



Shayne C. Gad

Safety Evaluation of Pharmaceuticals and Medical Devices

International Regulatory Guidelines

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 Springer

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*To my baby brother, Scott Michael Gad
(1950-2010)*

Preface

The inspiration for this text was the 1988 volume by Alder and Zbinden*, written before the ICH harmonization process for drug safety evaluation (or its ISO analog for device biocompatibility evaluation) had been initiated or come to force. Since then, much has changed in both the world and the practice of medicine and regulation of drugs. The intent of this volume is to provide similar guidance as to what nonclinical safety assessment tests need to be performed to move a drug into man, through development and to market approved (this intent was subsequently extended to cover the closely related medical device biotechnology and combination product fields) in a concise, abbreviated manner for all the major world market countries.

As when teaching on the subject of drug safety evaluation, the approach I have taken here is to first address the broadest scope “general case” for the regulatory nonclinical safety evaluation by ICH and ISO adhering countries, then to branch out to cover the differences in requirements associated with specific therapeutic areas (such as oncology), major routes of administration (with oral being the general case, other routes starting with parenteral, dermal, and inhalation are addressed). Large molecules biotechnology products are then considered, followed by special courses of product marketing approval, and finally the remaining national differences.

As will be seen, even for ICH countries there is (in mid-2009) continuing modification of the basic M3 guidance for small molecule drugs (R2 being released in step 2 in August of 2008) and S6 (for protein therapeutics) series guidances, and it is not expected that the situation captured and guidance offered in this volume will long withstand the need for regular updating. The drivers for such need will be new science, new ways of using therapeutic products, new concerns, and the influence of new major markets. Also, there will be new real or perceived drug safety concerns. Much of these effects translate to “regulatory creep” (unpublished changes in practice and expectations by different parts of regulatory agencies that proceed in an

* Alder, S. and Zbinden, Z. (1988) National and International Drug Safety Guidelines, M.T.C. Verlag Zollikon, Zollikon, Switzerland.

undocumented fashion almost from the moment a new regulatory guidance comes out), and tracking these changes in a published text approaches is a hopeless task.

It is also not intended that this volume addresses the specifics of study design and interpretation. There are several current texts which perform these tasks well (Gad and McCord, 2008 for devices, Gad 2009 for drugs, and Cavanaro 2008 specifically for biotechnology products) and in the details required. Adequate references are provided to guide the reader (user) of this volume directly to the details required.

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Introduction to Safety Assessment in Drug and Medical Device Development

Even with the globalization and harmonization of approval requirements for drugs and devices (under International Conference on Harmonization (ICH) and ISO, respectively), countries and regions continue to have some unique regulations and guidance as to the safety that drug and medical devices companies need to meet to gain market approvals. The world market for drugs and devices is large, although about 47% of the pharmaceutical market resides in the USA, with about 27% in Europe and 15% in Japan. The balance of the sales is spread across the remainder of the globe in smaller portions. This does not mean, however, that the applicant should ignore the requirements of other countries, e.g., China. Approval requirements in these countries can, at times, be as rigorous as any other regulatory authority domain.

In this era of rapid and expanding growth in the pharmaceutical and medical device industries, marketing has become fiercely competitive. The industry spends billions of dollars on the development of new drugs and devices, and with this level of investment would like to have every candidate reach the consumer market. However, the chances of any one candidate being successful are low. As the candidate drug makes its way through the regulatory and testing maze, each successive stage of development becomes more expensive. Therefore, the industry proceeds with some caution as it pursues the development of a drug. Drug companies continue to invest a great deal of capital into rapid screening technology to more quickly eliminate those compounds which show no promise for development. For example, the advent of the various “omics” technologies is just one technology that the industry is hoping which allows them to target specific disease endpoints and therefore a specific pharmaceutical. Regardless, potential candidate drugs “drop out” of the development process for several reasons, but frequently this is related to toxicity discovered during the preclinical phase or within the process of clinical development. Certainly, the lack of efficacy in the target population also accounts for a significant number of drugs being dropped from further development.

The safety of drugs and medical devices is among those issues of the most obvious and longest-standing concern to the public. A common factor associated with these agents and devices are that any risk associated with a lack of safety is likely to affect a very broad part of the population, including special and sensitive populations, with

those at risk having little or no option but to accept this risk. Modern drugs are essential for life in our modern society, yet there is a consistent high level of concern about their safety.

In this book, I examine the international regulations which establish how the safety of human pharmaceutical products and medical devices are evaluated. Clearly, the US Food and Drug Administration and its counter parts elsewhere play an enormous role in the approval of drugs and devices. In the last 10 years, however, the ICH has appeared on the scene in an attempt to gain similarities in guidance and regulations between the USA (Guidelines 1998), Europe (The Rules 1999), and Japan (Guidelines 1999), and other countries. It appears reasonable that additional countries continue to adopt the ICH guidelines as a means of encouraging consistency in drug approvals.

Global Pharmaceutical and Medical Device Markets

Both pharmaceuticals and medical devices compete today in a global market place, though one which serves (and is available to) different parts of the world's population to different degrees and in different ways. This globalization has become true in terms of regulation, marketing, origination, and production of products. The two industries have both much in common and numerous differences.

As we enter 2009, the global market for regulated drugs (as differentiated from dietary supplements, herbal products, and nutraceuticals) is estimated to incorporate some \$670 billion in 2006 US dollars. In 2006, there were 109 individual products with annual sales in excess of \$1 billion. The top 20 of these are presented in Table 1.

This concentration of total sales in a limited number of products (there are currently more than 21,000 approved drugs in the USA,¹ for example) is widely held to have distorted the therapeutic aspects of new drug development, but is now starting to undergo change (back to) a paradigm that looks to decrease emphasis on the \$1+ billion "blockbuster" drugs. This change is driven by both economic necessity on the part of the large pharmaceutical companies and the entry of an increasing number of "small players" into the market.

Widely misunderstood is the extent of the pharmaceutical R and D sector. While precise numbers are unavailable (and meaningless, as companies are continuously being started, merged, or going out of business, though the overall trend is to increase numbers), best estimates place the number of companies directly involved in discovering and developing new drugs in the USA and Canada at ~3,500 (in mid-2009), out of which some 350 are publicly traded. There is an equal number in Europe, and significant numbers in many other parts of the world (China, Australia, India, and Israel to name just a few other countries). While most of the public focuses on the very large companies, such as those in Table 2, there are many other

¹Plus, perhaps another 400 that are not formally approved, but are legally marketed.

