals and patients. This also implies a shift from population and regulation based pharmacovigilance to a patient centred pharmacovigilance.

The discrepancy between the way the rules and regulations are often being implemented and the needs of patients and healthcare professionals is a point of concern. In this chapter we describe the way the concepts of pharmacovigilance have developed over time, the current playground of pharmacovigilance, the influence of modern day's rules and regulations and possible ways to overcome the existing gap between the need for information of ADRs taking different stakeholders perspectives into account, and its availability and usefulness in daily practice.

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13.2 Introduction

In the past, pharmacovigilance was mostly focused on the detection of hitherto unknown adverse drug reactions (ADRs) of drugs approved for marketing. Unfortunately, this strict focus on the association between drug and ADRs does not always reflect the way ADRs are evaluated and handled in daily practice. For this reason the scope of pharmacovigilance has broadened over time, and this was first illustrated in 2002 with the WHO definition of pharmacovigilance as 'The science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug related problem' [1]. Also in the EU definition of an adverse reaction, 'A response to a medicinal product which is noxious and unintended', adverse reactions may arise from the use of the product within or outside the terms of the marketing authorisation or from occupational exposure [2]. Conditions of use outside the scope of marketing authorization may include, amongst others, off-label use, overdose, misuse, abuse and medication errors.

Since the characteristics of an ADR do not merely entail the reaction occurring when the drug is used according to the terms of marketing authorisation, a signal not only refers to a new ADR but also encompasses new aspects of known ADRs. For example, aspects such as the way drugs are used in daily practice and knowledge which can help understand, prevent and manage ADRs will become increasingly important in pharmacovigilance. The expanding scope is also reflected in the CIOMS definition of a signal: 'Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action' [3].

Another development in pharmacovigilance, which almost runs in parallel with the developments described above, is the growing recognition of the patient as a key player in pharmacovigilance. In the early 2000s, the first European countries started to accept patient reports to their spontaneous reporting systems. In the Erice Manifesto from 2007, an overview of challenges to be addressed in ensuring the continuing development and usefulness of the science of pharmacovigilance is provided. It describes active involvement of patients and the public in decisions about their own health and treatment of disease and discussions about benefits and risks of medicines as a possible road for success [4]. The role of patients as key players in pharmacovigilance was underpinned in the new pharmacovigilance legislation which contains several efforts to increase the involvement of the general public, and it made patient ADR reporting systems mandatory [5]. Whereas in the past, pharmacovigilance had mainly a strong clinical perspective, patient-reported information has become an important tool to elucidate the meaning and consequences of ADRs for those actually using medicinal products.

This new vision on the role of pharmacovigilance should allow for better adjusted information to the needs of regulators, clinicians and patients using medicinal products. The regulators need information about the safety of a drug on a population level which allows them to determine the balance between benefit and harm, also

taking the patient's perspective into account. Clinicians need information which can help them prevent or manage ADRs, and patients need information which can help them to recognise, understand and cope with the ADR. All this fits under the pharmacovigilance umbrella. However, many of the methods being used in pharmacovigilance today are not able to capture the information that is needed in order to really broaden its scope. Current methods are still primarily focused on the detection of unknown serious and often rare events and not on extending knowledge of the known, more common but often burdensome ADRs encountered by patients. Information on aspects like risk factors, time course, management and impact on the quality of life is needed by both healthcare professional and patient, especially in the event of common, non-serious events, which may pose a higher overall burden for patients instead of the rare, serious ones.

In this chapter we describe the way the concepts of pharmacovigilance have developed over time, the current playground of pharmacovigilance, the influence of modern day's rules and regulations and possible ways to overcome the existing gap between the need for information of ADRs taking different stakeholders' perspectives into account and its availability and usefulness in daily practice.

13.3 Current Developments

As a result of the implementation of new rules and regulations and the increased interest in drug safety, more data became available which were also more heterogeneous in nature. The reasons for the increase in the number of reports are manifold. The new EU legislation led to an increase of the number of reports to be collected and analysed at a central level instead of assessment and analysis at a local level. In addition, requirements for reporting ADRs changed and became more stringent. An example is the mandatory reporting of events from organised data collection systems like patient support programmes carried out by the pharmaceutical industry [6]. It is obvious that the reasons and motives to report these events differ from the situation in which reports are submitted in a true 'spontaneous' reporting setting. Both the EudraVigilance database at the European Medicines Agency (EMA) and the database maintained by Uppsala Monitoring Centre, the WHO Collaborating Centre for International Drug Monitoring, show an increase in the number of reports over the last few years [7, 8]. This is also the case for many other pharmacovigilance databases. Although some argue that a large number of reports are needed because it decreases the level of underreporting and may increase the chance of finding signals, underreporting is inherent to the nature of voluntary reporting. Reports received in this way should be considered as clinical concerns, based on a selection of an experienced healthcare professional or patient. A downside of the increasing number of reports is that it makes the analysis of its contents on a case-by-case basis more difficult and therefore should be preceded by disproportionality analysis. However, disproportionality analysis does not allow for the in-depth analysis of circumstances and clinical presentation of ADRs yet, let alone studying attitude and behaviour of HCPs and patients.

Modern-day spontaneous reporting systems make use of various sources of information, and these different sources call for various approaches in the data analysis. Spontaneous reports mirror clinical concerns and mainly serve as a first step in the detection of new signals. Their value lies mainly in the quality and description of the clinical data. Especially the narrative is important in this respect. Reports concerning cases of ADRs in literature may closely resemble spontaneous reports, but carry the risk that duplicates are filed by different pharmaceutical industries marketing the same drug.

Another source of information in spontaneous reporting databases is the data from organised data collecting systems such as patient support programmes. These reports usually describe all events that occurred during the use of the drug, irrespective of the strength of the causal relationship. Finally reports from prospective cohort event monitoring studies may be present that mention the possible occurrence of ADRs at various points of time, irrespective of the strength of the relationship. It is obvious that for signal detection purposes, although filed in the same database, these various data should be dealt with in a different way and cannot automatically be analysed together. In addition, without knowledge of the nature of these data sources, disproportionality analysis is difficult, and results may be less reliable.

13.4 Desired Focus of Pharmacovigilance

In the early days, pharmacovigilance was strongly focused on the relationship between drug and ADR itself. The widened scope of the collection, reporting, analysis and dissemination of information of ADRs came along with new fields of interest. Examples are drug safety during off-label use, abuse, misuse or occupational exposure and medication errors.

This raises the question how this information should be categorised and analysed. A major distinction can be made in information in respect to the ADRs itself and information about the way healthcare professionals and patients deal with the ADRs.

In respect to knowledge about the clinical aspects of ADRs, information on the signs and symptoms are crucial as well as information about potential risk factors and circumstances under which the ADRs occur. Information on the ADRs itself can be subdivided into knowledge about potential risk factors and circumstances under which the drugs are used present *before* the ADR occurs, the clinical aspects and impact *during* the occurrence of the ADR itself and information about the outcome and sequelae *after* the ADR ceased. Examples of risk factors are comorbidity, concomitant drug use, medical history or other patient characteristics such as genetic predisposition. The ADR itself can be characterised by its clinical symptoms, time to onset and course of the reaction. After the ADR ceased to exist, sequelae may be present that may influence the well-being of the patient. An overview of clinical aspects of ADRs is shown in Table 13.1.

Table 13.1 Examples of clinical aspects of ADRs before, during and after the occurrence of ADRs

	Before	During ADR	Afterwards
Clinical aspects	Risk factors, amongst which genetic polymorphisms and comorbidity and concomitant medication	Clinical symptoms Course of reaction	Outcome Sequelae

For treatment and managing the ADRs, the aforementioned information on the clinical aspects is important, but also information characterising our attitude and behaviour towards the ADR both by patients and healthcare professionals. How we react on ADRs is the result of the attitude and behaviour of many stakeholders, from which the patient and healthcare professional are the key players.

According to the theory of reasoned action of Fishbein and Ajzen, the actual behavioural intention is mainly a consequence of both attitude and subjective norms [9]. According to this theory, a person's behaviour is determined by two factors: first, the intention to perform the behaviour, and, second, that this intention is based on the attitude towards the behaviour, the subjective norms and the perceived behavioural control. Subjective norms are based on beliefs about how people will judge the behaviour in question. The perceived behavioural control is someone's perception on his actual ability to perform a given behaviour. For example, whether or not a patient, who experiences a possible ADR, actually visits his doctor (behaviour) first depends on his attitude towards his complaints. He may have the opinion that given the severity, treatment is desired for which a doctor's visit is needed or may think that stopping the use of the suspected drug will be beneficial and contact with his physician is therefore not needed. The subjective norm in this situation may be determined by his beliefs of what others think he should do in this situation given the symptoms he experiences; what do his relatives expect from him? When he is not able to go to work, does his employer expect him to visit his doctor? Finally his perceived behavioural control can be determined by the fact whether or not he can actually visit his GP. Likewise, whether or not a patient is admitted to a hospital (behaviour) by his treating physician is in the first place based on the physician's attitude towards the ADR. Does he consider the ADR as a life-threatening situation or is it likely to be self-limiting? The subjective norms can be determined by expectations of the patient or his family, but also information in professional guidelines. Finally, the perceived behavioural control is determined by the feasibility of admitting this patient to the hospital; are there any beds available at this moment?

As in the case of the clinical symptoms of the ADR, in different moments in time, attitude, subjective norms and actual behaviour may vary. Tables 13.2 and 13.3 show some examples of behaviour of patient and physician, based on attitude and subjective norms. Since elements of perceived behavioural control are highly personal, these are not mentioned in this table.

The information on the nature of the ADRs as presented in the textbooks and the summary of product characteristics (SmPCs) usually only provides knowledge about the existence of the relationship between drug and ADRs. To a lesser extent, other (clinical) aspects for instance, concerning timing, management, treatment and

Table 13.2 Attitude and behaviour from a patient's perspective and its consequences before, during and after the occurrence of ADRs

Patient	Before	During ADR	Afterwards
Attitude and subjective norms	Risk perception Feeling of control	Level of acceptance Coping ability	Experience
Behaviour	Adherence Off-label use Drug misuse or abuse Reading the SmPC Use of social media	Consumption of care Absenteeism from work	Consumption of care Absenteeism Adherence to future treatment

Table 13.3 Attitude and behaviour from a HCP's perspective and its consequences before, during and after the occurrence of ADRs

Healthcare professional	Before	During ADR	Afterwards
Attitude and subjective norms	Risk perception Acquiring knowledge on ADRs	Cautiousness Previous experience	Experience
Behaviour	Educational activities Adherence to guidelines Medication errors Off-label prescribing	Diagnostics Treatment of ADRs	Preventive measures Note contraindications Reporting ADRs

outcome, are mentioned. For healthcare professionals and patients, however, this information is vital.

With the widening of the scope of pharmacovigilance, it is obvious that the aforementioned aspects should be considered as well, and this will involve changes in conceptual thinking about the way pharmacovigilance is performed by different stakeholders.

13.5 From a Different Perspective to a Different Approach

In order to overcome the aforementioned issues, pharmacovigilance should make a shift from the focus of finding new, previously unknown associations and elucidating the frequency of events to the analysis of the content (meaning) of ADRs for both healthcare professionals and patients. This implies a shift from population- and regulation-based pharmacovigilance to a more patient-centred pharmacovigilance.

13.5.1 Type of Reporters

When talking about healthcare professionals in the context of reporters, one often thinks about medical doctors and in some countries also pharmacists. But increasingly, patients spend less time with their doctor and more time with specialised paramedic personnel such as nurses or nurse practitioners. By focusing on including this group as reporters, reporting could be increased as well as providing information on other than merely clinical aspects.

Another type of reporter which can contribute to pharmacovigilance is the patient's self. Patient empowerment has prompted patients today to be more involved in the decisions about their own care. Patient-reported outcomes (PROs) have become increasingly used in general healthcare and life sciences. PROs are defined by the FDA as any report of the status of a patient's health condition coming directly from the patient without interpretation of the response by a clinician or others, including self-perception symptom severity (absolute or relative to another report), and physical performance, but not information derived by others e.g. physical examinations or performance assessed by health care professionals [10].

One of the first broader applications of PROs in the safety surveillance of marketed products was the introduction of the general public as reporters to spontaneous reporting systems. One of the initial aims by targeting the general public as reporters was to increase reporting [11]. However, the contribution of patient reporting to pharmacovigilance goes beyond a quantitative contribution. Patients provide first-hand information about the ADRs, and these reports can lead to a better understanding of the patient's experiences of the ADR [12–14], including a more detailed information regarding quality of life including psychological effects and effects on everyday tasks [15, 16]. However, when more medical information is needed, follow-up with a HCP may be necessary and is always desirable.

Information from patients may also challenge the concept of what is considered a 'tolerable' ADR [17] since the severity of the ADR is a main motivation for patients to report [14, 18]. As with the concept of 'tolerability' of ADRs, it is important to be aware that the view of the concept of 'seriousness' of an ADR in the medical community may differ significantly from the views of patients [19]. Many ADRs would be regarded as non-serious according to internationally agreed professional criteria, while nevertheless being intolerable and considered serious and causing severe problems for patients [19, 20]. The distinction between 'seriousness', an outcome, and 'severity'—a degree or level—should correctly speaking be made. A severe rash is rarely serious, and death or a loss of the limb cannot be described as severe.

Patient reports also contribute to signal detection and have been crucial in identifying certain signals. Studies from the UK and the Netherlands have found positive effects from patient reporting on signal detection and that the inclusion of patient reports has not had a hampering effect on the signal detection as a whole [15, 21, 22].

13.5.2 Data Collection Methods

Spontaneous reporting is the basis for case-by-case analysis and is the method that contributes the most to regulatory actions [23]. However, if we want to broaden the scope of pharmacovigilance and expand the type of knowledge collected about ADRs, other methods for data collection need to be developed.

In the Netherlands, a web-based intensive monitoring system has been developed which uses the patient as a source of information. Patients are included at an inclusion point, and after registering online, the patient receives questionnaires by e-mail at specific points in time, allowing longitudinal data collection. In these questionnaires, questions are asked about drug use and possible ADRs. This system allows the collection of more information about drug use and ADRs such as the time course and management thereof. It also collects information on how the patient uses the drug and the impact of the ADRs on the quality of life. If it is clear when an ADR occurs, how long it persists, and what actions can be beneficial in the management of the ADR. This knowledge can help optimising pharmacotherapy for the individual patient. Because web-based intensive monitoring collects longitudinal data, it is possible to answer this type of questions [24]. Direct collection of information from patients also makes it possible to collect information regarding the impact of an ADR on the quality of life [25].

13.5.3 Use of Social Media

Most of the current pharmacovigilance data collection methods only work if the reporter makes a decision to contribute his information for pharmacovigilance purposes. As reporting systems are generally not very well known to the general public and the fact that most people do not take the time to fill in a report, one has to go looking for this information where the reporters themselves choose to share it. With the emerging technologies, patients increasingly share their experiences of drug use and ADRs on social media such as forums, blogs and social networks which can possibly become a new source of pharmacovigilance data. Due to quantity and near-instantaneous nature of social media, it provides potential opportunities for real-time monitoring of ADRs, greater capture of ADRs and expedited signal detection if utilised correctly [26]. However, in order to make use of this new source of information, methodologies which can capture the information need to be developed and validated. In addition, ethical questions have to be addressed since these data were not primarily shared for pharmacovigilance purposes.

13.6 Different Approaches in Signal Detection and Evaluation

At the end of the past decade, much effort was put in increasing the number of reports and the type of information provided, by implementing new sources of information. New methodologies and powerful analysis techniques enabled the

detection of small risks. The focus of all these efforts mainly lies in the confirmation of the existence of the ADR and finally estimating its incidence. Despite all these developments, there are still two main approaches in signal detection: the case-by-case analysis and disproportionality analysis.