Table 1 Top 20 selling pharmaceuticals (2006)

Rank 2005	Medicine	2005 sales (\$M)	2004 sales (\$M)	Company	Primary diseased medical use	First approval date(s)	Route(s)
1	Lipitor	12,986	11,587	Pfizer and Astellas Pharma	Cholesterol	Dec. 17, 1996	Oral
2	Plavix/Iscover	6,345	5,434	Bristol-Myers Squibb and Sanofi-Aventis	Thrombotic events	Nov. 17, 1997	Oral
3	Advair/Seretide	5,465	4,503	GlaxoSmithKline	Asthma	Nov. 23, 1999/Sept. 7, 1998	Inhalation
4	Norvasc	4,706	4,463	Pfizer	Hypertension	July 31, 1992	Oral
5	Nexium	4,633	3,883	AstraZeneca	Gastrointestinal disorders	Mar. 2000	Oral, Parenteral
6	Zocor	4,382	5,197	Merck & Co.	Cholesterol	Dec. 23, 1991	Oral
7	Zyprexa	4,202	4,420	Eli Lilly	Schizophrenia	Sept. 27, 1996	Oral, Injection
8	Prevacid/ Takepron	3,996	4,050	Tap Pharmaceutical and Takeda Pharmaceutical	Gastrointestinal disorders	May 10, 1995	Oral, Injection
9	Diovan group	3,676	3,093	Novartis	Hypertension	Dec. 23, 1996	Oral
10	Enbrel	3,657	2,580	Amgen and Wyeth	Rheumatoid arthritis	Nov. 2, 1998	Injection
11	Risperdal	3,552	3,050	Johnson & Johnson	Schizophrenia	Dec. 29, 1993	Oral, Injection
12	Remicade	3,547	2,920	Johnson & Johnson, Schering-Plough, and Tanabe	Rheumatoid arthritis	Aug. 24, 1998	Injection
13	Effexor	3,459	3,347	Wyeth	Depression	Dec. 28, 1993	Oral
14	Protonix/ Pantozol	3,428	3,105	Wyeth and Altana	Gastrointestinal disorders	Feb. 2, 2000/1994	Oral, Injection
15	Rituxan/ MabThera	3,334	2,711	Roche and Genentech	Non-Hodgkin's lymphoma	Nov. 26, 1997	Injection
16	Procrit/Eprex	3,324	3,589	Johnson & Johnson	Anemia	Dec. 31, 1990/May 4, 1995	Injection
17	Aranesp	3,273	2,473	Amgen	Anemia	June 11, 2001	Injection
18	Zolof	3,256	3,361	Pfizer	Depression	Dec. 30, 1991	Oral
19	Fosamax	3,191	3,160	Merck & Co.	Osteoporosis	Sept. 29, 1995	Oral
20	Cozaar and Hyzaar	3,037	2,824	Merck & Co.	Hypertension	April 14, 1995 and April 28, 1995	Oral

Table 2 Top 25 drug companies by sales (2005)

	Fourth-quarter 2006						Fully-year 2006					
	Earnings ^a		Change from 2005		Profit margin ^b		Earnings ^a		Change from 2005		Profit margin ^b	
	Sales	\$ millions	Sales	Earnings	2006	2005	Sales	\$ millions	Sales	Earnings	2006	2005
US												
Abbott Laboratories	\$6,218.0	\$1,153.0	2.8%	-2.0%	18.5%	19.5%	\$22,476.3	\$3,880.8	0.6%	-0.7%	17.3%	17.5%
Bristol-Myers Squibb	4,213.0	380.0	-16.1	-36.8	9.0	12.0	17,914.0	2,100.0	-6.7	-25.0	11.7	14.6
Eli Lilly & Co.	4,245.3	929.6	9.4	6.7	21.9	22.5	15,691.0	3,460.0	7.1	10.5	22.1	21.4
Johnson & Johnson	13,682.0	2,385.0	8.5	13.5	17.4	16.7	53,324.0	11,133.0	5.6	9.2	20.9	20.2
Merck	6,044.2	1,092.3	4.8	-22.0	18.1	24.3	22,636.0	5,513.0	2.8	-1.0	24.4	25.3
Pfizer	12,603.0	3,047.0	0.4	-15.1	24.2	28.6	48,371.0	14,982.0	2.0	3.5	31.0	30.5
Schering-Plough	2,650.0	204.0	32.2	61.9	7.7	6.3	10,594.0	1,121.0	11.4	316.7	10.6	2.8
Wyeth	5,220.0	903.5	10.0	21.0	17.3	15.7	20,350.7	3,735.8	8.5	14.6	18.4	19.9
Total US ^c	\$54,875.6	\$10,094.4	4.3%	-4.9%	18.4%	20.2%	\$211,357.0	\$46,470.6	3.4%	5.4%	22.0%	21.6%
Europe												
AstraZeneca	\$7,154.0	\$1,445.0	13.8%	17.8%	20.2%	19.5%	\$26,475.0	\$4,392.0	10.5%	13.1%	16.6%	16.2%
GlaxoSmithKline	11,675.0	3,331.0	0.9	4.1	28.5	27.6	45,501.0	15,297.0	7.2	13.6	33.6	31.7
Novartis	10,053.0	1,663.0	16.1	23.0	16.5	15.6	37,020.0	7,202.0	14.9	17.3	19.5	19.1
Roche	NA	NA	NA	NA	NA	NA	34,495.0	7,525.0	18.4	33.6	21.8	19.3
Sanofi-Aventis	9,712.0	1,818.0	5.0	-4.6	18.7	20.6	37,460.0	9,295.0	3.9	11.1	24.8	23.2
Total Europe ^c	\$38,594.0	\$8,257.0	7.9%	7.5%	21.4%	21.5%	\$180,951.0	\$43,711.0	10.5%	16.6%	24.2%	22.9%
Total all companies ^c	\$93,469.6	\$18,351.4	5.8%	0.3%	19.6%	20.7%	\$392,308.0	\$90,181.6	6.6%	10.6%	23.0%	22.2%

Note: European company results are converted at Dec. 31, 2006, exchange rate, except for AstraZeneca and Novartis, which report in dollars

NA not available

^aAfter-tax earnings from continuing operations, excluding significant extraordinary and nonrecurring items

^bAfter-tax earnings as a percentage of sales

^cPercentages were calculated from combined sales and earnings

midsize and small companies. Significantly, innovation of new molecular entities (NMEs) arises primarily in the smaller companies.

One factor to consider in the regulatory requirements for the early development of new therapeutic entities is the degree of entry barrier which costs may present to the smaller, innovative companies.

A second complicating factor in considering the “pharmaceutical” market sector is the diversity of products involved. The most basic expression of this is the division of drugs into “small molecules” (which currently constitute ~two-thirds of both applications for clinical evaluation of a new drug in humans (INDs and CTAs) and two-thirds of current drug market approvals) and biotechnology products (which constitute the other third). The challenges in both developing and assessing the safety of these are very different and the regulation of their safety assessment is profoundly different. As is also seen, if one considers further division into therapeutic claim areas (oncology, anti-infectives, cardiovascular, CNS ...), the differences become even more marked. Most of what is presented and discussed in this volume speaks to regulatory requirements for nonclinical safety assessment in the general case for either small molecules or protein therapeutics. The reader is advised to bear in mind that the general case model that is first presented is almost never applied.

The medical device industry and product sector composed of a wide range of health care products which can be generally be expanded into three categories – devices, in vitro diagnostics, and radiation emitting systems and imaging systems (X-rays, MRIs, CAT scans, etc.) – has approximately \$210 billion in annual sales. These sales are fragmented across a tremendous range of products, and while there are some “blockbuster” devices with sales in excess of \$1B/year (several of the brands of drug-coated stents come to mind), individual product sales and profit margins per unit sale tend to be smaller, and product life cycles are much shorter than those of drugs.

Again, exact counts on companies engaged in the discovery and the development of new medical devices (or, in the device sector, frequently in the incremental improvement of existing devices by the 510(K) process) are not available, but a good estimate for 2008 would be half the number of pharma companies similarly engaged. That is, some 1,700 companies in the USA and an equal number in Europe. Sales are concentrated in the top 20 such companies, as summarized in Table 3.

Because this volume is directed at regulatory nonclinical safety assessment requirements, most of our focus is on the specific device portion of the industry, for only those who have direct patient contact. In an interesting side bar, the imaging systems that are used therapeutically (primarily as diagnostic tools) frequently require or/are enhanced by systemically administered imaging agents – which are regulated as drugs, not devices (Gad and McCord 2008; Thompson 2008).

There is a significant hybrid area here – combination products, which include both device and drug (small molecule or biologic) components. These are addressed in a separate chapter of the book, though currently there is no dedicated regulatory arm (such as a center within the FDA dedicated to only their regulation) in any major market country (Gopalaswamy and Gopalaswamy 2008; Siegel 2008).

Table 3 Top 20 medical device companies by sales

Company	Sales (\$billion)
Johnson & Johnson	15.6
GE Healthcare	11.3
Baxter International	9.5
Medtronic	9.1
Tyco Healthcare	9.1
Siemens Medical Solutions	8.7
Philips Medical Systems	8
Boston Scientific	5.6
Stryker	4.3
B.Braun	3.8
Guidant Corp.	3.8
Zimmer Holdings	3
Becton, Dickinson & Co.	2.7
Kodak Health Imaging	2.7
Hospira	2.6
Smith & Nephew	2.4
St. Jude Medical	2.3
Fresenius	2.2
3M Healthcare	2
Cardinal Health	1.9

Additionally, it should also be pointed out that there is an economically small but therapeutically vital area that is truly biologics but not therapeutics. The primary products here are blood and blood products (plasma, platelets, and clotting factors) which collectively have annual US sales of \$ 7–8 billion.

And finally, the excipient component of the pharmaceutical industry (sales for which were not included in the previous figures) must be considered. Once primarily regulated by NGOs (non-governmental organizations), such as USP and International Pharmaceutical Excipients Council (IPEC), these essential ingredients have come to have regulatory nonclinical safety assessment requirements close to those of the active drug components themselves. In 2007, sales in this area were ~\$14 billion.

Legislative Considerations

With ICH as the base case, there are three major regulatory bodies – FDA, EMEA, and MHLW. For FDA (in the USA), Congress passes laws that provide the scope of legal intention and enforcement. Such legislation is translated to laws, which are published in the US Code (USC). The regulatory body is charged with interpreting the law into a regulation that is published in the Federal Register. At that time, the public often has the opportunity to provide comments on the proposed regulation. On review and response to these public comments, the regulatory body codifies the

proposed regulation into the Code of Federal Regulations (CFR). The CFRs are a series of volumes for each federal department or agency charged with administering and enforcing the regulations. For the pharmaceutical and medical devices, the regulations are published in CFR 21. This title also covers foods, veterinary products, and cosmetics. As these topics are discussed elsewhere in this book, here we briefly review those parts of 21 CFR that are applicable to human health products and medicinal devices.

General regulations that apply to drugs are in Subchapter C (parts 200–299). This covers topics, such as labeling, advertising, commercial registration, manufacture, and distribution. Of most interest to a toxicologist would be a section on labeling (Part 201, Subparts A–G, which covers Sections 201.1 through 201.317 of the regulations) as much of the toxicological research on a human prescription drug goes toward supporting a label claim. For example, specific requirements on content and format of labeling for human prescription drugs are covered in section 201.57. Directions for what should be included under the “Precautions” section of a label are listed in 201.57(f). This includes 201.57(f) (6), which covers categorization of pregnancy risk, and the reliance upon animal reproduction studies in making these categorizations is made quite clear. Other specific risks identified in *in vitro* or animal studies are likewise specifically called forward. That is, it has to be emphasized that much basic toxicological information must be summarized on the drug label (package insert). This section of the law is quite detailed as to what information is to be presented and the format of the label presentation. Indeed, what the FDA ultimately approves is a drug or device label.

The EMEA arose from a different place. In 1950, in a speech inspired by Jean Monnet, the French Foreign Minister Robert Schuman proposed integrating the coal and steel industries of Western Europe. As a result, in 1951, the European Coal and Steel Community (ECSC) were set up, with six member state countries. The decision basis for this organized group rested with an independent, supranational body called the “High Authority” (RAPS 2005).

In the early days, the focus was on a common commercial policy for coal and steel and a common agricultural policy with other policies added as the need arose. It took some time for the Member States to remove all the barriers to trade between them and to turn their “common market” into a genuine single market in which goods, services, people, and capital could move around freely. The “Single Market” was formally completed at the end of 1992. Since 1992, other policies have come into force within EU, including a common currency (in most member state) animal testing ban for cosmetics (Seventh Amendment to the Cosmetics Directive), and formation of the European Medicine Agency (EMA). There remain, however, a number of regulatory and legislative issues.

The EU has grown in size with successive waves of accessions, and currently has 27 member countries. Other nonmember European countries (such as Switzerland) generally adhere to EU practices as to drug and devices safety regulation. The Treaty of Nice (which came into force on February 1 of 2003) lays down new rules governing the size of the EU institutions and the way they work. It was to be replaced in 2006 by the new EU Constitution, but such did not get approved.

In Japan, the safety and use of drug and medical devices are managed by the Ministry of Health, Labor and Welfare (MHLW). In 2001, the MHLW was created through the merger of the Ministry of Health and Welfare with the Ministry of Labor as part of a program for reorganizing the government ministries. The MHLW was originally established in 1938 and has had the authority for the improvement and promotion of social welfare, social security, and public health. It consists of the ministry proper, affiliated institutions, councils, local branches, and an external organization. The ministry proper includes the Minister's Secretariat, 11 bureaus, and the Director-General for Policy Planning and Evaluation. Councils include the Social Insurance Council, Pharmaceutical Affairs and Food Sanitation Council (PAFSC), and other organizations. Affiliated institutions include national hospitals, the National Institute of Health Science. Local branches are regional bureaus of health and welfare and prefectural labor bureaus. The external organizations are the Social Insurance Agency and the Central Labor Relations Commission.