13.6.1 Case-by-Case Analysis

In the case-by-case analysis, but also in the clinical setting, various aspects are taken into account when deciding if a certain event actually is an ADR or not. When assessing multiple reports concerning the same association, some cases may contribute to a larger extent to the signal than others based on the completeness of the report and the quality of the clinical content. The extent to which these cases contribute to the signal may vary according to the personal judgement of the assessor and the reporter. Reporting of ADRs or case reports should come along with a clear motive of the reporter why he chooses to share his observations. Although some promising developments are made in approaches to assess the completeness of the reports [27], the interpretation of the information in respect to the contribution of various types of information requires clinical skills. There is a close link between reporting ADRs and publishing case reports in scientific literature. Both aim at informing other healthcare professionals about observations that do not fit in the previous experience [28, 29]. Multiple similar observations might underpin the chance for the existence of a true signal.

13.6.2 Disproportionality Analysis of Drug-Event Combinations

With the growing number of reports, disproportionality analysis is a method we cannot do without as a first step in the assessment of signals. The increasing sizes of databases leave us no other option than using a statistical tool as a filtering step in the analysis of these large datasets. Basically, the number of reports on the association between suspected drug and ADR is compared to the same association in other drugs in the database. This approach has originally been developed as a screening tool to highlight associations that might have been missed by the case-by-case analysis. In contrast to the case-by-case analysis, in disproportionality analysis all reports that are used have an equal weight and contribute equally in the calculation not taking the quality of the information provided in the report into account. In addition, in order to categorise ADRs in a database, they are coded with, for example, MedDRA or WHO-ART, reducing the clinical richness of a report to a simple set of codes. Most analyses take place at this coded level, and by doing this a lot of information provided in a report goes unanalysed. The strength of the causal relationship and level of documentation are not used in most routine statistical disproportionality

analyses; however methods are being developed where this is taken into account [30]. By omitting this information, there may be a potential risk that relevant signals that would have been selected based on the clinical judgement of all cases could be missed.

A stepwise approach in which the case-by-case approach is combined with disproportionality analysis might be useful in the heterogeneity of most datasets, which are used for signal detection. However, a detailed clinical and pharmacological assessment of the signal remains necessary for a proper evaluation.

The fact that the strength of a causal relationship not merely depends on the numerical correlation between drug and suspected ADR was already mentioned by Sir Bradford Hill [31]. Nevertheless, the numerical strength of the association still is considered as the most contributing factor in causality though other aspects might contribute as well. Examples are the time relationship between drug and ADR, the pharmacological plausibility and the test conducted to examine the ADR. The aforementioned aspects should also be used to make the signal detection process more efficient.

Databases containing data from healthcare professionals become increasingly important for the detection and signal strengthening of ADRs. When a patient contacts his doctor, the reason for an encounter is usually a condition for which he may be treated with a medicinal product. For instance, HCPs most often encounter the frequently occurring and non-serious ADRs. These ADRs are rarely noted in a structured way or only mentioned as free text, unless the signs and symptoms are serious. For instance, the coding system International Classification of Primary Care (ICPC), used by general practitioners, does have a code for the occurrence of an ADR, but the clinical diagnosis or symptom associated with this ADR itself is usually not noted as an ICPC code. As long as pharmacovigilance is not a part of daily routine in clinical practice, it is questionable if these data on minor ADRs would have been noted at all. Nevertheless for more serious and rare events, observational databases can be helpful in signal detection and strengthening and allow for an estimation of the incidence or a quantification of the strength of the relationship.

13.6.3 Signal Detection of Information Characterising ADRs

Studying information that characterises the ADR itself has been considered secondary to the study of the detection of the ADR. Nevertheless, case reports serve as a valuable tool for studying the circumstances under which the ADRs occur. Additional information can be asked for in the event a report is incomplete or when the information from case reports gives rise to additional studies to retrieve this information. This approach has proven to be an efficient way of retrieving additional information [32]. The introduction of proactive methods in the collection of pharmacovigilance data may enable a more efficient process and valid selection of signals and may also focus on the circumstances under which the ADRs occur.

Selective monitoring for potential signals, already identified in the risk management plan, is part of routine pharmacovigilance in the pharmaceutical industry, but not yet in the majority of national pharmacovigilance centres, and could be used in a more proactive approach in data collection.

Intensive monitoring schemes offer the possibility to actively monitor drugs in daily circumstances. Examples of these systems are the Lareb Intensive Monitoring (LIM), the former Intensive Medicines Monitoring Programme (IMMP) in New Zealand and the Prescription-Event Monitoring (PEM) in the UK [33–35]. In respect to more common adverse drug reactions, prospective cohort event monitoring has shown to be a promising tool to retrieve information on ICE in conjunction with information on efficacy.

13.7 Different Approaches in Communication About ADRs

Pharmacovigilance focuses not only on the collection and analysis of information of possible ADRs but also about providing adequate feedback. However, the implementation of the knowledge of ADRs in clinical practice is still a point of attention. Despite all efforts from marketing authorization holders (MAHs) and regulatory authorities, it can still be bothersome to get the message across and actually change the behaviour of healthcare professionals and patients [36–38]. Whereas in modern days, the majority of information is transmitted electronically, the formal communication in respect to drug safety is still taken care of in the form of drug DHPCs, which does not line up with the current way of communicating to both healthcare professionals and patients, and the use of additional electronic communication methods may be helpful [39].

We believe that there is a need for more detailed information for each individual ADR. The information presented in the SmPC and patient information leaflet (PIL) is already abundant, but quite limited to information about the frequency of ADRs and very little information about the time course and the management of ADRs. In addition PILs are difficult to read [40]. This comes along with the paradox that on one side we need more information to get a better view on the meaning of ADRs for the patient, but on a patient and HCP level, we need less information to assure that it is properly taken into account and actually used. Information technology might enable a more efficient presentation of this information on the clinical course and impact on the QoL in patients that would better fit in with the needs of the patient and HCP.

Since there are multiple stakeholders in pharmacovigilance, it is important to tailor the information for the needs of a specific group. At the moment, pharmacovigilance is very much focused on information fulfilling the needs of regulatory agencies but less focused on what HCPs and patients need. It is the task of the pharmacovigilance community, in dialogue with HCPs and patients, to find out what clinical practice actually needs and how this should be presented in a way that lines up with the needs of those who use this information.

13.8 Considerations

There is still a big gap between the theoretical knowledge of ADRs and their occurrence, course and impact on the lives of patients in daily practice. Also knowledge on attitude and behaviour in respect to the use of specific drugs and the occurrence and prevention of ADRs is not readily available. The discrepancy between the way the rules and regulations are being implemented and the needs of patients and healthcare professionals is a point of concern. Each person has its individual chance for developing ADRs, but also the reaction to treatment is highly individualised. For each patient the balance between efficacy and harm may differ. Balancing this risk can only be made on personal grounds and when information to make an individual estimate both for harm and for benefit is available. Information about benefit and efficacy, both in respect to the ADR itself and its influence on attitude and behaviour of the patient and healthcare professional, should be collected simultaneously in prospective cohort studies in both preclinical and post-approval studies.

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Chapter 14
Herbal and Traditional Medicines, Now and Future

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14.1 Background

Herbal medicines (HMs) include herbs, herbal materials, herbal preparations (comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials) and finished or manufactured herbal products found in pharmaceutical dosage forms (tablets, capsules) [1]. Although there are few reliable estimates of the prevalence in use of HM [2], the market for HM continues to expand rapidly and has grown into a multibillion-dollar industry across the world [3]. The influence of religious, sociocultural, and socioeconomic issues, traditional practices and belief in the use of HM is evident, particularly in Chinese, Indian and African societies. Documented use of HM in Western societies is also high [4, 5]. Among consumers, there is widespread belief that remedies of natural origin are safe. Worldwide, most HM can be obtained from various sources without a prescription.

Until now, there are no longitudinal data for prevalence of use of HM worldwide. The market research data indicate increasing sales of licensed and unlicensed HM [6–8]. This suggests that large numbers of people are using HM.

As with all medicines, HMs have been shown to have the potential to cause adverse effects which are related to a variety of causes, including inherent properties such as the presence of toxic constituents, adulteration, mistaken use of the wrong plant species, incorrect dosing, errors in use and contamination. Furthermore, HM can affect pharmacokinetic and pharmacodynamic properties of conventional

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drugs and thus can cause herb–drug interactions [9]. For these reasons, there is an increasing awareness of the need to maintain and continue to develop pharmacovigilance for HM.

The use of HM must take into account their safety, efficacy, consistency and quality. The safety of these products requires strict control for the presence of adulterants, the dosage labelling, contraindications, manufacturing techniques and a list of all ingredients. In some countries, there is often no requirement to list each ingredient of every ingredient on the label. There is also no requirement to precisely state the dose of active ingredients contained in herbal preparations in some countries. Under these conditions, HM safety can be difficult to monitor in the post-market setting. This situation can be better controlled through pharmacovigilance processes and regulatory controls [10].

The current model of pharmacovigilance with all tools and methodologies was developed for conventional drugs. HMs present unique challenges for pharmacovigilance.

14.2 Challenges

The characteristics of HM and the ways in which these products are named, sourced and utilised constitute challenges for their pharmacovigilance.

14.2.1 Names and Nomenclature

Unlike conventional medicines, names for HM include the Latin scientific name, the common or vernacular names, the pharmaceutical name or pharmacopoeial name (when it exists) or the specific herbal drug names (as used in traditional Chinese medicine) [11]. Herbal prescriptions, product packaging or labels may have one or more of these (sometimes no label) depending on source and regulatory status of the product. These have to be interpreted with care as even the scientific names may have synonyms. The common or vernacular name is the least precise, and the same name may be used for plants from different genera or species and so should be avoided if possible. The common name may be misleading or confusing if used on raw plant material or unlicensed HM. To avoid ambiguity, it is desirable that the genus, species and part of the plant are listed somewhere on the product or packaging of the raw material. Even a botanically correct label does not necessarily confirm that the product contains what is listed on the label. In cases of serious adverse reactions where specific toxins are suspected (e.g., from an inadvertent inclusion of a toxic herb through misidentification), then laboratory analysis of the product/herb may be advisable to verify the reports. Where regulatory requirements

exist for manufacturers to meet good manufacturing practices, such quality problems will be minimised, but not altogether eliminated.

14.2.2 Chemical Composition

HMs are chemically complex with hundreds of constituents. Many of these chemical constituents are unknown, and even for HM with well-documented chemical constituents; very few specific constituents responsible for pharmacological activity are fully understood. The constituents are not uniformly distributed throughout a plant, and for the majority of HM, only a specific plant part (s), such as seeds or root, is (are) used for medical purposes. In addition, the constituents are likely to vary both qualitatively and also quantitatively between different batches of plant starting material in relation with inter- and even intraspecies variation in constituents, growing conditions in relation with climate and soil, harvesting time (year, season, time of day) of some HM and transportation, drying and storage. These factors may have great impact on the quality and efficacy of the final formulation of HM.

14.2.3 Methods of Processing

The method of extraction can influence the chemical composition of herbal preparations or products. Indeed, if the active constituents of raw medicinal plants (or parts of plants) are heat-labile and the method of extraction used is decoction, the active ingredients in these conditions are easily decomposed and subject to a loss of characteristic properties by the action of heat. Precise and standardised processing is required to reduce the potential toxicity or side effects of HM. The concentration of potentially harmful phytochemicals may be substantially increased by extraction of raw material with organic solvents.

Extraction can alter the expected biological/clinical effects, compared with the original plant part, by separating and removing chemical ingredients that can be adjuncts to the active compound (s) and result in either or both increased and decreased effectiveness or toxicity.

14.2.4 Other Ingredients

Oil, vinegar and honey are used for their biological activity in, or for the processing of, traditional medicinal drugs. Quality control of excipients used for processing herbs is especially important as they may introduce toxic contaminants, as is the case when frying in peroxided oils [12] or may interact with HM.

14.2.5 Manufacturing

Good practice and standardised manufacturing are crucial to the quality of HM and traditional medicine. Manufactures should be identifiable and should strictly follow the criteria for the identification of the medicinal herbs with quality control as recommended in the "WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants" [13].

14.3 Conditions of Herbal Medicine Use

14.3.1 Self-Medication

Patients tend to self-prescribe HM without consulting a professional herbal practitioner or other health professional. HM can be bought over the counter from pharmacies, supermarkets, markets or the Internet without any consultation with a health professional.

14.3.2 Herbal Practitioners

Both prescribers and dispensers are a useful source of information on HM adverse reactions. They are not necessarily recognised as HM adverse reactions reporters or even excluded from some pharmacovigilance reporting systems. Herbalists often prescribe or/and dispense herbal mixture preparations or products in a processed or powdered form, which may make identification of a product difficult in the case of an adverse reaction.

14.3.3 Prescribing Information and Package Leaflet

The prescribing information and package leaflet constitute an important source of information for both clinician and mainly patients/consumers, as a guide for rational HM use and administration. Where regulations exist, licensed products are required to carry information on ingredients, dosage, indications and cautions, contraindications and potential interactions on their labels [14]. In the absence of such regulations, this labelled information may be absent or substantially incomplete. In African countries, there is an absence of HM in the National Essential Medicines lists. A lack of standard treatment guidelines or national HM pharmacopoeia is a major challenge when it comes to the implementation of rational use of HM; hence, the risk of occurrence of adverse effects can be very high resulting from errors in their use by both traditional health practitioners and consumers [10].

14.3.4 Adulterated HM

Poor quality, contaminated or adulterated HMs are serious patient safety threats. This is now a truly global phenomenon. Consumers in all countries are at risk from these unsafe products. Quality issues in HM include adulteration with undeclared synthetic pharmaceuticals, contamination or adulteration with undeclared heavy metals and HM of poor manufacturing quality including those without active ingredients and HM with misidentified ingredients [15].

14.3.5 Inappropriate Combination with Conventional Drugs

As the popularity of herbal medicines increases, it has become common practice that HMs are used in combination with conventional drugs. This polypharmacy is increased in populations using multiple pharmaceutical drugs such as the elderly and persons with certain disease conditions, such as those with HIV/AIDS. HM affects the pharmacokinetic and pharmacodynamic properties of conventional drugs and thus can cause herb–drug interactions [9]. However, there is not enough information or adequate analysis to estimate the magnitude of the problem [16, 17]. An example is seen with the alkaloids obtained from species of *Ephedra* (Ephedraceae), administered as HM or as products containing synthetically prepared ephedrine and pseudoephedrine. The alkaloids can cause adverse cardiovascular events associated with arrhythmias, palpitations, tachycardia, myocardial infarction and death [18, 19]. Ephedrine raises blood pressure and induces peripheral vasoconstriction. Consumption of caffeine in *Coffea arabica* L. (Rubiaceae) or present in the same HM or in drugs, and in association with ephedrine, increases the cardiovascular risk [20, 21]. The danger of using ephedrine-containing products is higher in patients who are sensitive to the effects of sympathomimetic agents (i.e., patients with hypertension, hyperthyroidism, diabetes mellitus, psychiatric conditions, glaucoma, prostate enlargement, seizure disorders and cardiovascular disease) [22].

In the future, it is important for health professionals, consumers and other interested stakeholder groups, including regulatory authorities and suppliers of herbal medicines, to be aware of the possible adverse effects and drug interactions caused when herbal medicines are co-administered with conventional drugs. Consumers frequently self-select herbal medicines, without the advice of a qualified health provider [23]. They should be encouraged to disclose their use of herbal medicines to their physicians and pharmacists, who will then be aware of potential HDIs and should report them to national pharmacovigilance centres. It is often the case that both patients and health professionals forget, or are reluctant, to discuss HR. More effective communication between all these partners is needed, and information must be accessible to all [24] so that responsibility of safety information is shared.

14.4 Regulation

14.4.1 Limitations of Premarketing Safety Studies

Even for conventional drugs, preclinical tests and clinical trials are not fully adequate assessments of safety due to the limitations of animal models, and insufficient number of controlled human subjects, and a lack of reflection of real-world use patterns. In many jurisdictions, including in many where there is premarket authorisation of HM, preclinical and clinical studies are not required.

14.4.2 Regulatory Framework and Quality Control

The legal situation regarding HM varies from country to country. In some, phytomedicines are well established, whereas in others they are regarded as food and therapeutic claims are not allowed. The various legislative approaches for HM fall into the following categories [25]:

- Same regulatory requirements for all products
- Same regulatory requirements for all products, with certain types of evidence not required for herbal/traditional medicines
- Exemption from all regulatory requirements for herbal/traditional medicines
- Exemption from all regulatory requirements for herbal/traditional medicines concerning registration or marketing authorisation
- Herbal/traditional medicines subject to all regulatory requirements
- Herbal/traditional medicines subject to regulatory requirements concerning registration or marketing authorisation

Developing countries often have a great number of traditionally used herbal medicines and much folk-knowledge about them but have few registration criteria to establish these traditionally used herbal medicines as part of the drug legislation. In these countries, there is often no regulatory framework for HM. For example, in Africa among 25 countries who are members of the WHO International Programme for Drug Monitoring, only five of them have regulatory status and quality control of their HM products [26].

The European Union Directive (2004/24/EC of 31 March 2004) [27] sets out the regulatory framework for traditional herbal medicines and what must be done with existing products that do not have a registration. Manufacturers or importers of these existing, non-registered products were given a transition period in which to either submit them to the Medicines and Healthcare Products Regulatory Agency for registration under their implementation of the scheme specified in the Directive, the traditional herbal medicines registration scheme [28] or withdraw them from the market. The UK differs slightly from the rest of Europe in that herbal practitioners

have been regulated since 2012 allowing for unlicensed manufactured HM to be prescribed following a face-to-face consultation [29].

Some international regulatory frameworks include provisions for the mandatory reporting of adverse reactions by manufacturers [14]. However, reporting by medical or herbal practitioners is not mandatory. Therefore, in instances where the products used are compounded or distributed directly by practitioners (and therefore unlicensed), any resulting adverse effects would not enter into the pharmacovigilance system. Even where stringent regulatory frameworks exist, the ultimate safety of HM will still depend on appropriate use and the high quality of the products.

Appropriate use is strengthened by the ability of regulatory systems to mandate the inclusion of information on labels. Such critical information would include appropriate dosing instructions and indications for use, messages to recommend seeing a healthcare professional should symptoms not resolve as well as cautions and contraindications.

14.5 Methods for Pharmacovigilance of Herbal Medicines

14.5.1 Reporting Method

The pharmacovigilance of HM is still a relatively new concept and may not exist in many countries. The minimum information required for a report of suspected adverse reactions for HM is the same as for conventional drugs. A single reporting format covering all health products, including HM, is beneficial to enhance the efficiency of reporting. Where regulatory systems exist, the format should provide for the reporting of the authorisation number (if any) of the HM product to allow unambiguous identification of the product, its ingredients and the manufacturer. Instructions to provide the product ingredients and/or the label of the product will help with identification in the case where the authorisation number is not available or in the case where a regulatory system or premarket authorisation of HM does not exist. Additional information beneficial for a full assessment of an adverse reaction suspected to be associated with a HM includes the part of medicinal plant used; preparation methods, route and methods of administration, dose used and the name of the manufacturer/supplier. Ideally, the reporting format should also make available a space to indicate whether a sample of the suspected HM is available. Although often difficult to obtain, samples are particularly important since their analysis will provide information about the composition of the HM and also for the botanical identification and possible analysis for quality and the presence or absence of contaminants or adulterants. Education of reporters about the information that should be sent for collation and assessment is essential (see below). A well-designed reporting format is a very useful aid to capturing information on suspected HM adverse effects, but education of potential reporters is equally important.

14.5.2 Spontaneous Reporting Schemes

The spontaneous reporting of adverse reactions for HM (as for any medication) will suffer from under-reporting. The under-reporting of HM adverse reactions is heightened for a number of reasons including the perception by consumers and many healthcare practitioners that HM is safe and could not be responsible for the adverse reaction and that not all health professionals know that reactions to HM can be reported [14]. Spontaneous reporting systems are in the early stages of development in some parts of the world such as Africa [26]. To increase the quantity of adverse reaction reports for HM in Canada and the United States, manufacturers are required to report serious or serious, unexpected adverse reactions [14]. Educational activities may also increase the quality and quantity of spontaneous reports for all potential reporters.

14.5.3 Prescription Event Monitoring

The methodology of prescription event monitoring (PEM) in monitoring the safety of newly marketed prescription drugs is well established [30], and its contribution to pharmacovigilance of conventional medicines is known and evident, but this method is of little use for pharmacovigilance of HM in most countries since HMs are not, or are rarely, prescribed. This is a possible important future perspective for the better monitoring of HM.

14.5.4 Signal Detection

With some HM, with enough numbers of reports of suspected adverse reactions, it may be possible to obtain proportional reporting ratios. But the comparison is often only made against the rest of the adverse reaction database including all health products (essentially conventional medicine reports), rather than only against the subset of herbal adverse reaction reports. It is certainly possible that the patients using HM may, overall, have a different health profile than those taking conventional medicines. The assumptions made in proportional analysis and the importance of the effect have been discussed only in the context of conventional medicines [31]. In the future, it will be important to find out more about the characteristics of users of HM, and it seems essential to be careful about the choice of the comparison group when any type of observational studies are performed.

Until now, in many countries where the pharmacovigilance of HM is well developed, because of the relatively small number of reports of suspected adverse reactions associated with MH, signals are detected simply by numbers of reports [32] or the heightened and focused surveillance of certain problematic herbs. Efforts should be directed at determining the value of sources other than the scientific literature

and traditional pharmacovigilance systems, for information on HM adverse reactions. For example, it has been recognised that poison control centres hold a great deal of information on the adverse effects of herbal products [14, 26]. The ability to capture national data on adverse reactions from poison control centres would improve signal detection in this area.

14.5.5 Causality Assessment

Causality assessment, or the linking of the observed adverse event to the suspected HM, is a pivotal step in the proper assessment of such effects and subsequent risk management activities. There are many different methods proposed for causality assessment such as algorithmic, probability based and expert analysis. The important factors in assessment are the temporality between the exposure to the suspect substance and the adverse reactions, the role of coexistent disease and medication as alternative etiologic possibilities and the examination of a plausible pathophysiologic mechanism of the suspect product or ingredient (s). But there is a particular challenge in relation to HM reactions with regard to product quality. There are many reports of the adulteration of HM with prescription drugs, contamination with heavy metals and cases where the product contains misidentified herbs. These quality issues can create significant challenges in attempting to link a herb or other ingredient to the reaction. Other stages in the evaluation are difficult with respect to HM, including the quantification of risk, as there is often no reliable way of determining the number of individuals exposed to the precise HM product in question. Also because of the limited clinical data on safety and efficacy of HM in many countries, and the quality and completeness of the HM reports, benefit-risk analysis can be difficult. Accurate and complete data is, again, essential.

14.6 Communicating Herbal Medicine Safety Concerns

The requirements for successful communication including the timing, the content and the method of delivery of messages regarding HM safety concerns should mirror those used for conventional medicines. However, communicating information on HM safety concerns presents some additional obstacles such as the fact that healthcare professionals are unlikely to know which of their patients are using HM unless their patients discuss this use or are asked. In addition, most users of HM get these medicines from outlets without seeking professional advice.

Many means may be used to disseminate the information about HM safety concerns identified through pharmacovigilance activities. Adverse reaction newsletters, information bulletins and risk communications are issued by many regulators. Newsletters and information bulletins may be specific to HM or may cover both HMs and conventional medications. In any case, the open, transparent, timely and efficient knowledge transfer of safety information is critical to inform consumers,

patients, manufacturers, herbalists and international regulators. Information may also be shared via articles in professional journals, conferences, courses, mass media, targeted messages for consumers and Internet websites of regulators or other pharmacovigilance centres [26]. Direct communication with consumers is also important, given the possibility that healthcare professionals may not know that their patients are using HM. Such communication may include alerts and warnings on the websites of government agencies (which are often picked up by the mass media), information articles issued by regulators and even information provided at points of sale.

14.7 Traditional Medicine Contributions to Primary Health Care

The contribution made by traditional medicine to the modern system of medicine is worth noting. Some well-established drugs have been developed by scientists from plants. Examples known: salicylic acid, used traditionally to reduce pain and inflammation, is originally a derivative from plants of the *Salix* genus and which gave rise to the synthesis of acetylsalicylic acid; theophylline, used traditionally to open airways, comes from a plant source, *Catharanthus roseus*; pilocarpine, used to reduce pressure in the eyes, is from the plant *Pilocarpus jaborandi* [33].

14.8 The Future for Pharmacovigilance of Herbal Medicines and Traditional Medicines

The future for pharmacovigilance of HMs and traditional medicines largely depends upon improving pharmacovigilance systems for HM. Some of these factors will already be present in some pharmacovigilance systems:

14.8.1 Safety, Efficacy and Quality of Herbal Medicines

The use of HM must take into account their safety, efficacy, consistency and quality [34–37]. The safety of HM requires strict control of quality and manufacturing techniques and requirements for appropriate labelling (dosage, indication, strength, ingredient listings, contraindications, cautions and warnings, etc.) [32, 38]. Essentially this means applying the principles of good governance to all steps in the process from sourcing the raw materials to the delivery of a therapeutic product for use by patients. Currently, this full structure is not in place in many countries of the world. The safety and effectiveness of HMs directly rely on the quality of the product.

14.8.2 Herbal Medicines Regulatory Framework

Adequate regulatory frameworks for herbal products are needed to effectively protect consumers and patients. Where premarket assessment or market authorisation of HM are not part of a country's regulatory system, the presence of a robust and well-defined post-market surveillance can add a level of protection by detecting adverse reactions and poor-quality products. Even where premarket assessment and licensing of HMs exist, post-market surveillance is a necessity to monitor for reactions to poor-quality products (e.g., contaminated products) and for potentially unknown risks resulting from real-world use (e.g., herb–drug interactions). Without a specific premarket environment, the listing of acceptable HM and the listing of safe combinations of HM and conventional drugs can be provided as a guide to patient care [39].

The mandating of adverse reaction reporting of market authorisation holders exists in some countries, such as the United States and Canada. In these countries, serious and serious unexpected reactions must be reported to national pharmacovigilance centres. This partially reduces the under-reporting associated with herbal medicines. In some countries, provisions also exist for companies to maintain an annual summary of adverse reactions to herbal medicines, which is to be submitted to regulatory authorities if requested.

14.8.3 Herb–Drug Interactions

The clinical importance of herb–drug interactions depends on many factors associated with the particular herb, drug and patient, as well as the specifics of the use of both. HM should be appropriately labelled to alert consumers to potential interactions when concomitantly used with drugs.

During any preoperative evaluation, physicians should be familiar with the potential preoperative effects of commonly used herbal medications, in order to prevent, recognise and treat potentially serious problems associated with their use and interactions with conventional drugs. Populations with specific disease conditions may be more at risk of herb–drug interactions due to their reliance on multiple prescription drugs and the use of alternative medicines. HIV/AIDS patients are such an example and often use alternative medicines in combination with their pharmaceutical drugs [40].

14.8.4 Patient Categories

The widespread use of HM in pregnancy and during the breast-feeding period indicates an increased need for documentation about their safety and efficacy in these populations. Adequate information on the efficacy and safety is largely lacking for

the majority of HM, so they cannot be recommended during pregnancy and lactation unless there is evidence to the contrary.

As noted above, certain patient populations make more use of HMs, often in combination with conventional drugs. Treating physicians should be aware of this potential use and should question patients about the use of HM.

Specific education with regard to providing healthcare professionals information on HM use and to report any adverse reactions experienced would be valuable in such patient populations. Education to specific patient advocacy groups could be used to help inform their stakeholders of the importance of these factors.

14.8.5 Awareness

It is important for health professionals, consumers and other interested stakeholder groups, including regulatory authorities and suppliers of HM, to be aware of the side effects and drug interactions caused when herbal medicines are administered with conventional drugs. Patients should disclose their use of herbal medicines to their physicians and pharmacists, who then will be aware of HM adverse reactions and potential herb–drug interactions.

It is imperative that physicians are aware of all medications, both conventional and HM that their patients are taking, in order to provide the best care. This should be possible by direct patient questioning. Physicians must regularly ask their patients about their use of HM, particularly elderly patients [41] and those whose disease is not responding to treatment as expected. Physicians and other healthcare providers should be aware of the extent of a patient's self-medication with alternative therapies [42].

14.8.6 Communication and Education

Effective communication between all pharmacovigilance partners where HM is concerned is required, and safety information must be shared and accessible to all [43]. Various methods can be considered to reach all relevant target audiences, such as involvement of the mass media and patient/consumer associations (including translation into local languages where appropriate and essential for the public at large), education of health professionals via the delivery of adverse reaction bulletins or articles and meetings and education about the implications for HM providers, academics, researchers/scientists and the pharmaceutical and herbal medicine industries. Communication must be an inclusive network, well structured, collaborative and adapted to the local and cultural situation.

The inclusion of information on HM as a source of therapy could be included in academic programs. Pharmacological aspects of phytotherapy should be included in the regular medical and pharmacy curriculum [44]. Improvements in the education of all healthcare professionals should be made with regard to the principles and practice of pharmacovigilance. The addition of such a subject to the curriculum of both conventional (medical) and alternative (naturopathic, chiropractic) schools would inform these practitioners of the importance of discussing the use of HMs with their patients, as well as how to recognise and report adverse reactions.

14.8.7 Scientific Research

Scientific recommendations on the use of HMs and their co-administration with conventional therapy should be based on all available scientific data including case reports but also on quality published data, where they exist. While the evidence database on HM and drug interactions continues to grow, there is still limited information on the potential safety concerns with HMs in general, including information with respect to herb–drug interactions. Current data are generally insufficient to predict the incidence of HM use, HM adverse reactions or herb–drug interactions. Thus, the use of HM and herb–drug interactions need to be investigated through greater research, particularly by meta-analysis of prospective and clinical studies using large population samples in order to avoid the problems with individual susceptibility [45]. Prospective randomised clinical trials assessing HM and herb–drug interactions would be valuable.

Exchange of data and research results among countries should be encouraged and supported by improvement in international conventions. Funds available for scientific and medical research should also be directed into clinical trials of HM

A key factor in any scientific study of HMs is the need to positively identify the herbal material being used. Many published reports of adverse reactions do not include an analysis of the suspect products. Such information is critical to enable a complete assessment of the case, in order to confirm if the reaction is associated with the herb in question or due to contamination, adulteration or plant misidentification.

Despite the challenges associated with the current scientific knowledge on HM, there are opportunities to improve, including the use of omics and predictive toxicology [14]. The use of these newer methods of analysis provides the opportunity to gather more information on the safety of HMs, in a more rapid manner. Combining traditional testing methods (e.g., animal use) with these types of assays will aid in obtaining a more complete picture of the safety of HMs.

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Chapter 15
The Concept of 'Health'

Shirley-Ann van der Spuy

Health is a fundamental human right and could be considered one of the most important assets to human beings. The World Health Organization (WHO) defines health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. The right to health was recognized in the 1948 Universal Convention on Human Rights, and since then many international reforms and charters have recognized the need to commit to and protect these rights [1].