Regulations: Human Pharmaceuticals

In the USA, the regulations specifically applicable to human drugs are covered in Subchapter D, Parts 300–399 of the *CFR*. The definition of a new drug is covered in Part 310(g):

A new drug substance means any substance that when used in the manufacture, processing or packaging of a drug causes that drug to be a new drug but does not include intermediates used in the synthesis of such substances.

The regulation then goes on to discuss “newness with regard to new formulations, indications, or in combinations.” For toxicologists, the heart of the regulations can be found in Section 312 (IND) and Section 314 (NDA). These sections describe the Investigational New Drug Application (INDA) and the New Drug Application (NDA) processes, respectively. These processes and applications are described further in this book. The major focus of a toxicologist working in the pharmaceutical industry is on preparing the correct toxicology “packages” to be included to “support” these two types of applications.

For medical devices, the regulations are included in 21 CFR, and are defined at part 201. For the toxicologist, parts 812 and 814 describe the need to demonstrate the safe and effective use of medical devices, and the processes for obtaining approval for a medical device. These processes include obtaining a license to market the device by submitting to the FDA a 510(k) premarket notification or a Premarket Application (PMA). More detail of these processes is included in different places within this book.

In a nutshell, the law that requires solid scientific evidence of safety and efficacy before a new drug or medical device is permitted in clinical trials or placed into the market.

In Europe, the process for regulatory drug approval is similar. A Marketing Authorization Application (MAA) is prepared according to standard format and

submitted to the medicine's bureau of EMEA. For human pharmaceuticals, the applications are reviewed by the Committee for Medicinal Products for Human Use (CHMP). It must be remembered that this is the EU process, but each national member country may have additional regulations that must be complied with prior to marketing of a drug in Europe. Drugs are reviewed as Part A or Part B drugs, with Part A drugs having the more formidable process since these are biotechnology-derived products. Part B drugs, are the usual drug products, NMEs, new indications, etc.

The process in Japan is likewise similar to that of Europe and the USA. The Pharmaceuticals and Medical Devices Agency (PMDA) is an independent administrative organization charged with review of new drug and medical device products. Within this organization, there are many different branches each having responsibility for the review of drugs or medical devices.

The diversity of regulations and practices for drug approval cause pharmaceutical companies to spend an enormous amount of resources on developing applications, following different standards for preclinical and nonclinical programs as well as time and resources to satisfy the regulatory processes for clinical trials in these three regions (Mathier 2000 and Gad 2009). Because of this diversity, representatives from the regulatory authorities came together in the late 1980s and early 1990s to attempt at harmonizing the process for drug approvals. This was and remains a challenging task. With time, however, the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) came into being. Japan, Europe, and the USA represent the major pharmaceutical market for the world, and these regions have the most influence on guidance documents that are prepared and revised. However, other countries (rest of the world, ROW) follow the developments within ICH and tend to follow the guidance offered by ICH. It remains important for the registration of pharmaceuticals to be aware of local country regulations. For example, China is becoming a major economic force in many aspects. Placement of pharmaceutical manufacturing facilities and the marketing of drugs in China can represent a significant economic advantage to companies.

This book was designed to provide a review of the process for international drug and medical device approvals. However, it is also recognized that guidance is an evolving practice within the regulatory community such that some guidance referenced in this book may be out-of-date tomorrow. It is important for all involved in this industry to stay alert to the ever changing regulatory environment, particularly in those countries where these processes are in their infancy. Unfortunately, there is no single source of information as a means to monitor these changes, although there are some organizations that monitor the regulatory community and publish regulatory alerts, sometimes on a daily basis. Regardless, the author hopes that this volume provides the toxicologist and regulatory specialist an overview of the international regulations for drugs and medical devices that prove valuable. Because of the very fact that most drugs are marketed in Europe, Japan, and the USA, much of the focus of this book concentrates on these three regions.

Special Cases: Biologics and Combination Products

It would be easier if we could confine our considerations to just traditional small molecule drugs and medical devices, as we knew them but a few decades ago. However, these have been joined by therapeutic proteins and peptides, cell therapies, combination drug device therapeutics, gene therapies, and most recently nanotherapeutics. We should expect this parade to continue through our life time and with it new promises and new concerns.

Traditionally, and for all too long, the approach to assessing new concerns has been to retain all existing test paradigms and add more special ones thought to be specific for the newly perceived potential risks. The problem is that not only has such an approach added costs, time in development, and increased needs for test animals (especially, those more publicly sensitive, such as primates and dogs), but the resulting piecemeal (as opposed to integrative) evaluation has also failed to substantially improve the prediction of clinical system/organism wide effects.

Indeed, it can even be argued that it has caused us not to recognize potential adverse effects until they appeared in clinical practices. At the same time, the conservative nature of the regulatory bodies has caused the ICH/ISO guideline approach to lead safety evaluations to become checklist exercises with the use of ever more dated checklists. Integration into new design/assessment paradigms is essential – and yet, not likely soon.

Strategies for Development

While harmonization and societal concern for safety are driving the regulatory processes for device and drug development to become increasingly similar, they are still more different than alike. As a result, strategies for product development and the associated nonclinical safety assessment must be considered separately.

Drugs

The driving truths behind strategies in developing new drugs are:

1. Most molecules fail. While the true success rate is certainly greater than the often quoted one-in-ten-thousand, it is clear that only 3–5% of those that enter initial clinical evaluation (that is, for which an IND “opens”) become marketed drugs. This rate varies depending on therapeutic class (oncology drugs dosing a rate as low as 1–2% and CNS therapeutics being only somewhat higher—Pangalas et al. 2007; Rang 2006; LaMattina 2008).
2. The cost of developing drugs is high – while not the currently quoted “average” of \$1.2 B, just getting to the point of an IND opening costs a minimum of \$2.2 M (plus the cost of drug synthesis). Biological therapeutics are more expensive yet to get to IND-\$4.5 M. And costs of development go up sharply with time/

progress – subsequent to a plain vanilla first-in-man (FIM) trial, outlays come to be spoken of first in tens of millions, and (frequently) before a marketing approval filing, in the hundreds of millions. Once the decision is made to develop a molecule into a drug, the process takes years. Again, one can dispute how many (from 5 to 16 about covers the range), and at no point up to the end is success (achieving marketing approval and economically successful therapeutic use) assured.

These truths conspire to produce the principal general goals behind drug development strategy:

1. Kill the losers as early as possible, before too much money is spent on them
2. Do all you can to minimize the calendar time spent in developing a drug

These principles produce a spectrum of strategies in the nonclinical safety assessment of drugs, best illustrated by looking at the two extreme cases.

Do Only What You Must: Driven by financial limitations and the plan that, at an optimal point in development (most commonly after either FIM/Phase 1 trials or a “proof of concept” Phase 2 trial), the candidate therapeutic is licensed to or partnered with a large company, only the technical and regulatory steps necessary to get a molecule to this point are to be performed. For those pursuing this case, the guidance provided by this book should prove essential (though not generally completely sufficient). This approach is summarized in Fig. 1.