One of the key aspects of ensuring the right to health is that all services, goods and facilities must be available, accessible and of good quality. It's important to remember that the concept of health is not only a consequence of medical treatment but includes the right to safe food and drinking water, sanitation, nutrition, housing, work environments, education and gender equality [1].

Pharmacovigilance is defined by the WHO as 'the science and activities related to the detection, assessment, understanding and prevention of adverse effects or other drug related problems'.

In May 2002, the WHO developed the WHO World Alliance for Patient Safety to encourage countries to focus on the safety of its patients by promoting the reporting of adverse events and fostering a culture of learning from these to minimize medication errors, accidents and system failures [2].

One of the primary functions of pharmacovigilance is to continually monitor the benefit-risk profile of medicinal products, thereby supporting health programmes, enhancing patient care and ensuring patient safety in an effort to facilitate better health.

Fundamentally, therefore, we could redefine pharmacovigilance as 'the continued assessment of clinical care to ensure the obligation to protect the human right to optimal health is respected and fulfilled; and where this is found to be deficient, to implement appropriate measures to limit its infringement or deficiency'.

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With current trends in pharmacovigilance moving towards continued risk assessment to ensure the benefits of medical care always outweigh the risks they present, this alignment with the concept of protecting 'health' is an important one.

15.1 Politics and Pharmacovigilance

Developing countries face greater challenges to sustain health, with a struggling viable infrastructure. Having limited financial resources and the lack of education and expertise, these countries cannot help but fall short of protecting health in many ways. It is not surprising then to think that the expectations of patients and their idea of quality care in these countries are quite different to those of us in the developed world.

For many of these patients, ill health or disability has far-reaching consequences, such as limited or no employment, no payment or financial assistance, limited access to medical care and possibly even the threat of starvation. In many of these communities, disease sufferers are ostracized, marginalized and discriminated against. It's important to understand for individuals from these countries that satisfying the simplest and, for many, the most basic of needs can provide great improvements and has far-reaching consequences.

Conversely, developed countries have the infrastructure, regulatory framework, financial power, education and therefore expertise required to support the drive towards ever higher standards of healthcare. Statistically they make up a minority share of the world's population yet produce the lion's share of pharmacovigilance information.

The drive must surely be to extend the reach of pharmacovigilance across these barriers to ensure a thorough global assessment of medical care can be captured. Pharmacovigilance needs to be reflective of the world's population as a whole and be able to assess patient risk for all. More than half of the world's population is now living in urban areas, and this figure grows year on year [3].

James Manyika, Director of McKinsey Global Institute, highlights four key forces that will shape the future: [4]

1. A shift in economic activity to emerging markets resulting in industrialization and urbanization in these developing countries.
2. Accelerated technological advances with digital and mobile technologies being adopted at unprecedented rates.
3. Spreading and increasing subfertility rates resulting in the elderly outnumbering the working age and the pressures this presents.
4. Increasing global connections resulting in new competition and opportunities.

Looking at the bigger picture, pharmacovigilance needs to maintain an awareness of how these trends could be used constructively to enhance the detection, assessment and management of the risks associated with medical and therapeutic intervention, the primary goal of which is to protect patient health.

15.2 The Burden of Pharmacovigilance

Primum no nocere is Latin for 'first, do no harm'. The physicians' oath makes a promise to patients to exercise due diligence, care and good judgement when prescribing beneficial treatments and to do everything in their power to protect patients from harm, never administering an unnecessarily harmful substance nor advising on its use [5].

The thalidomide tragedy over 50 years ago had a profound influence on the pharmaceutical market, resulting in the birth of pharmacovigilance in an effort to prevent such disasters from occurring again [6]. The product never went through any preclinical testing. However, many years of post-marketing experience have highlighted the fact that clinical trials are limited in their ability to detect adverse consequences associated with medical treatments.

The European spontaneous reporting mechanism provided important evidence to support the withdrawal of five out of six products between the years 1999 and 2001. Likewise, during the following 9 years (2002–2011), 19 drugs were withdrawn from the EU market for safety reasons, and the evidence for these withdrawals was derived primarily from post-marketing surveillance of spontaneous reporting systems [7].

Adverse reactions to drugs and the treatment thereof place an additional economic burden on governments and increase the overall cost of healthcare. Adverse events are listed as the fourth leading cause of death in the US ahead of diabetes, HIV and automobile accidents [8]. In France it is estimated that as many as 123,000 patients consult their GPs every year about adverse drug reactions (ADRs), and many of these result in hospitalization. The US and Canada report that ADRs are responsible for as many as 30 % of all hospital admissions. Similarly, Australia and Europe report ADR-related hospital admissions to be as high as 18 % and 10.6 %, respectively [9].

The US estimates ADRs cause millions of injuries each year, with the cost of treating these cases as high as 30.1 billion US dollars annually. The main costs of such treatment were attributed to wages, disposable goods and medications. In addition, we must also consider the cost to the patient in time off work, possible loss of income and any subsequent consequences as a result of these events [7]. These are costs developed countries can ill afford let alone those with much more limited resources.

These figures encourage health regulators to support any drives or initiatives to promote evidence collection during the post-marketing phase and are a clear and resounding admission of the importance of enabling the spontaneous reporting process. As such, the challenge remains as to how to access this data quickly and cheaply and in ways for it to add value to existing pharmacovigilance reporting frameworks.

Currently the World Wide Web presents significant challenges for global pharmacovigilance with Internet sales of prescription drugs bypassing regulators and any means to control product quality and integrity. Educating the patient about pharmacovigilance is the next step in the treatment development process.

Whilst technology has the power to work towards enhancing the safety surveillance of drugs, it too has the power to cause harm to vulnerable consumers who remain ignorant of the risks of medicinal products. Counterfeit or unapproved drugs bought from rogue traders pose a huge threat to public health [10]. Since 2004 the MHRA has had ten instances of batch recalls due to counterfeit products, which have managed to penetrate the legitimate supply chains [11].

15.3 The Pharmaceutical Framework

The industry pressures that led to the thalidomide disaster remain prevalent within the industry today, and the interwoven nature of global business-to-business interactions adds multiple layers of complexity. As such, it is important to identify who the pharmacovigilance stakeholders are, understand their role in healthcare and assess their impact on treatment outcomes.

Pharmacovigilance oversight is far reaching and does not start with the end user (i.e. the patient) reporting an adverse reaction (even though their well-being is the primary focus of our attention) but begins much sooner in the preclinical and clinical trial process. Collection of toxicity data in animal studies and subsequent safety data collected during human studies is where the seeds of pharmacovigilance germinate for any medicinal product. During this process, safety and efficacy remain a clear focus, and the construction of reference safety information occurs during these early stages.

Following this, the testing of the product in various formulations occurs and confirmation of the manufacturing process. Any changes within the manufacturing process, packaging methods and supply change need to be risk assessed by pharmacovigilance to determine the likely affect on the product and how these effects may adversely impact the patient.

The quality of the product and batch-to-batch consistency must be ensured prior to release of the product onto the market, relying on the co-operation of chemical manufacturers of active ingredients and supporting excipients, the pharmaceutical drug manufacturer and associated testing laboratories.

Furthermore, packaging and labelling companies need to be aware of the necessity to include pharmacovigilance in the design of artwork and changes to print runs. The distribution and logistics of sale and supply are equally important to ensure products requiring specialized storage conditions are met and maintained to ensure the product remains stable and continues to be suitable for use, including good governance from quality-assured ingredients through satisfactory protocols for all assessments and research to the final delivery systems to patients.

The collaborative business-to-business partnerships to enable global distribution of products need to be carefully managed to enable emerging safety issues to be identified early and communicated effectively between parties. As such contractual obligations must be overseen by pharmacovigilance to maintain safety across the spectrum of its global markets. The network of these intercompany relationships

can be complex and requires good business-to-business training, facilitation and open-transparent communication between parties.

Finally, the system to ensure prescribers and patients are supported by the company to ensure their products are used safely and effectively includes pharmacovigilance, through the product complaints process and the reporting of adverse events.

New drug reactions often come to light in isolated well-documented incidents during the post-marketing phase [12]. It's important therefore to ensure the highest standards are maintained and for experienced companies to encourage and educate global partners who are perhaps not as familiar or experienced with the practice of pharmacovigilance and therefore threaten to weaken any existing pharmacovigilance system, reducing its efficiency and disabling its true intention.

The future of pharmacovigilance relies on a collaborative unity between multiple stakeholders to ensure the right to health is respected, protected and fulfilled. Two key stakeholders at the epicentre of the pharmacovigilance process are unmistakably the patient and the prescriber.

15.4 The Primary Stakeholder: The Patient

Not all patients are equal. It's important to remember the patient is a multifaceted individual who is a product of their environment and life experience. We claim to be a global village, yet we are divided on so many levels by varying degrees of social, economical and geographical differences. Understanding these differences is key to understanding the patient, what's important to them and how to make healthcare effective for them.

Cultural diversity is a challenge more so for developed countries and requires consideration. As multicultural societies, developed countries must ensure treatment is non-discriminatory, cultural and religious beliefs are respected, and care is provided to enable the patient to continue to enjoy life and pursue their life plans. Clinicians need to be aware of the cultural background of patients and how this might influence their perspective on illness, the provision of care and their perception of quality care. Patients need to feel their physician understands them, both clinically and holistically.

Our global population is more educated and has immediate access to more information than ever before. This trend is unlikely to slow, and the use of online resources can only increase as developing countries also gain access to these technologies.

Healthcare systems need to evolve to accommodate the changing needs of the patient population, taking a more 'patient-centred' approach that is holistic, empowering and tailored to suit the needs of the individual. Patients want more freedom and information to make informed decisions on different treatment options, to enable them to make the right decision for themselves. Many patients want to be active participants in the decision-making process and want to work with clinicians

who listen and are open to discussion [13]. In spite of this, however, there must be a willingness and time for healthcare professionals to take responsibility for ensuring that those patients who are unable or unwilling to make decisions on their therapy are supported adequately in whatever way is necessary.

In developing countries where access to physicians and quality healthcare is limited, empowering the patient to become an integral part of their own treatment protocol is of paramount importance.

Building on this concept, encouraging patients to report adverse reactions helps them to be active participants in their treatment process and works towards improving their knowledge about health issues [12].

15.5 The Patient and the Prescriber

Prescribing physicians and supporting healthcare professionals are in key positions to educate the public on how to report adverse drug reactions. For patients experiencing adverse events, the Internet is often the starting point to confirm their suspicion of the adverse reaction and determine a possible causal association with their treatment.

The consumer is increasingly making use of the Internet to educate themselves about their health concerns and disease conditions. Studies have shown that whilst these tools can provide a possible diagnosis, they are frequently wrong with the correct diagnosis listed first in only 34 % of evaluations [14].

Technology is viewed as obstructive by some healthcare professionals, and when presented with a patient's findings, their negative reaction can alienate the patient and stifle open communication. The UK's NHS choices website reports visitor rates in excess of 15 million per month, and in the US, more than a third of adults use the Internet to self-diagnose [14].

It is important to engage with the patient and interpret their 'home research' as a means to take responsibility for and be proactive about their condition. The healthcare professional should be encouraged to consider and discuss this research, present their own clinical interpretation and recommend a course of action, thus including the patient in their treatment choices.

Patients are notorious for non-disclosure and at times blatantly dishonest. An article in *Newsweek* claims as many as 30–40 % of us 'stretch the truth' about smoking, risky sex, alcohol intake, recreational drug use and use of other medications or alternative medical treatments [15].

A study of diabetic patients by Beverly et al. (2012) found that although patients reported positive relationships and high levels of confidence in their physicians, as many as 30 % avoided discussions on self-care, withholding information about their diets, exercise, blood glucose checks and other concomitant and self-prescribed medications. The main reasons for non-disclosure were reportedly a fear of being judged and of disappointing their doctor [16].

In December 2008, the *Journal of the American Medical Association* reported that 1 in 25 adults aged 57–85 are putting themselves at risk of major drug interactions through the use of prescription and non-prescription drugs and dietary supplements. Physicians are unaware of this because they do not ask, or patients are reluctant to report such use [17].

A Canadian study conducted in 2010 [18] discovered that patients who experience an adverse drug reaction whilst taking natural health products were unlikely to report these to either their healthcare professional or the Canadian authorities. Once consumers suspected an ADR, they used a process of elimination, re-challenge and other investigative searches to assess their symptoms.

Reasons for not reporting included taking responsibility for their own actions, concerns that physicians would not support their decision to use natural products or a reaction they were not concerned about and judged to be mild or non-serious. Consumers were either unaware of the mechanisms in place to enable reporting of such events or believed the process would be complex.

A recent *BMJ* article mentioned that patients tended to be more honest when interacting with a computer and submitting data via online surveys or questionnaires [19].

15.6 Current Challenges of Pharmacovigilance

- Access to advanced technologies

This year 30 countries in Western Europe and Asian advanced economies dominated as leaders in the global ICT revolution. These high-income countries have education systems and policies that drive digital innovation in ways inaccessible to emerging markets. This essentially means the technology gap is widening and, although developing countries have made great strides towards network readiness, their progress is slow and in some areas facing stagnation. Developing markets that have made considerable improvements include, Lithuania, Malaysia, Latvia, Kazakhstan, Armenia and Georgia. In Africa, countries like Kenya, Nigeria, Tanzania, Lesotho and Madagascar are experiencing the benefits of market reforms [20].

In developing countries information and communication technologies reduce inequalities, take people out of poverty and create employment opportunities. However, access to the Internet remains inaccessible to large parts of the world, and it's important to consider these issues when planning or interfacing with any local pharmacovigilance system in these sectors [19]. On the other hand, the rapid development in IT and the use of smartphones does provide some opportunities for even resource-poor countries to 'leapfrog' over the use of cumbersome paper-based systems for communication including reporting adverse drug reactions.

The ever-expanding global scope of these technologies presents opportunities to empower consumers to self-report suspect adverse reactions to regulatory

authorities, companies and healthcare professionals. However, patient reporting is a fairly new concept to pharmacovigilance, with the Netherlands accepting direct patient reports since 2003 and the UK in 2005. Sweden has accepted patient reports since 1978 and Australia since 1964, and the US has always encouraged patient reporting [21].

- Consumer awareness of pharmacovigilance

Considering the longevity of patient reporting in Australia, a consumer survey conducted in 2013 to assess consumer awareness showed reporting rates were in decline, with only 5.7 % of ADR reports to the TGA made by patients between 2003 and 2009 and reporting rates down by 3 % in 2011. Lack of awareness of reporting mechanisms available to consumers is thought to be the major limiting factor [22].

Spontaneous reporting is the most cost-effective method of post-marketing drug surveillance, but concerns about 'false-positive' drug-event associations have been raised. The disadvantage is the lack of any control group and understanding the risks within the unexposed population. Begaud (1993) concluded that the probability of this occurring was extremely low, and for rare events such as toxic epidermal necrolysis and agranulocytosis, the reporting of more than three cases would constitute a strong signal. The duration of treatment (3 months or less) for many drugs further reduces the risk of false-positive associations [23].

- Sharing of past experiences

An online survey of 9,113 pregnant women found that general awareness of the thalidomide tragedy was declining. Their perception of risk to their pregnancy presented by OTC and prescription medicines were lowest in women aged 31–40, in women for whom it was not their first pregnancy and those working in the healthcare sector [24].

The important contribution that patients can make to areas where access to information such as pregnancy exposures, medication errors, product misuse or abuse, long-term use, occupational exposures and other vulnerable groups (excluded from clinical trials) should not be underestimated. These are key areas where little to no clinical data exists and where most risk management plans show gaping holes in their data.

- Emerging economies

As one of the most populated continents, Asia is home to nearly 60 % of the world's population and has the third largest pharmaceutical market comprising up to 70 % of total global value. This region is dominated by generic medicines, but strong growth is expected as Japan and Singapore strengthen their presence in the patent market and the number of clinical trials grows year on year. China is predicted to become the second largest pharmaceutical market, yet their pharmacovigilance systems were only implemented 15 years ago [25].

In 2011, Japan conducted a feasibility study to assess online patient reporting of ADRs. Patient feedback was extremely positive, stating they would use the system again and recommend it to friends and family. Users understood how their

information would contribute to the data collection system and wanted to share their experiences and warn others or help prevent reoccurrence. One important factor noticed in this study was patients' expected to receive some type of feedback after filing their report, although with few wanting advice or clinical input [26].

- An expanding pharmacovigilance scope

Based on the requirements for allopathic medicinal products, the EU has expanded regulatory requirements to include herbal medicines, traditional Chinese and Indian medicines, cosmetics and medical devices through a registration approval process, now required to show a pharmacovigilance system is in place. These products are sold predominantly as self-selected goods, with little or no interaction with a healthcare professional, thus placing the responsibility of care directly on the consumer.

Herbal or natural remedies have little or no scientific or clinical data to support their proposed mechanisms of action and therapeutic claims. This fact alone provides a strong argument to drive patient reporting forward as a means of plugging this black hole in our dataset and enabling further assessment of these compounds.

In June 2013 the MHRA announced that like other nicotine products, it would regulate e-cigarettes as medicinal products [27]. This precautionary approach to substance use is likely to grow, and the scope of pharmacovigilance will extend into more and more varied and challenging markets.

15.7 The Future Face of Pharmacovigilance

Statistics for 2015 released by National ICT Accessibility Framework (ITU) place Internet users as high as 3.2 billion, of which 2 billion live in developing countries. This represents a sevenfold increase of 6.5 % in 2000 to 43 % in 2015. Mobile subscriptions are up from 738 million in 2000 to 7 billion subscriptions across the globe. The expansion of the mobile broadband has increased 12-fold since 2007, and ITU reports that in 2015 up to 69 % of the world's population will have access to 3G, of which 3.4 billion of these will be people living in rural areas [28].

There are 196 countries in the world today, and over 120 of these are members of the WHO Programme for International Drug Monitoring [29]. Broadband is now affordable in 111 countries, accounting for less than 5 % of a person's gross national income.

Our population of young people, aged 10–24, has reached 1.8 billion, with more young people in the world than ever before in the history of mankind. It's astounding then to realize that 90 % of these young people live in developing countries [30]. Herein lie our future mothers, fathers, doctors, scientists and patients. These are the future stakeholders in pharmacovigilance.

The time to educate patients and empower them to contribute to pharmacovigilance is now. The future of pharmacovigilance clearly lies in supporting the

developing world to establish simple, workable, cost-effective and easily accessible frameworks for adverse event reporting.

In 2012 the US FDA passed the Safety and Innovation Act (FDASIA) to call for new and innovative ways to identify sources of post-marketing safety data. A study conducted to assess Twitter as a possible source of such information was carried out between 1 November 2012 and 31 May 2013 through the analysis of 6.9 million tweets resulting in the isolation of a 4,401 strong candidates for potential AE reports. Nearly three times as many reports were identified through Twitter than were reported to the FDA by consumers [31]. This highlights the fact that consumers hold a huge amount of untapped data.

A pilot study conducted in Cambodia assessed the feasibility of using SMS text messages to enable patients to report adverse events. Although the study group was small, the response rates of participants were extremely high (71.7 %). High rates were attributed to patient education on the use of the tool and the use of short, simple reply codes. This created a positive outcome, proving that these strategies can be effective [32].

The Patient-Reported Outcomes Safety Event Reporting (PROSPER) consortium aims to provide patients with a 'voice' in safety data collection, promoting the patient's perspective and the use of 'real-world' data to better evaluate the benefit-risk profile of drug treatment. Evidence has shown that patients are better at identifying potentially serious AEs earlier than clinicians and improve data accuracy [33]. In Europe the WEB-RDR project is investigating smartphone patient reporting as well as the potential of the Internet to provide new drug safety insights (http://www.imi.europa.eu/content/web-radr).

We must be forward thinking in engaging the patient as we enter a 'patient-centred' era in healthcare, where the patient's perspective, preferences and experiences should be considered through every stage of drug development. Data collection should be geared towards consumers, using less formal language and enabling transmission of test results or other clinical reports, without the need for clinical interpretation [32].

15.8 Closing Summary

The underlying thread for the future shows a huge role to be played by the expanding access to online resources and mobile technologies and their use by both healthcare practitioners and consumers. This online medium presents a number of challenges, which are in direct conflict. The unregulated issue around the potential for patients to purchase unsafe medicines and cause themselves potential harm versus the use of this tool as a means to gather information about their disease condition and its treatment.

There needs to be a system to ensure patients are educated about the important contributions they can make to pharmacovigilance by providing every opportunity to give clear directions to local reporting schemes.

As the reach of these online technologies, via mobile devices, social media and other online portals, expands globally, we need to be prepared to use this to promote pharmacovigilance and enable patients to access reporting mechanisms more easily. In addition, the reporting process should be simplified to enable efficient reporting of any drug-related concerns by the public, and appropriate feedback must be provided to keep participants engaged.

Pharmacovigilance is an essential contributor to patient care, the objective of which is the early identification of important risks to ensure the best treatment outcomes are achieved to sustain the overall health and well-being of the patient.

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Chapter 16
Impact of Referral Procedures on the Interaction of RMP and PSUR

Elizabeth Storz

With the European legislation for pharmacovigilance, a number of new requirements for the monitoring of the safety of medicinal products were introduced in 2012. This change of the legislation of human medicines in the European Union was the biggest change for about 17 years. It was the result of a review of the European safety monitoring system for human medicinal products, which led to changes of the existing legislation concerning pharmacovigilance and to their adoption.

Specifically Directive 2001/83/EC was amended with Directive 2010/84/EU [1] as well as Regulation (EC) No. 726/2004 was amended with Regulation (EU) No. 1235/2010 [2]. The extent of the Directive for example was increased quite a bit with the number of articles in Title IX (Pharmacovigilance) increasing from 9 to 29. Additionally a new Commission Implementing Regulation (EU) No. 520/2012 [3] was enacted including various requirements on operational aspects for the new legislation with regard to pharmacovigilance.

It was emphasized that all these new requirements regarding pharmacovigilance needed to be applied regardless of the type of marketing authorization (centralized, decentralized, mutual recognition, or national). The main objectives of the new provisions that were introduced in 2012 were to harmonize pharmacovigilance requirements across the European Union and to make clear roles and responsibilities of the marketing authorization holders because there had been some areas in the previous legislation that had been confusing and not very clear. Furthermore, it was anticipated to decrease administrative burden and workload for both Competent Authorities and the marketing authorization holders in order to free up resources by simplifying processes and avoiding duplication of effort.

So in the following article a good look will be taken at some of the new requirements, and it will be analyzed if the intended objectives of the new legislation from

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the perspective of marketing authorization holders – mainly decrease of workload and administrative burden as well as simplification of processes – were achieved.

Some specific requirements which were amended in 2012 concerned risk management plans (RMP), periodic safety update reports (PSUR), and referral procedures for medicinal products.

16.1 Legally Required Documents: RMP and PSUR

Risk management plans (RMPs) as well as periodic safety update reports (PSURs) are legally required documents for medicinal products and are the primary pharmacovigilance documents. Both documents are stand-alone documents which need to be complete in their own rights and which have different regulatory purposes as well as different objectives. Nevertheless, the two documents as such are complementary. In order to prevent duplication of effort, it was anticipated that certain modules of both documents may be common to both so that they can be used interchangeably. The new modular structure of RMPs and PSURs was introduced with the new legislation and was intended to facilitate updating by the marketing authorization holder and submission of the document to different regulatory authorities. The legal basis for both risk management and periodic safety update reports is laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 as well as in Commission Implementing Regulation (EU) No. 520/2012 [1–3].

The definition for RMPs is provided in Article 1 No. 28c of Directive 2001/83/EC according to which an RMP is "a detailed description of the risk management system" [1]. References for the legal basis for RMPs can be found in various articles throughout Directive 2001/83/EC (Articles 8(3), 21a, 22a, 22c, 104, 104a, 106(c), and 127a), Regulation (EC) No 726/2004 (Articles 6, 9(4), 10a, 23(3) and 26(c)) and Commission Implementing Regulation (EU) No. 520/2012 (Articles 30 to 33 and Annex 1). Especially Annex 1 of the Implementing Regulation is very helpful as it provides the mandatory format of the RMP with an overview of the required modules.

The main objective of an RMP is risk-benefit management and planning in the pre- and postauthorization phase. Formerly the RMP's main objective was managing of risks retrospectively only. However, it was acknowledged that the risk-benefit balance of a medicinal product can only be assessed properly if the risks are taken into account in the context of the benefit.

The RMP consists of seven parts [3]. In particular the safety specification, which is one part of the RMP, is subdivided into modules so the content can be tailored to the specifics of the medicinal product and modules can be added, removed, or reused in other documents, for example, in PSURs.

The required content of a PSUR is laid down in Article 107b of Directive 2001/83/EC [1] as well as in Article 34 of the Commission Implementing Regulation (EU) No. 520/2012 according to which a PSUR contains summaries of data relevant to the benefits and risks of the medicinal product, a scientific

evaluation of the risk-benefit balance, as well as data relating to the volume of sales of the medicinal product and any data relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product. It should be remarked that with the new format the evaluation of the benefit in comparison to the risks was strengthened. The mandatory format of the PSUR is laid down in Article 35 of the Implementing Regulation as well as in its Annex II which depicts an overview of the modules with their required numbering. Additionally some legal requirements for PSURs are laid down in Regulation (EC) No 726/2004 (Articles 9(4), 14(2), 25a, 26(1) and 28). However, the main legal requirements for PSURs can be found in Directive 2001/83/EC in Articles 107b to 107 g.

The main objective of a PSUR is an integrated, comprehensive, concise, and critical overall assessment of the risk-benefit balance of the medicinal product taking into account new information in the context of cumulative information on risks and benefits in the postauthorization phase at defined time points in the lifecycle of a product.

16.2 Interaction of RMP and PSUR

As already described above, the "modular approach" of the PSUR aims to minimize duplication and improve efficiency during its preparation and review along with other regulatory documents such as the safety specification in the RMP, by enabling the common content of particular sections where appropriate to be utilized interchangeably. Table 16.1 depicts some common sections between the PSUR and the RMP.

Table 16.1 Common sections between PSUR and RMP

PSUR section	RMP section
Part III, section 3 – "*Actions taken in the reporting interval for safety reasons*"	Part II, module SV, section – "*Regulatory and marketing authorizaton holder action for safety reason*"
Part III, subsection 5.2 – "*Cumulative and interval patient exposure from marketing experience*"	Part II, module SV, section – "*Nonstudy postauthorization exposure*"
Part III, subsection 16.1 – "*Summary of safety concerns*"	Part II, module SVIII – "*Summary of the safety concerns*" (as included in the version of the RMP which was current at the beginning of the PSUR reporting interval)
Part III, subsection 16.4 – "*Characterization of risks*"	Part II, module SVII – "*Identified and potential risks*"
Part III, subsection 16.5 – "*Effectiveness of risk minimization (if applicable)*"	Part V, section – "*Evaluation of the effectiveness of risk minimization activities*"

Adapted from [4] and [5]

For example, the postmarketing cumulative patient exposure data are needed in subsection 5.2 of the PSUR as well as in part II, the safety specification, in module SV of the RMP. Additionally the format of the RMP and PSUR each requires a summary of safety concerns, and therefore they need to be included in both documents.

So how does the maintenance of a PSUR as well as that of an RMP have an impact on the other document? During the preparation of a PSUR, the marketing authorization holder should consider whether any identified or potential risks discussed within the PSUR are important and require an update of the RMP. Furthermore, the conclusion within the PSUR that is submitted to the Competent Authority needs to be reflected in the RMP as well. In these circumstances, a revised RMP including the new important safety concern should be submitted with the PSUR and assessed in parallel. However, not every important identified or important potential risk may necessarily become a safety concern discussed within the RMP. But if during the PSUR assessment process by the Competent Authority new safety concerns are identified the RMP needs to be updated and submitted to the Competent Authority by the marketing authorization holder.

Analyzing the mentioned requirements for these two legally required documents for a medicinal product, it can be seen clearly that just the creation and constant maintenance of a RMP and a PSUR alone impose quite some workload on the marketing authorization holder. Furthermore, the interaction of these documents in terms of required updating vice versa and the resulting additional workload cannot be disregarded in terms of additionally required staff at the marketing authorization holder.

However, as if this was not enough, referral procedures may also have an impact on information that needs to be included in RMPs and PSURs and requires timely and time-consuming updating.

16.3 Impact of Referral Procedures

With the new pharmacovigilance legislation, the concept of referral procedures was revised. Directive 2001/83/EC was amended and Article 107i referral procedures, so-called Urgent Union Procedures, were introduced. The already existing Article 31 referral procedures were now classified as so-called pharmacovigilance referrals [1]. Furthermore, if only medicinal products are involved that were authorized by the centralized procedure, so-called Article 20 referral procedures according to Regulation (EC) No. 726/2004 are initiated. These however are not initiated so often due to the nature of the marketing authorizations concerned in the referral procedures.

Referral procedures in general are initiated when there are concerns over the safety or benefit-risk balance of a medicinal product or a class of medicines. Reasons why a referral may be started can be related to an urgent safety issue on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities

such as considerations of suspension or revocation of the marketing authorization, refusal of the renewal of a marketing authorization, prohibition of the supply of a medicine, or major changes in the marketing authorization such as deletion of indications, reduction of the recommended dose, or new contraindications [1, 2]. These would be triggers for an Article 107i referral procedure.

After evaluation of data from pharmacovigilance activities and if the interest of the Community is involved and if, as a consequence, there are concerns relating to the quality, safety or efficacy of a medicine or a class of medicines an Article 31 procedure would be initiated. Furthermore, none of the criteria which would trigger an Article 107i procedure should be met.

All referral procedures follow the processes and timeframes laid down in Articles 107j to 107k of Directive 2001/83/EC and additionally of Article 32 for Article 31 procedures of the same Directive.

Finalization of both types of referral procedures – Article 107i or Article 31 – mainly result in further provisions such as changes of the product information, creation of information and educational material for patients and healthcare professionals, implementation of risk minimization measures or the initiation of post-authorization safety studies (PASS), as well as post-authorization efficacy studies (PAES).

As an outcome of most of the referral procedures, a change of the product information will be necessary. A much more complex provision is the requirement of performing a post-authorization safety study. PASS are defined in Article 1 No 15 of Directive 2001/83/EC as "any study relating to an authorized medicinal product conducted with the aim of identifying, characterizing or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures" [1].

Where a PASS needs to be conducted pursuant to an obligation resulting from a referral procedure, the results that arise from these studies need to be included and assessed in the PSUR of the medicinal product in question which then might have an impact on its benefit-risk balance. Additionally, the conduct of the study itself needs to be mentioned in the PSUR. Vice versa a change of the benefit-risk evaluation during assessment of a PSUR might trigger a referral procedure.

Furthermore, results concerning newly identified risks from the PASS conducted might need to be included in the RMP as well, if necessary. For medicinal products that did not have a RMP prior to the start of the referral procedure, a measure arising from the referral procedure or due to results from the imposed PASS might be that an RMP needs to be generated as a completely new document.

However, referral procedures might have an additional impact: educational material for patients or healthcare professionals is one kind of risk minimization measure with the aim of supplementing the information which is provided in the summary of product characteristics (SmPC) and the package leaflet (PL). Educational material as such is part of the RMP. So as a requirement resulting from a referral procedure, it is possible that updating of existing educational material becomes necessary. Moreover, it could be required to create completely new educational material after all.