Minimize the Risk of Subsequent Failure: This is considered the traditional big company model. Studies and technical tasks are not limited to the minimum, but rather are augmented by additional components. Development proceeds through a series of well-defined and carefully considered “go/no go” decision points. This approach is summarized in Fig. 2S. Many of the additional components are either limited, non-GLP forms of studies which are required later (such as Ames, acute toxicity, hERGs at only one concentration and 7 day to 4-week repeat dose studies), or studies which are inexpensive and could be done later (CYP inhibitors and induction, metabolic stability, and longer than required repeat dose toxicity studies before proceeding into Phase 2). Exactly, which “extra” components are included vary from company to company, and frequently reflect past experiences.

The studies performed to meet regulatory nonclinical safety assessment requirements (which must be considered to include all of the supportive toxicokinetic and metabolism activities and studies) can be thought of as belonging to three major categories.

- (a) Those necessary to support the successful filing/opening of an IND, CTA, or equivalent application, and of the subsequent FIM clinical studies.
- (b) Those required to support continuation of clinical evaluation and the development of a drug, up to and through successful Phase 3 studies.
- (c) Those studies required to support a successful marketing approval application (NDA, BLA, or equivalent), but only required as such. This group is typically exemplified for carcinogenicity studies and the formal reproductive (as opposed to developmental) toxicity studies.

Which studies fit into what category is somewhat fluid and influenced by what patient population is served (therapeutic claim) and the mechanism of action of the drug.

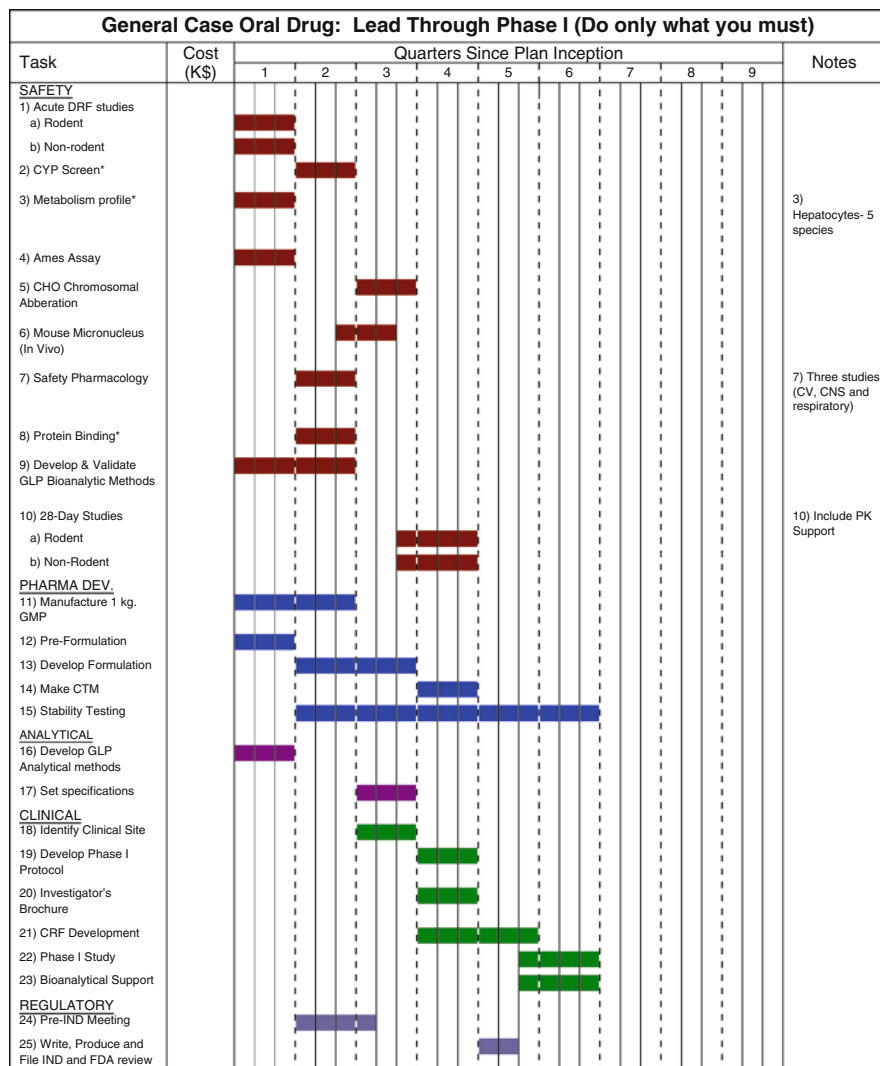


Fig. 1 General case oral drug: lead through Phase I (Do only what you must)

What You Need to Know to Start

This book seeks to build understanding from a specific starting point the so-called general case. To understand how the safety assessment of a specific drug, however, needs to be assessed requires understanding the drug itself and its intended use.

Start with knowing what the specific therapeutic claim is intended to be. Knowing this tells you what are the characteristics of the patient population and if any special safety concerns they may have. Also, what is the expected and accepted mode of administration for drugs to treat this disease – is it oral, intravenous, dermal? Also