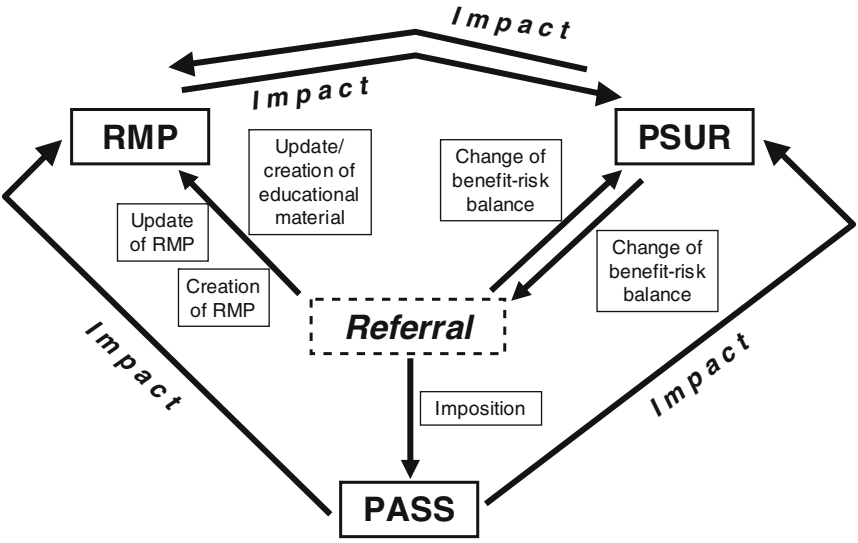

Fig. 16.1 Impact of referral procedures on RMPs and PSURs and interaction with PASS

To give an overview, the impact of referral procedures on RMPs and PSURs as well as interaction with PASS is depicted in Fig. 16.1.

As described before, referral procedures can have various effects such as an impact on RMPs in terms of updating or creation of a new one as well as being a cause for imposing a PASS. Furthermore, the results from a referral procedure might either lead to a change of the risk-benefit balance of a medicinal product which has an influence on the PSUR or a referral procedure might be triggered due to changes of the risk-benefit balance which has been identified from a PSUR.

16.4 Conclusion

So this raises the question whether the aims of the revised pharmacovigilance legislation were achieved? In summary, it can be stated that the timely update of PSURs and RMPs with current data coming from a continuous benefit-risk evaluation as well as keeping oversight of new requirements possibly coming from referral procedures is a permanent and time-consuming challenge for marketing authorization holders. It can clearly be emphasized that one of the main objectives of the revised pharmacovigilance legislation, namely, decrease of administrative burden and workload for the marketing authorization holders, was not achieved. With all the new requirements that need to be taken care of, a simplification of processes was also not accomplished. Not even the concept of having some common parts of RMPs and PSURs in order to avoid duplication of effort can be counted as having a huge impact on decrease of workload in general. It even can be stated that due to the

increase of legal requirements and the resulting additional amount of work, the demand for pharmacovigilance personnel has increased and will even be increasing further. Furthermore, as the number of newly started referral procedures seems to be increasing steadily, it is unpredictable whether a marketing authorization holder's medicinal product might be concerned by such a procedure and whether a temporary increased need of pharmacovigilance personnel might be the consequence.

So does the mere existence of RMPs and PSURs make medicinal products safer? The answer is: yes and no! No, because there had been PSURs already before the revised pharmacovigilance legislation came into force. Furthermore, RMPs had existed for some products as well and PASS had also been conducted. On the other hand, yes, because the marketing authorization holder now is forced to monitor the impact of changes in the risk-benefit balance of his medicinal products even more closely than before as he needs to take care of changes in RMPs and PSURs and those documents impacting each other. Additionally, the legal basis for PASS has become much more regulated since the changes of the pharmacovigilance legislation and therefore more information concerning the risks and benefits of medicinal products can and will be gathered from these studies which will then have an impact on their safety.

So from the marketing authorization holder's perspective, an enormous amount of effort needs to be applied due to the new legal requirements and there is no clear perspective at the current state of how to change the situation.

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Chapter 17
Other Sources of Information for Monitoring Drug Safety: Now and in the Future

Marco Tuccori and Magnus Wallberg

The choice for mankind lies between freedom and happiness,
and for the great bulk of mankind happiness is better.
George Orwell, 1984

The main goal of pharmacovigilance has always been considered the earliest possible identification and characterization of adverse drug reactions (ADRs), with the aim of issuing strategies to minimize as much as possible the exposure of patients to a risk that is not balanced by a major benefit. This process forces each new drug to pass through three different safety filters: preclinical studies, pre-authorization clinical trials and post-authorization studies, the latter including spontaneous reporting of ADRs and observational studies. Each of these filters has breaches that may delay the identification of risks related to the pharmacological treatment, with a consequent injury that accumulates overtime to such an extent to involve millions of people.

Particularly, spontaneous reporting of ADRs and observational studies have been developed as specific drug safety assessment tools in the attempt of overcoming the well-known limitations of randomized clinical trials. However, these approaches have relevant limitations too. The current research in drug safety is going therefore in the direction of overcoming these limitations by considering new sources of data or new analytical approaches. The observation of what is ongoing in present days may provide valuable clues to make reliable predictions about the future. It is just a matter of identifying the footsteps on the ground and following their direction.

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17.1 Current Limitations of Spontaneous Reporting of Adverse Drug Reactions

The limitations of spontaneous reporting of ADRs have been largely debated in the medical literature [1]. The main and most known issue is definitely under-reporting. There are clinical situations in which under-reporting is the consequence of the difficulty of discriminating a drug-related problem from a problem related to patient's underlying diseases. This happens frequently when the disease being treated has important comorbidities such as cancer, diabetes and rheumatoid arthritis. Similarly, when the incidence of an event is so frequent in the population due to non-drug-related causes, a causal role of a drug is poorly considered, such as in the case of cardiovascular events. However, in the majority of cases, the reason for under-reporting consists of the inability to consider the activity of spontaneous reporting of ADRs as a high-priority business in daily life clinical practice. We must recognize that the attempt of placing an imposition of a continuous culture of spontaneous reporting of ADRs among healthcare professionals has had limited success and that the global system of spontaneous reporting of ADRs is sustained by a narrow group of caregivers and with a large contribution from patients. This does not mean that spontaneous reporting of ADRs is useless but simply that this approach exploits only a minimal percentage of its actual absolute potential.

The second major limitation of spontaneous reporting of ADRs is usually the lack of a reliable denominator of exposure. Therefore, the best pharmacoepidemiological information that databases of spontaneous reporting of ADRs can provide is a disproportionality among reports, which represent the base for signal detection [2].

The third major limitation of spontaneous reporting of ADRs is the poor quality of data. Theoretically, spontaneous reporting of ADRs should represent the base for the conduction of observational studies, thus providing essential clinical details for the study design, such as time of onset, concomitant diseases and concomitant drug treatments. This information is very often incomplete or partially provided by the use of proxies (i.e. the use of antihypertensive drugs as a surrogate marker of hypertension). Poor quality of spontaneous reporting data may affect the design of subsequent observational studies, and, in the worst possible scenario, it may lead to draw mistaken conclusions about a risk associated with a treatment.

17.2 Current Limitations of Post-authorization Observational Studies

The possibility of performing observational studies has grown exponentially in the last 20 years due to the advances of information technologies that progressively moved data from paper to electronic media. Furthermore, the computers' power

evolved as well, thus currently allowing the management of huge sets of data which were not manageable before. This epochal change has represented a huge advantage for the possibility of investigating on the clinical outcomes of pharmacological treatments. However, it has enabled the conduct of observational studies using different data and expertise to such an extent that it has led to multiple studies conducted on the same topic yielding vastly different results [3, 4]. This happens also because, differently from randomized clinical trials, there are no standard rules for the conduction of observational studies. The final result is that among the thousands observational studies published every year, only a small percentage achieve an acceptable level of quality and can be taken into account for both clinical and regulatory decision-making.

The capacity of investigating rare clinical outcomes represents one of the major limitations of observational studies. Studies conducted on rare events require huge populations that are available only in large administrative databases. In this setting, completeness of data may depend on the possibility of linking together different administrative databases (i.e. databases containing exposure information with databases containing outcome information), and database linkage depends on the possibility of creating a communication between databases, since these may have different coding systems. Codification may also represent a problem when the coding systems do not allow the identification of a specific clinical problem. It is surprising, for instance, that the association between statins and rhabdomyolysis could not be efficiently investigated until 2009 using the United Kingdom Clinical Practice Research Datalink (a very well-known large database of primary care records which has been used repeatedly for drug safety studies), since the code for "rhabdomyolysis" was not included before in the READ dictionary (the code system used in the database) [5, 6]. The problem of database communication is not limited to the linkage of two different databases recording different data for a geographically defined population, but it can be even greater when the pooling of databases containing information on geographically different populations is required to improve the power of the sample. Therefore, harmonization between databases represents a key issue to be resolved.

Similarly to spontaneous reporting, data quality is one of the main issues of observational studies performed on administrative databases. Since these databases have been set up with different aims (usually the economic management of healthcare services), they often contain limited and poorly recorded clinical information, especially for data not relevant for the recording purposes [3]. For instance, smoking habit and alcohol consumption are essential covariates for investigating many clinical outcomes, but these are rarely accurately recorded and appropriately codified. Sometimes the information of interest is available only for a proportion of patients, and this may require the use of artificial approach such as the creation of categories for the unknown exposures or the computation of a multiple imputation. This issue does not pertain to administrative databases only but also to disease- or treatment-based registries, which represent a higher quality source of data, although they are usually smaller than administrative databases.

17.3 Overcoming the Limitations: Projects for the Pharmacovigilance of Tomorrow and the Quest for New Sources of Safety Information

The aforementioned important limitations in the capacity of early detection of ADRs are the subject of some important pharmacovigilance international projects that are drawing the lines of the future pharmacovigilance [7]. These projects, aimed at integrating rather than replacing the traditional approaches, will be briefly outlined in the following paragraphs.

17.4 The EU-ADR Experience (2008–2012)

EU-ADR database network is comprised of seven established European healthcare databases located in three countries (Italy, the Netherlands and Denmark). These databases include primary care databases (Health Search, Integrated Primary Care Information, Pedianet) in which both clinical information and drug prescriptions are recorded, and comprehensive record linkage systems in which drug-dispensing data from well-defined populations is linked to a registry of hospital discharge diagnoses and other registries collecting clinical information (the Aarhus University Hospital Database, PHARMO and the regional Italian databases of Lombardy and Tuscany) [8].

The EU-ADR network has follow-up data from 1995 to 2010 on over 20 million patients. Drug exposure is estimated using date of dispensing/prescription and delivery systems/dosing regimen, according to characteristics of each database. Due to event coding heterogeneity, a harmonization system using Unified Medical Language System (UMLS) concepts has been issued, and database owners have constructed queries for data extraction. Data was processed locally and then pooled utilizing Jerboa™ (accesses multiple healthcare databases without sharing identifiable data) [9]. Drug prescriptions and dispensations are locally coded using the national product codes, which differ among countries. Most countries, however, link these product codes to the Anatomical Therapeutic Chemical (ATC) classification system [10]. The ATC level 5 code is used as the drug code in the EU-ADR input files. Databases in EU-ADR use one of four nomenclature systems to describe the events: the International Classification of Diseases (ICD9-CM and ICD10) [11], the International Classification of Primary Care (ICPC) [12] and the READ Code (RCD) classification [13]. These different terminologies are mapped using the Unified Medical Language System (UMLS) [14]. The UMLS is a biomedical terminology integration system handling more than 150 terminologies including the four used in the EU-ADR project. Ascertainment of the event of interest from the databases follows an iterative process with seven stages: (1) event definition using clinical criteria established from literature; (2) identification of UMLS concepts corresponding to the event; (3) revision and validation of medical concepts by

database owners and pharmacovigilance experts; (4) translation of the medical concepts into each database terminology; (5) extraction of data and computation of event rates; (6) comparison of query structure—to detect and harmonize eventually any major disagreement across databases; and (7) creation of event input files for Jerboa™. EU-ADR has demonstrated the feasibility of combining diverse and differently structured data in an effective way to detect comparative risks of potential adverse drug events and pave the way for large-scale drug safety monitoring. The common data framework described takes advantage of multiple, routinely collected, aggregated healthcare data while minimizing sharing of confidential patient-level information [15, 16].

17.5 The Observational Medical Outcomes Partnership (OMOP) and the Observational Health Data Sciences and Informatics (OHDSI) (2008–2013 and Ongoing)

The Observational Medical Outcomes Partnership (OMOP) was a 5-year partnership between public and private institutions officially started in 2008 through an initiative of the United States Congress and the Food and Drug Administration. The aim was to inform about the appropriate use of healthcare administrative databases for the conduct of observational studies aimed at investigating on drug effects [17, 18]. The project aimed at identifying the most reliable way to analyse enormous volumes of data collected from heterogeneous sources that are different types of longitudinal data sets. Researchers from academia, industry and governmental institutions worked for 5 years to achieve the following goals: (1) conduct of a methodological research for the empiric evaluation of the performance of several analytical approaches for the identification of true associations and in the avoidance of false associations; (2) development of tools and skills to transform, characterize and analyse different and heterogeneous sources of data used for recording purposes in the spectrum of the activities provided by healthcare systems; and (3) sharing of tools to be used by a larger research community to collaborate in the progress of science.

After the end of the project, the scientific community is still using the OMOP Common Data Model and OMOP dictionaries for several research purposes. These tools were made available and maintained on http://omop.org/CDM (last accessed November 2015). The OMOP demonstrated the possibility of creating a common structure that can receive several types of observational data (reimbursement claims and electronic healthcare records) from several sources, in many different formats and collected for different purposes. It has successfully developed and tested a broad range of statistical tools and methods able to achieve an active surveillance over drug safety.

Some of the tools created by OMOP include the Common Data Model, a common system for organizing observational data in a standardized fashion (Fig. 17.1),

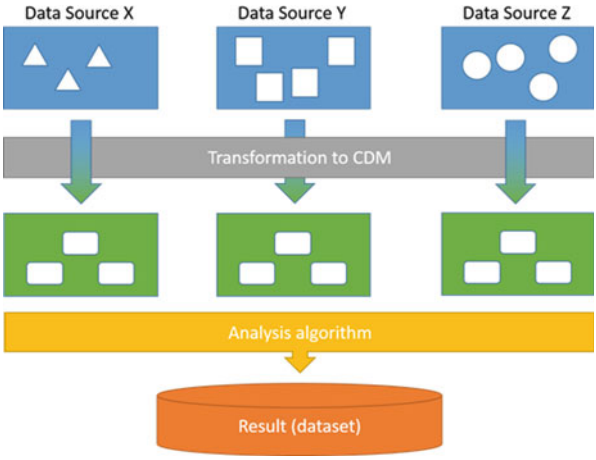

Fig. 17.1 The different data sources (X, Y and Z) are transformed to common data models and common coding standards. On the transformed data sets, algorithms adjusted to and develop for CDM can be used to retrieve desired results facilitating an analysis including all available, disparate data sources. To provide data protection and ownership, the CDM data sets can be located at different sites, only pooling the result set

endowed with a system for data extraction from different data sources and convert other formats to the OMOP format (extract, transform and load—ETL).

Moreover, a code dictionary for the definition of the outcomes most frequently used in observational studies (Health Outcomes of Interest, HOI) has also been created. The Observational Source Characteristics Analysis Report (OSCAR) provides a systematic approach for summarizing all observational healthcare data within the OMOP Common Data Model. OSCAR creates structured output of descriptive statistics for all relevant tables within the model to facilitate rapid summary and interpretation of the potential merits of a particular data source for addressing active surveillance needs. Data can be checked by Generalized Review of OSCAR Unified Checking (GROUCH), a tool able to produce a summary report for each data source of warnings of implausible and suspicious data observed from the OSCAR summary (such as pregnant men or women with prostatic diseases). Finally, OMOP has developed the Natural History Analysis programme (NATHAN) that produces a standardized report to summarize characteristics about the population of interest, including demographic factors (age and gender), comorbidities and concomitant medications and health service utilization prior to, during and after the event onset.

Notably, the OMOP inspired the creation of Observational Health Data Sciences and Informatics (OHDSI), an international network of researchers and observational health databases with a central coordinating centre housed at Columbia University [19]. The mission of OHDSI is to change medical decision-making by creating reliable scientific evidence about disease natural history, healthcare delivery and the effects of medical interventions through large-scale analysis of observational health databases for population-level estimation and patient-level predictions. Similarly to OMOP, this network created interesting open source tools for the standardization and harmonization of research (http://www.ohdsi.org).

As of November 2015, the OHDSI network has access to data sets covering 600 million patients owned by around 100 member organizations from ten countries. Note that the validation of some data sets included in the network is currently

ongoing, and therefore the population actually covered is probably smaller. Although each member organization can access only its own data, any query developed independently for investigating a specific health concern can be, in theory, replicated in all data sets since the network uses the same common data model and the same coding standards. The characteristics of the different sources and the data must however be carefully considered.

17.6 The SENTINEL Project (2008–Ongoing)

The SENTINEL project was started in the United States in 2008 as a long-term effort to create a national electronic system for the monitoring of the safety of drugs approved by the FDA [18]. This initiative represents a reply to the requirements of the Food and Drug Administration Amendments Act which included the need for a collaboration among academia, governmental institution and private groups for the development of a system able to provide information from multiple healthcare administrative data sources to assess the safety of medicinal products. This project has been activated as a pilot project named Mini-Sentinel, focused not only on drugs but also on vaccines (in a dedicated section named Post-Licensure Rapid Immunization Safety Monitoring, PRISM) and biologic drugs including blood derivatives (named Blood Safety Continuous Active-Surveillance Network, Blood-SCAN).

Mini-Sentinel routinely analyses electronic healthcare data to answer FDA concerns about drug safety. The system does not require the voluntary transmission of data to FDA by patients or caregivers. It may be used to evaluate the impact of regulatory decisions (dear doctor letters, black box warnings) on the appropriate use of drugs. Furthermore, it can provide quick replies (days or weeks) to requests for information by FDA in case of emergencies associated with safety issues with drugs. Mini-Sentinel reports provide aggregate data to protect patient's privacy.

The Mini-Sentinel programme is currently able to evaluate healthcare records for 100 million people, 2.9 billion prescriptions, 2.4 billion visits and 38 million hospitalizations due to acute events (http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM268035.pdf). Mini-Sentinel activities are focused in three directions: (1) assessments (including exposures to medical products, occurrences of particular diagnoses and medical procedures, health outcomes among individuals exposed to medical products, impact of FDA's regulatory actions and interventions); (2) methods (including development of methods, identification of clinical outcomes through the evaluation, implementation and validation of codification systems); and (3) data activity; Mini-Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control over electronic data in their existing environments. A key benefit of the distributed approach is that it minimizes the need to share identifiable patient information.

The Mini-Sentinel Common Data Model standardizes administrative and clinical information across Data Partners in a way very similar to the approach used

by the OHDSI network described in the previous section. When these two common data models were compared [18], both fulfilled the purpose for which they were created, even though the conceptual designs differed slightly. The main difference in the outcome of the analysis comes from the implementation of the algorithms.

17.7 The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) (2009–Ongoing)

The Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) is a project managed by 34 partners representing the different stakeholders, coordinated by the European Medicine Agency (EMA), started in September 2009 [20], and funded by the Innovative Medicine Initiative (IMI) which is a large-scale public-private partnership between the EU and the pharmaceutical industry association (EFPIA). The main aim of the project is the strengthening of the monitoring of the benefit-risk ratio of pharmacological therapies through the development of a set of novel tools and methods that will improve the capacity of early detection of ADRs. Different sources of data are considered and the information integrated to achieve a definition of the benefit-risk balance. The project is intended to test each of these new methodologies in real-life situation to provide the stakeholders (patients, prescribers, health authorities, pharma companies) with accurate and useful information to support the risk management and the continuative assessment of the benefits of a drug. A standard structured methodology is being developed and tested for data mining, signal detection and assessments in several kinds of data sets, including spontaneous ADR report databases, registries and other administrative electronic databases. Tools are being developed also for combination of results of clinical trials, spontaneous reporting and observational studies, comparing Bayesian models, multi-criteria decision analysis and other analytical methods, including strengthening of modelling and improving results presentation. Direct collection of data from patients is considered a priority. PROTECT will test a web-based (including also mobile applications and mobile written message transmission systems) data collection system dedicated to patients using a natural language. Transferability of data recorded from patients into a common language and the possibility of creating a link with registries and administrative healthcare databases will be also tested.

The project is organized in seven work packages (WPs), four of which dedicated to the development of new approaches and new methodologies. Particularly, WP2 is concentrated on the development, testing and dissemination

of methodological standards for design, conduct and analysis of pharmacoepidemiological studies aimed at investigating several safety issues with the use of different data [21]. WP3 is focused on the development of new methodologies and to the evaluation of the existing approaches for the signal detection from spontaneous ADR reporting, electronic health records and clinical trials. For instance, in September 2015 WP3 published a dictionary with the Medical Dictionary for Regulatory Activities (MedDRA) terms and codes of all the expected ADRs related to drugs authorized by EMA with centralized procedure in Europe (http://www.imi-protect.eu/adverseDrugReactions.shtml). WP4 is dedicated to the development of new approaches for collecting data from consumers using modern forms of communications, like the web or the smartphone applications. The involvement of consumers will allow collecting data about lifestyle, diet and use of over-the-counter (OTC) drugs that are not usually recorded in healthcare administrative databases. In this setting PROTECT WP4 promoted an exploratory study aimed at monitoring, via internet, the use of drugs in a population of pregnant women, and this has given very good results [22]. WP5 is dedicated to the development of methods for the evaluation of the benefit-risk ratio and includes underpinning modelling and result presentation with a particular emphasis on the graphic approach.

17.8 WEB-RADR (2014–Ongoing)

The WEB-RADR project (http://web-radr.eu/) [23], led by a consortium of several pharmacovigilance and pharmacoepidemiology stakeholders and funded by IMI, was launched in September 2014 with the main aim of developing methods to mine social media data (for instance, by improving free text mining algorithms) and mobile technologies for reporting of adverse events by patients and healthcare providers. This project is organized in seven work packages, and each of them is coordinated by a dedicated institution. For instance, WP2b is coordinated with the World Health Organization Uppsala Monitoring Centre, and it is aimed to develop and link new and existing analytical tools for the analysis of social media content for pharmacovigilance purposes. The main social media streams being analysed are Twitter and Facebook, but also some more specific streams originating from patient communities have been mined (WP2a). The data being captured is manually curated as the last step of the mining process and made available in the tool MedWatcher Social.

The smartphone app (WP3a) will be developed to report according to existing reporting standards to streamline processing of data, but it is also designed to "reward" the reporters/users by providing safety information about selected drugs. The data collected by the app will be investigated and compared with data collected with traditional approaches.

17.9 The Future: The Natural Evolution Towards a Global Management of Health and Drug Safety

From the aforementioned examples, we can point out that the most relevant issues in the assessment of drug safety in the future will be:

(a) *Harmonization of codes*: definitions and data format—drugs and medical events will be codified using a globally recognized and approved codifying system. Likewise, all demographic and clinical information will be codified and organized on the basis of a common data model. Alternatively, a linking terminology which can translate between different coding systems could be developed.

(b) *Harmonization of methodologies*: common analytical standard must be established and regulatory decision-making should be based on results obtained with these standardized methodologies. A specific pharmacoepidemiological standard should be issued based on the characteristics of the exposure (drug of interest) and of the outcome (adverse event), since each drug-event association should be analysed in the context of its clinical setting and features.

(c) *Improvement of the quality of data*: misclassification due to poorly recorded data represents a major challenge. Healthcare professionals should be stimulated to improve the quality of their records perhaps by economic incentives. This strategy was successfully issued in primary care in the UK with a great improvement of the quality of data, thus allowing to assess the effect of variables that are usually not available in administrative databases (i.e. body mass index, smoking habit) [24].

(d) *Involvement of patients*: patients may contribute to improving the quality and the completeness of data, thus allowing the conduction of valuable investigations [25]. Patients are evolving their informatics skills over years, and in the future each patient (including elderlies) will be able to share or record personal health information, via, for example, the web, mobile devices or wearable recording devices. This possibility will surely be exploited in drug safety assessment in the future. This includes also the possibility for patients to give a unique informed consent for the use of personal data to overcome privacy-related issues.

(e) *Avoiding multiple data entries*: a large waste of time and energy is today dedicated to the multiple data entries since same data are often recorded in different databases. Furthermore, investigators involved in observational studies dedicate a lot of time to the linkage of different databases containing the information of interest. It is reasonable to expect that in the future, observational studies will be conducted in unique databases containing all the information recorded with a single data entry which will be updated over time by multiple data entries.

(f) *Huge sample sizes*: the possibility of investigating drug safety for rare events, rare exposures or even rare clinical situations is strongly linked to the possibility of having a huge sample of patients. This goal can be achieved only with

multinational databases that share their information using standardized codes. It is likely that the creation of multinational databases will be progressive, and each country will be included in the groups only upon the achievement of specific quality standard requirements. It is likely that developed countries will help developing countries to be included in the multinational database by supporting a technological improvement plan.

(g) *Balancing risks and benefits*: it is indubitable that drug benefits play a prominent role when a regulatory decision has to be taken as a consequence of safety issues. Unfortunately, few observational studies can currently provide information to clearly establish a benefit-risk balance clearly, due to the lack of standardized methodologies. Future investigation on drug safety should be able to provide information about the benefits of a treatment also for a more appropriate decision-making process.

17.10 Will Pharmacovigilance Be Like Orwell's "Big Brother"?

In the future, it is likely that each human activity that requires data registration will be regulated by the use of personal electronic IDs (eID). These eIDs will be used not only for accessing health services but also for other activities including school registrations, insurance applications, tax payments, gym memberships, credit cards, registrations for the use of mobile phone applications, access to social networks and even any purchasing in shops. This could, for example, be achieved through apps which are authorized to identify the user via personal eIDs. This system will be able to provide a measure of every parameter for each person, including tobacco or alcohol consumption, diet, physical activity, income and instruction degree. These eIDs could be standardized and used in each country, thereby allowing the monitoring of a huge population of patients using high-quality data. Active data trackers able to automatically record clinical parameters in real time are already available and will be implemented in the future, thus allowing the continuous monitoring of the patients [26]. These data could be analysed routinely and automatically for the assessment of the benefit-risk balance of a drug, thus allowing the regulatory agency the best possible information for decision-making. Analysis should be based on standardized methodologies that can be implemented any time a new validated approach will become available.

The main challenge with this "big-brother-style" approach would be the protection of the privacy of individuals. These eIDs could assign a unique code to the persons that will anonymize their information at different levels thus guaranteeing privacy. However, ensuring that these codes cannot be actually broken without patient permission will represent a hard challenge. This scenario can be a little scaring, but based on the current global process of life digitalization, it is more than plausible. We can only hope that data will be used wisely.

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Chapter 18
Ecopharmacovigilance

Giampaolo Velo

"Our home – Earth – is in danger. What is at risk of being destroyed is not the planet itself, but the conditions that have made it hospitable for human beings" [1]. Al Gore, Nobel Peace Prize for his efforts to increase public awareness of the seriousness of the environmental situation, wrote this in 2007. Chemical substances, including pharmaceuticals, could contribute to the problem.

The need for global action was recognized internationally for the first time in October 2015 at a meeting led by the United Nations Environment Program in Geneva. The move was a small but significant development: for the first time, drug industry and nongovernmental bodies formally agreed that humans and ecosystems need protection from pharmaceutical pollution and will aim to produce chemicals in a way that minimizes ill effects on human health and the environment [2]. During the twentieth century, more than 100,000 new chemicals have been put on the market and used in everyday life, in industry and agriculture, many of which being pharmaceuticals. This was "blindly" carried out without considering the direct and indirect consequences on human health, animal species, and the environment [3]. Every year, an estimated 100,000 tons of antimicrobials are used all over the world [4, 5]. The countries that consume most drugs are, in descending order, the USA, Japan, France, Germany, Italy, Spain, and the UK [6]. Where do these substances end up, once used by men? The answer is: in the environment (Fig. 18.1).

As a matter of fact, pharmaceutical substances are eliminated from the body through urine and feces, either in unchanged form or as metabolites, and still partially active (Fig. 18.2); processes employed in sewage treatment plants, though, are often ineffective in removing them, and they have been therefore detected in rivers, lakes, seas, groundwater, and even in drinking water.

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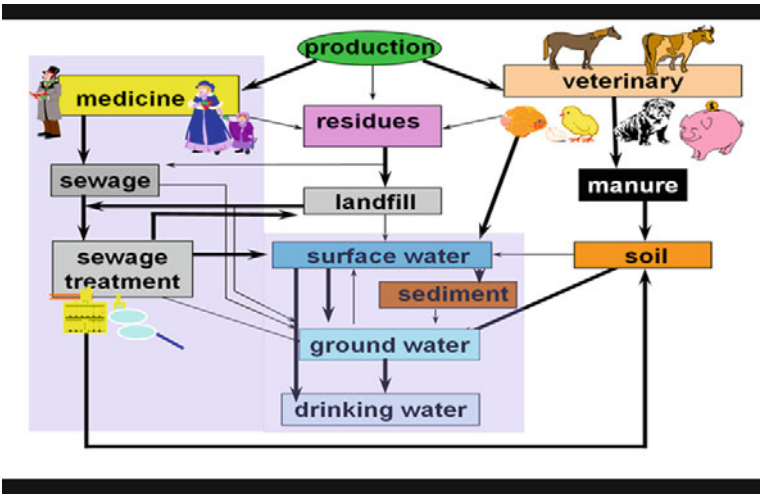

Fig. 18.1 Distribution of drugs in the environment [7]

A considerable part of pollution from drugs is also determined by their improper disposal. In 2012, the clinical pharmacology section of the University Hospital of Verona carried out a study called "Progetto Ecofarmaco," which involved 24 % of the 220 pharmacies in the province of Verona [8]. According to the study, 22 % of the 8,414 people included discarded, unused, or expired drugs in the garbage, the toilet, or the sink, thereby contributing to the contamination of our ecosystem (Fig. 18.3). When considering that every year, around 30 million packets of drugs are distributed in the province of Verona alone; this result gives food for thought and should not be underestimated. Verona data are consistent with those from a review by Tong et al., who surveyed recent literature on attitudes and practices to medicine disposal methods, as reported by patients, and on the various medication disposal and destruction systems around the world [9].

We must keep in mind the pharmaceutical industry, which is the starting point for large amounts of pharmaceuticals entering the environment and especially in emerging countries such as India, as confirmed by several publications [10, 11]. Samples from the effluent of a wastewater treatment plant serving about 90 bulk drug manufacturers in India – a major production site of generic drugs for the world market – contained by far the highest levels of pharmaceuticals reported in any effluent. The concentration of the most abundant drug, ciprofloxacin (up to 31,000 μg/L), exceeded levels toxic to bacteria by over 1000-fold, and such high levels of several broad-spectrum antibiotics raise concerns about resistance development [12].