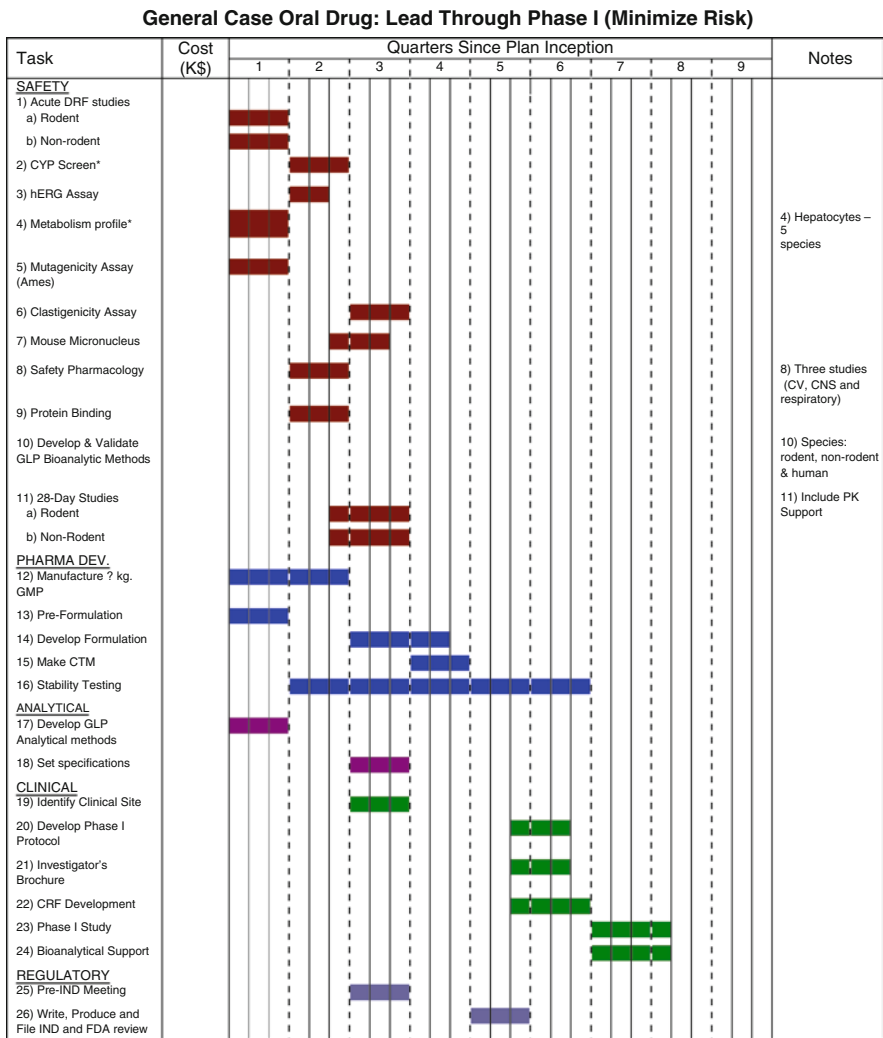


Fig. 2 General case oral drug: lead through Phase I (Minimize Risk)

determined by the claim is the expected treatment regimen, and the length of treatment (for any one individual) required to establish efficacy, and therefore to support label claims.

Devices

Strategies for achieving the regulatory approval of devices and for the conduct of nonclinical safety (for devices and their constituent materials, this is called biocompatibility testing) are usually much more straightforward.

Approval routes for a device in the USA are almost entirely limited to either the 510(K) or PMA routes. The extent of biocompatibility testing or data required for either of these routes (or the minor other means of approval available) are not different. Rather, they are determined primarily by the testing defined as necessary under ISO-10993 and/or the USFDA G-95 “Blue Book” Memorandum². Which testing is required by each is in turn determined by the nature and duration of potential patient exposure to the device (Gad and McCord 2008).

As with pharmaceuticals, the exact therapeutic claim for a device may engender additional special testing requirements (as with cardiovascular or neurological devices, for example).

Unlike with pharmaceuticals, not all new medical devices require clinical testing. Use of constituent materials which already have approved the use in devices with similar (or more stringent) patient exposure profiles may allow the use of data (or literature references to biocompatibility testing) to stand in place of some formal testing. So a significant aspect of device development strategy is to seek to use already approved materials to the maximum extent possible.

The major timing (or phasing) of testing determinant is whether clinical testing (and therefore an IDE or equivalent) is to be required to support device approval. If it is so, such testing as is necessary to support the safety of patients must be done before the IDE is filed.

All required testing must be performed under GLPs, and generally should be completed before a marketing application is submitted (for the data must be in the application).

To a greater extent than even the ICH process for pharmaceuticals, the ISO process has harmonized biocompatibility testing requirements globally – the USA, Canada, EU, Switzerland, and Japan all adhere to and *prima facie* accept ISO-10993 adherence. However, as new ISO 10993 standards have been added, the entirety has become less than coherent.

Additional Sources:

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Japan Pharmaceutical Manufacturer Association (JPMA). www.jpma.or.jp/english/.

European Medicines Agency (EMA). www.emea.eu.int.

Food and Drug Administration, Center for Drug Research. www.fda.gov/cder.

Food and Drug Administration, Center for Devices and Radiological health. www.fda.gov/cdrh.

²It should be noted that there is minimal difference between the testing required by these two guidelines.

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Drugs: The General Case

One must start one's consideration of the general case approach to nonclinical safety assessment from some fundamental assumptions about the drug under development or to be developed. The first assumption is that the primary intended route of therapeutic administration is oral, as is indeed the case for the vast majority of both existing and new drugs. Most aspects of nonclinical safety assessment do not depend on route, and in later chapters we consider in detail the situations where the use of other routes influences what is done for nonclinical safety assessment, and why.

A sort of subset assumption in the general case is that drug administration frequency (or regimen) is once daily, though this assumption is less frequently made (in real life) than the oral route assumption. The regimen assumption has its earliest origin mostly in experimental laboratory practice.

The next major assumption in the general case and, indeed a driving force behind the writing of this book is that the International Conference on Harmonization (ICH) process has been quite effective. Indeed, as late as the early 1990s, after Alder and Zbinden (1988) wrote their short text over viewing regulatory safety testing requirements, the situation was that one could not begin to describe a general case. The sole written guidance in the USA was a document authored by Edward Goldenthal and entitled *Total Drug Quality*. Dating to the 1970s (FDA 1971 – also see Goldenthal (1968)) and almost not available in print technology and societal expectations rapidly made its guidance obsolete.

More to the fact, the variation in requirements in other countries was extreme, though in many cases most significant in the details (Mathieu 2000). While they have continued to evolve (and add new testing requirements to the regulatory expectations), it is only ICH which has made the global pharmaceutical market for new drugs as we know it possible. Table 4 lists the current (September, 2007) operative ICH guidances on nonclinical drug safety evaluation.

In late 2008 the specific ICH guidance for oncology (59) the nonclinical safety assessment of oncology products become available in draft form.

Regulations, costs, and risks acceptance along with adherence to the phased process of clinical drug development have caused the task or flow of performances of regulatory nonclinical safety assessment studies to be considered as occurring in three sequential parts.

Table 4 Current operative ICH guidance on nonclinical drug safety evaluation

New codification as per July 2009		Previously coded
Carcinogenicity studies		
S1A	Need for carcinogenicity studies of pharmaceuticals	S1A
S1B	Testing for carcinogenicity of pharmaceuticals	S1B
S1C(R1)	New title: dose selection for carcinogenicity studies of pharmaceuticals and limit dose Previously: dose selection for carcinogenicity studies of pharmaceuticals	S1C
	Addendum to S1C: addition of a limit dose and related notes (in S1C(R1))	S1C(R)
Genotoxicity studies		
S2A	Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals	S2A
S2B (R2)	Genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals	S2B
Toxicokinetics and pharmacokinetics		
S3A	Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies	S3A
S3B	Pharmacokinetics: guidance for repeated dose tissue distribution studies	S3B
Toxicity testing		
	Single dose toxicity tests	S4
S4	Duration of chronic toxicity testing in animals (rodent and non rodent toxicity testing)	S4A
Reproductive toxicology		
S5(R2)	New title: detection of toxicity to reproduction for medicinal products and toxicity to male fertility Previously: detection of toxicity to reproduction for medicinal products	S5A
	Maintenance of the ICH guideline on toxicity to male fertility: an addendum to the guideline on detection of toxicity to reproduction for medicinal products (in S5(R2))	S5B(M)
Biotechnological products		
S6	Preclinical safety evaluation of biotechnology-derived pharmaceuticals	S6
Pharmacology studies		
S7A	Safety pharmacology studies for human pharmaceuticals	S7A
S7B	The non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals	S7B
Immunotoxicology studies		
S8	Immunotoxicity studies for human pharmaceuticals	S8
Joint safety/efficacy (multidisciplinary) topic		
M3(R2)	Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals	M3(R2)
E8	General considerations for clinical trials	E8

IND/FIM Enabling

The nonclinical studies required to initiate initial clinical studies of pharmaceuticals in human beings are variously labeled as “IND enables” or “FIM enabling.” The initiation of a program to conduct such studies is a major step in the advancement of a therapeutic candidate into actual development. For many drugs, it comprises the only regulatory nonclinical safety work that is ever done as they are not considered for further development after Phase 1 (ICH 1998 and 2008). All the safety studies that are required to be done should be performed in compliance with Good Laboratory Practices (GLPs). This means that certain preparatory steps must be performed before the studies are commenced to achieve such compliance.