Other research analyzed surface water and groundwater in the area: two lakes showed very high concentrations of ciprofloxacin (up to 6.5 mg/L), cetirizine (up to1.2 mg/L), norfloxacin (up to 0.52 mg/L), and enoxacin (up to 0.16 mg/L); six village wells were contaminated with drugs, some of them at more than 1 mg/L [13]. Several drugs have been traced in the environment in western countries as

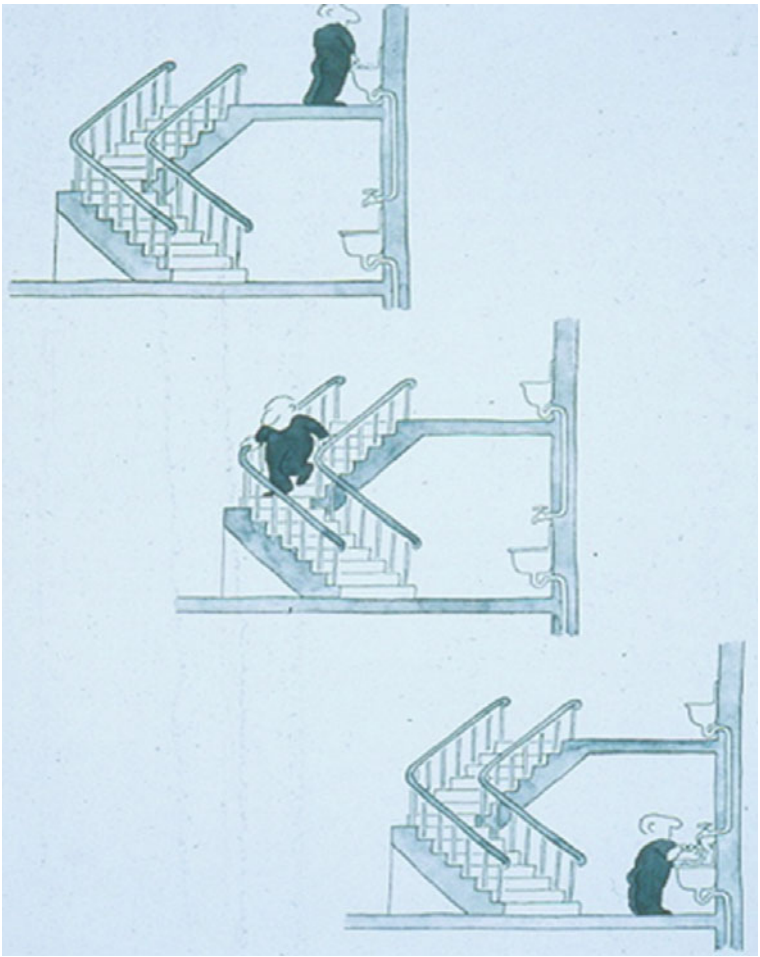

Fig. 18.2 The short cycle of water [7]

well: fluoxetine in the Thames [14], cocaine in the river Po [15], and antidepressants, antiepileptics, and statins in the Niagara River and in the lakes Ontario and Erie [16]. In rivers and lakes, compounds belonging to the following classes of drugs were also discovered: penicillins, tetracyclines, quinolones, macrolides, sulfonamides, anti-inflammatory analgesics, cardiovascular drugs, lipid regulators, diuretics, antidiabetics, gastrointestinal drugs, central nervous system drugs, bronchodilators, estrogens, anticancers, and contrast media [17].

We should emphasize that drugs may pollute even our tap water (Table 18.1).

In February 2011, the French National Agency of Health Security reported that a quarter of the analyzed French drinking water samples contained traces of pharmaceuticals, in particular antiepileptic and antianxiety drugs, and on May 30 of the same year, a Plan National sur les Rèsidus de Mèdicaments dans l'eau (PNRM) was

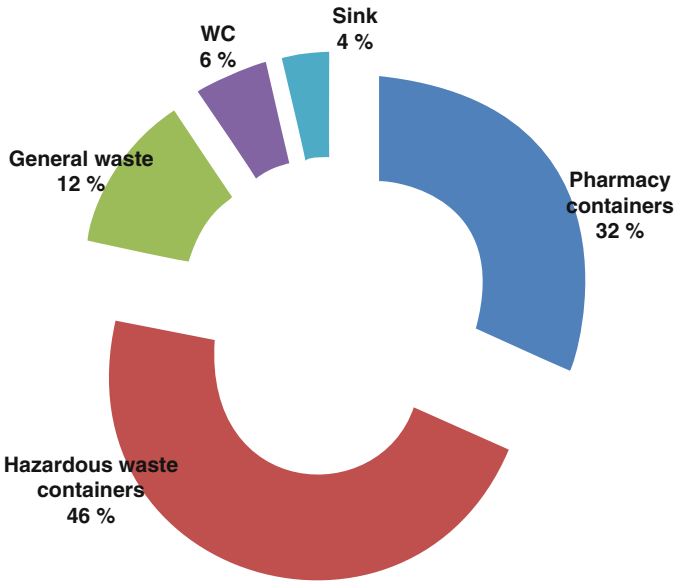

Fig. 18.3 Ecofarmaco project [8]

Table 18.1 Drugs detected in drinking water in many countries [18]

Compound	Therapeutic group	Maximum conc. (ng l^{-1})	Country	Reference
Bezafibrate	Lipid regulator	27	Germany	Stumpf (1996)
Bleomycin	Anti-neoplastic	13	UK	Aherne (1990)
Clofibric acid	Lipid regulator	+	UK	Fielding (1981)
		70	Germany	Stumpf (1996)
		165	Germany	Stan (1994)
		270	Germany	Heberer (1997)
		5	Italy	Zuccato (2000)
Carbamazepine	Anti-epileptic	24	Canada	Tauber (2003)
		258	USA	Stachelberg (2004)
Diazepam	Anxiolytic	10	UK	Waggot (1981)
		23	Italy	Zuccato (2000)
Diclofenac	NSAID	6	Germany	Stumpf (1996)
Gemfibrozil	Lipid regulator	70	Canada	Tauber (2003)
Ibuprofen	NSAID	3	Germany	Stumpf (1996)
Phenazone	NSAID	250	Germany	Zuhlke (2004)
		400	Germany	Reddersen (2002)
Propyphenazone	NSAID	80	Germany	Zuhlke (2004)
		120	Germany	Reddersen (2002)
Tylosin	Antibiotic	1.7	Italy	Zuccato (2000)

announced [6]. The *Magazine d'Information Universitè Paris-Sud 11* advertised it in a peculiar way "Vous prendrez bien un petit comprimé. dans votre verre d'eau!," that is, "You're taking a tablet with your glass of tap water." The aim of the study was to understand the environmental and health consequences, in order to intervene following a precautionary approach. The European Community suggests one applies the precautionary principle "where preliminary objective scientific evaluation indicates that there are reasonable grounds for concern about the potentially dangerous effects on the environment, human, animal or plant health" [19].

18.1 The Present of Ecopharmacovigilance

Ecopharmacovigilance (term coined by Giampaolo Velo in 2007 [20]) can be defined as the science and activities concerning detection, assessment, understanding, and prevention of adverse effects or other problems related to the presence of pharmaceuticals in the environment, which affect both human and the other animal species.

The problem of the presence of drugs in the environment has only been discussed for few years, and many countries are now working on it. Scientific societies such as the International Society of Doctors for the Environment (ISDE); the World Health Organization (WHO), which has organized a meeting in Singapore in 2009 on "Pharmaceuticals and Personal Care Products (PPCPs) in Drinking Water"; and the Ettore Majorana Foundation and Centre for Scientific Culture, in Italy, have been active on this issue. In 2009, the Erice Statement on communication, medicines and patient safety stated that "the presence of widely dispersed drugs and drug metabolites in the environment poses a potential direct, and indirect, risk to humans.

- The nature and extent of the potential risks must be further investigated and assessed.
- Safe disposal of medicines must be promoted, and appropriate facilities set up and used.
- Further measures may have to be taken to reduce drug discharge into environment, including education.
- The promotion of rational drug use should reduce the volume of medicines finding their way into the environment." [21]

In September 2010, the workshop "Ecopharmacovigilance: Which Future?" was organized at the French Académie Nationale de Pharmacie; in November 2010, the International Society of Pharmacovigilance (ISOP) organized the workshop in Ghana "Ecopharmacovigilance for a Healthy Future"; in October 2011, the workshop "Drugs in the Environment: Ecopharmacovigilance for Better Health" was held at the Royal Society of Medicine in London (RSM) [22]; in September 2014, the European Commission (SANCO and Environment Directorates) organized the "EU Workshop on the Development of a Strategic Approach to Pollution of Water by Pharmaceutical Substances" in Brussels, just to name some of the international events in which various issues concerning ecopharmacovigilance were treated and discussed.

In order to assess the risks posed by pharmaceuticals in the environment to human beings and animal species, a European project called Pharmas was launched, with the establishment of a consortium of organizations from the academia, research, and industry. The project concentrated in particular on two classes of drugs, antibiotics, and anticancer agents, which are widely used nowadays [23].

18.2 The Risks for Animal Species

The presence of drugs in the environment is due to the damage of several animal species. Numerous data demonstrate the damaging effects of the presence of drugs in the environment on some species of animals, in particular fish. There is evidence of the effect of estrogens from hormone replacement therapy, oral contraceptives, and endogenous human production on their endocrine system. Even at low concentrations (a few nanograms/l), their presence in the aquatic environment seems to contribute to the "feminization" of male fish such as rainbow trout, which, being exposed to estrogenic chemicals present in rivers, produce proteins typical of female [24, 25]. Although found in freshwater at the level of one part per billion, these substances would cause in male Rutile fish (*Rutilus rutilus*) the development of intersex species and eggs in the testes [26, 27]. Similar changes were found in bream, carp, and barbel resulting in a modification of the male–female ratio. Kidd et al. carried out an interesting research in the Canadian Experimental Lakes Area. For 7 years, they introduced estrogen 17α-ethinylestradiol into the lake in a concentration of 5–6 ng/L-1, which resulted in almost extinguishing the minnows (fathead minnows) that inhabited those waters [28].

Some studies compared alligators in lakes Apopka (heavily polluted by estrogen-like substances) and Woodruff, in Florida. When compared to the alligators from the uncontaminated Lake Woodruff, the Lake Apopka alligators showed a reduction of 24 % in penis size and 70 % in testosterone levels [29].

The massacre of vultures (*Gyps bengalensis*) in Pakistan caused by diclofenac is well known. Over 95 % of their population died for acute renal failure, since they fed with the carcasses of livestock treated with this drug, highly toxic for the birds [30]. At concentrations found in freshwater, diclofenac also causes lesions in the kidneys and in the gills of rainbow trout [31].

18.3 Risks for Humans

What can the harmful effects of the presence of drugs in the environment be for men? Concentrations are low (wastewater and sewage, 100–1000 ng/l; rivers and lakes, 10–100 ng/l; drinking water, 1–10 ng/l; seas, 0.1–1 ng/l), and therefore, we

may only speak of potential risks for men. However, we know that sex hormones are pharmacologically active at very low concentrations, and exposure to antibiotics may contribute to bacterial resistance. We must not forget that the effects of chronic exposure to drugs even at very low levels in humans are unknown, and the same is true in the case of interactions between multiple drugs at such low concentrations, but ingested over a lifetime. Special populations, such as infants and children, pregnant women, elderly, and patients with specific diseases, could modify the kinetics and metabolism of drugs and may be particularly vulnerable to such exposure. Finally, it should be remembered that the ecosystem is not made up of isolated compartments, and medicines may enter the food chain in different ways. It may be interesting to remember the publication by Carlsen et al., stating that sperm concentrations in men had fallen by almost 50 % from 1940 to 1990 [32]. Such news attracted much media attention, and a causal connection among humans and environmental chemicals, which mimic estrogens, was considered. However, a final conclusion has not been reached [33, 34].

Margel and Fleshner published in BMJ an article according to which there is a correlation between oral contraceptives and prostate cancer incidence. The hypothesis is that this effect is mediated by environmental estrogens [35]. As indicated by the authors, it is an ecologic study, and therefore, the topic should be further investigated. In 2012, a correction regarding the study appeared on BMJ, stating that the correlation of prostate cancer mortality rates with oral contraceptive use was not statistically significant and that a more correct title would have been "Oral contraceptive use is associated with prostate cancer incidence: an ecologic study" [36]. These substances would be ingested with drinking water, and this makes us understand how drugs excreted by our bodies may reach the environment and even drinking water.

The emergency of bacterial resistance to antibiotics is an important issue to be considered [37, 38]. An interesting example is avoparcin, used in many European countries since the late 1970s as a growth promoter in livestock (particularly poultry) and chemically similar to vancomycin. In the 1980s, many cases of vancomycin-resistant enterococci were observed in some European countries, but only in the 1990s that bacterial resistance was associated with the widespread use of avoparcin in farms [39]. In 1997, avoparcin was therefore banned as a growth promoter from farms of all member countries of the European Community [40]. However, even 8 years after the ban, the bacterial resistance persisted on farms, not only in animals but also in agriculture staff [41]. Antibiotics are also used to control bacterial infections in fish and are regularly added to the water of aquariums. Their massive use can lead to the appearance of resistant strains of bacteria. To get an idea of the scale of the phenomenon, every year more than 45 million fish are imported in the UK alone, and it is estimated that about 14 % of UK households have an aquarium [42].

An interesting Australian study indicates that the presence of aquariums containing tropical freshwater fish in the home is a risk factor for multidrug resistant *Salmonella* Java infection, particularly in children aged less than 5 years [43].

18.4 Regulatory Framework

The various directives show the attention paid at European Commission level. The Directive 2004/27/EC of the European Parliament and of the Council requires pharmaceutical companies to submit an environmental risk assessment as part of the application for marketing authorization under the centralized procedure, which is indicative of the importance that is attached to pollution from drugs in the environment. Article 8 establishes the need for environmental impact assessment, case by case, before taking any specific action [44]. For veterinary medicinal products (Directive 2004/28/EC), instead, when the environmental risk is unacceptable and the management of risk is not possible, the marketing authorization is not granted [45].

A 2010 directive, the 84/EU of the European Parliament and of the Council, states that "The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem. Member States should consider measures to monitor and evaluate the risk of environmental effects of such medicinal products, including those that may have an impact on public health" [46].

In August 2013, the new text of the legislation concerning "Priority substances in the field of water policy" was approved. The commission established "a watch list of substances selected from among those for which the information available indicates that they may pose a significant risk at Union level to, or via, the aquatic environment and for which monitoring data are insufficient." Three drugs (diclofenac, 17-beta-estradiol, and 17-alpha-ethinylestradiol) were included in the watch list, "in order to gather monitoring data for the purpose of facilitating the determination of appropriate measures to address the risk posed by those substances" [47].

18.5 What Actions?

How can we intervene?

- Teaching of pharmacology, including their metabolites and excretion forms, at university level for all relevant health professionals should be promoted.
- Promotion of rational use of drugs by health professionals, thus reducing the volume of medicines entering the environment as well.
- Better education on drug use by consumers.
- Better education on disposal of medicines by citizens as well as health professionals.
- More technologically advanced systems for the purification of wastewater with the use of ultraviolet and oxidation processes to decrease the pharmaceutical residues, also in hospitals where the use of drugs is extensive and particularly toxic classes are administered.
- Ensuring that there is adequate monitoring for environmental contamination and particularly in water for drinking and for the preparation of food.

- More research directed toward the so-called green drugs (benign by design), easily biodegradable in the environment. The biodegradability of a drug should be considered by physicians as an added value when prescribing to patients.
- Promoting the precautionary principle: we must not deny the risks, simply because they are less than certain. Instead, we should endeavor to know in advance the possible damage to human health and the environment, in order to be able to prevent it.

There is much to think about and a lot to do. This is a world in which we swim, but of which we know very little!

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