1. Sufficiently pure drug substances must be produced and characterized.
2. An appropriate GLP compliant analytical method must be developed and validated to verify the purity of the drug substance.
3. GLP compliant bioanalytical methods (to measure amounts of drug present in plasma or serum of selected test species (typically a rodent and nonrodent) must be developed and validated for the concentration range anticipated.
4. The stability of either the drug substance or Active pharmaceutical ingredient (API) under appropriate storage conditions and in the anticipated animal dosing formulation must be demonstrated.
5. One or more suitable dosing formulations must be developed, such formulations are typically uncomplicated at this point, but tend to channel later efforts to develop more sophisticated formulations.

Once these steps are performed suitable studies (as described in Chapter “IND Enabling Toxicology Programs”) need to be conducted to support the filing of an IND (in the USA), CTA (in the EU), or equivalent. These studies typically include acute and repeat dose systemic toxicity studies in a rodent and nonrodent species, genetic toxicity, and safety pharmacology studies.

With these in hand, after a regulatory review period initial (Phase 1 and perhaps early Phase 2) clinical studies may be conducted.

To Support Continued Clinical Development

The IND enabling studies typically support repeat dose clinical studies up to a couple of (four at most) weeks in duration. Drugs more often than not require longer term than four weeks of dosing clinical trials than there to reach market (ICH, E8) which means that longer term (than the typical 28-day IND enabling repeat dose toxicity studies) must be conducted in both selected rodent and nonrodent

species. Additionally developmental and reproductive toxicity studies are usually required to allow the inclusion of a broader range of patients in clinical trials. Such longer term repeat dose studies are generally conducted in incremental steps so that Clinical studies through Phase 3 can be conducted. Chapter “Nonclinical Safety Evaluation Studies Conducted to Support Continued Clinical Development” addresses this part of the safety assessment process.

To Support Marketing Approval

The last distinct part of the nonclinical safety assessment study package generally consists of studies, which are not required until a marketing application (in the USA, a New Drug Application (NDA) or Biological License Application (BLA)) is submitted. This group is usually limited to carcinogenicity studies (if required) and the final parts of the reproductive toxicity package.

Though there may be some special requirements that arise in specific situations Chapter “Supporting Marketing Applications” presents the general approach to this part of the safety package.

Subset: Special or Hazard Studies

All that has been presented so far are appropriate and required for almost all new therapeutics. By the routes other than oral, however, there are additional expected studies which address issues of local tissue response to administer clinical dosage form (or drug product).

What is to be tested is the clinical formulation about to be evaluated in humans. As said, formulation may change several times over the course of clinical development; these tests may need to be repeated several times (for each new formulation). The tests are truly hazard tests – they are generally performed with a strictly defined protocol, with results being evaluated using a set in accordance with subjective preclinical scale, against which it is determined to be pass or fail.

The tests include such studies as hemolysis (for *iv* products), pyrogenicity (for parenteral products), sensitization (for dermal products), and route specific irritation assays (eye, skin, muscle, mucosal, nasal, and so on).

These studies are expected but the expectations are not clearly spelled out in any single guidance indeed. To some degree they are desirable not in a regulatory guidance at all, but rather in the appropriate pharmacopeia (in the USA, this is the *USP – United States Pharmacopeia*).

ICH Requirements: The Global General Case

The ever changing and growing number of ICH guidelines¹ provides the conceptual starting point for assessing the safety of new medicines, whether they are small molecules or proteins, while a review of Table 5 makes it clear that these two sets of structures remain viewed as vastly different and raising different concerns (ICH 2004).

Continued revisions of guidance should be taken as an exception, for in no other way the growth of knowledge of therapeutics and of means and mechanisms of therapeutics producing adverse events are accommodated.

So from these and associated requirements (such as USP), our general case arrives.

Table 5 Comparison of protein therapeutic agents with small-molecule drugs

Parameter	Proteins	Small Molecules
Drug substance	Heterogeneous mixture; broad specifications during development; specifications may change during development	Single entity; high chemical purity; exception; racemic mixtures; specifications well defined early in development
Drug product	Usually intravenously or subcutaneously	General oral; few formulations during development
Impurities	Difficult to standardize	Purity standards well established
Bridging requirements	Significant for drug substance	Bioequivalence procedures
Biological activity	May mimic naturally occurring molecules; primary mechanism of toxicity; predictive based on mechanism	Less predictive
Nonspecificity	Variable significance	Usually significant; drug—drug interactions
Chronic toxicity	Lack of models because of species-determined biological specificity and antigenicity	Models sometimes relevant
Impurities	Toxicity not a major issue; may impact immunogenicity	May be significant; purity standards well established

G.C Gad (2009) Drug Safety Evaluation (2nd ED)

¹ Always remember that these are not regulations, and such allow for flexibility – particularly on the part of regulation.

The First Rule

Presented above and throughout this volume is the general case, what usually is expected to be done (and is prescribed in the guidelines). Only – rarely in the case of any specific drug that such a general case applies. This book seeks to point out the exceptions and exclusions that apply, but undoubtedly has missed some.

So *Caveat emperor* – The reader should always remember the first rule is *that the general case never fully applies*.

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IND-Enabling Toxicology Programs

The challenge of drug discovery and drug development to the pharmaceutical toxicologist is that a drug is supposed to have a biological function and requires a scientific understanding of mechanistically based toxicity. Furthermore, drug development allows the toxicologist become somewhat flexible in developing the toxicology program that allows the entry into early stage clinical trials.

As noted in previous sections of this book, FDA and ICH regulations require that the “safety and efficacy” of a drug be demonstrated prior to approval and, hence, commercialization. For the toxicologist, the design and conduct of nonclinical studies to demonstrate the safety of the drug prior to a clinical trial is of prime importance. The early drug development toxicology program should be designed to initiate Phase 1 clinical studies where the tolerability of the drug is examined in (usually) health volunteers. The IND includes the narrative of the toxicology studies completed and the justification of the dose level(s) selected for the Phase 1 trial. Similar procedures are in place in other major countries (ICH 2008). In the UK, for example, a Clinical Trials Certificate (CTC) must be filed or a clinical trial exemption (CTX) obtained before clinical trials proceed.

The principle responsibility of the toxicologist in developing the IND is to design, conduct, and interpret appropriate toxicology studies to support the initial clinical study and then design the appropriate studies necessary to support each additional phase of clinical investigation. A description of the studies that would be needed to “open” the IND is described later in this chapter, but it is important to first describe the content of the IND.

The FDA has issued guidance for industry on the content and format of the IND. Although this guidance was developed over 10 years ago, it continues to represent the basis for the submission of the studies to support the initiation of a Phase 1 clinical trial. At the time of this writing, the agency was preparing to revise this guidance. The content of the IND is shown in Table 6 from (21CFR312.23). Many of the sections identified in this are self-explanatory although a few notable exceptions are discussed below.

Section 3 of the IND is to provide a general description of the drug, formulation to be used in the clinical trial, a brief description of the anticipated pharmaceutical claim and, most importantly, the clinical hypothesis and description of the clinical

Table 6 Content of a standard Investigational new drug application

IND section number	Section description
1.	IND cover sheets (form FDA-1571)
2.	Table of contents
3.	Introductory statement and general (clinical) investigation plan
4.	Reserved
5.	Clinical investigator's brochure
6.	Proposed clinical protocol(s)
7.	Chemistry, manufacturing, and control information
8.	Pharmacology and toxicology information
9.	Previous human experience with the investigational drug
10.	Additional information
11.	Other relevant information

study to be undertaken to examine that hypothesis. Section 4 is the “Reserved” section. In a regulatory context, this section can be used by the FDA for any other consideration for the IND. However, the agency would have to prepare a federal notice describing what is intended for this section until it becomes no longer “Reserved.” This would be a long, drawn out process before this section is changed. That said some divisions of FDA have recently taken to asking that the clinical plan be placed in Section 4. Section 7 is for the chemistry, manufacturing, and control materials – that is, the chemistry materials. Section 8 that contains the toxicology, pharmacology, and pharmacokinetics/metabolism information is the largest single section of the IND, and for the toxicologist represents the major section of the IND.

Sections 10 and 11 allow the Sponsor to provide to the FDA any other information considered to be relevant to the “approval” of the IND. These sections can describe the use of radiolabeled drugs in the clinical trial and a description of the safety of the radiation-absorbed dose, drug dependency, and clinical studies associated with the proposed drug, pediatric studies and/or an assessment for the use of the drug in pediatric populations, etc. Overall, these sections permit the Sponsor to tell the agency about special circumstances that potentially impacts the approval of the IND and drug. For a more thorough description of these sections, the reader is referred to the texts prepared by Mathieu (2005).

An issue that often arises in the development of the IND is the inclusion of reports. Often, sponsors are on a self-imposed tight timeline for the submission of the IND and initiation of clinical trials, particularly the small pharmaceutical companies, to ensure that capital investments continue against certain milestones. Therefore, the sponsor submits draft, unaudited reports with the IND. According to the existing guidance, this is acceptable to the FDA but is not desirable. If unaudited reports are submitted, the Sponsor must finalize the reports within 120 days of initiation of the clinical trial. If the integrated summary in the IND was based on unaudited draft reports, then the sponsor needs to submit to the agency an update of the summary by 120 days after the start of the clinical trial identifying differences between the unaudited report and audited, final report. Most often differences

between reports do not occur, but this should also be started in the revised narrative. As noted previously, at the time of this writing, the FDA is intending to revise this guidance, and may require that audited reports be included with the IND although the reports could remain as a draft report.

The Good Laboratories Practice (GLP) Act (21CFR58) specifies standards for study planning, personnel training, data recording, and reporting, etc., was codified in 1978 in response to perceive shoddy practices of the operations of a select few laboratories involved in the conduct of preclinical safety studies (Swidersky 2007). The passage of the GLPs revolutionized the standards of practice of toxicology studies, and this regulation is, in some circles, considered a yard-stick to measure the adequacy of preclinical studies. This is somewhat unfortunate since numerous studies have been conducted over the years as non-GLP but remain studies conducted under good scientific principles. Regardless, with the submission of preclinical studies to the FDA, there is an expectation that the preclinical toxicology studies be conducted according to GLPs. During the last few years, enforcement by the agency of GLP studies has focused on test article characterization to include analytical verification of the "...identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article..." (21CFR58.105). In early drug development, particularly for small pharmaceutical companies, the resources may not be available to undertake the analytical or bio-analytical work according to GLPs. Although this does not usually result in the nonapproval of an IND, Sponsors are strongly encouraged to do these analyses by GLPs, thereby avoiding scrutiny of other data by the agency.

During the last 8–12 years, the FDA has encouraged Sponsors to meet with the respective FDA division prior to undertaking many of the pharmacology and toxicology studies and before the submission of the IND. Generally, industry has reacted positively to the pre-IND meeting although these meetings have become an additional burden to the FDA. Nevertheless, these meetings have often defined for the Sponsor the expectations by the FDA in terms of preclinical testing requirements and the development of the clinical protocol. In preparation for the pre-IND meeting, the Sponsor needs to submit to the agency a package (briefing package) that contains a summation of all available pharmacology and toxicology data as well as any CMC information pertinent to the drug formulation intended for the Phase 1 trial.

Tabular summaries of the pharmacology and toxicology data and an overall narrative are critical to ensure that agency understands the potential toxicity and pharmacological activity of the drug substance. Although the format of the tabular summaries is not specified, it is often best to format the tabular summaries similar to the format described in the Common Technical Document (CTD), a format that is required for the New Drug Application (NDA).

For the briefing package, specific questions to the agency should be developed where there are questions about the preclinical or clinical program. The intent of these questions is to gain concurrence with the FDA about the preclinical studies the Sponsor intends to undertake as well as questions related to CMC and the clinical program. An outline of the pivotal protocols with specific endpoints to be

measured should be considered, particularly where these toxicity endpoints would be important for specific pharmaceutical categories. The ideal outcome of the pre-IND meeting is that the FDA agrees with the Sponsor, but the Sponsor must keep in mind that the FDA has access to an incredible database of information of drugs, and that database could include drugs of similar structure and action as the Sponsor is intending to examine. Therefore, it is incumbent on the Sponsor to listen to the agency's opinion and advice regarding the development of the drug.

Toxicity Testing: Traditional Pharmaceuticals

Most often, the regulatory development and approval of drugs proceeds in a somewhat fixed and orderly way. As there are always exceptions to the rule, drug development for special case therapies, e.g., AIDS, cancer, do exist where the timeline for safety assessment can be shortened or the "requirements" for testing vary from the usual small molecule requirements.

The 1938 FD&C Act required safety assessment studies, but no consistent guidelines were available. Testing guidelines were first proposed in 1949 and published in the *Food, Drug and Cosmetic Law Journal* that year (Burns 1983). Following several revisions, these guidelines were issued as *The Appraisal Handbook* in 1959. While never formally called a *guideline*, it set the standard for preclinical toxicity test design for several years. The current basic guidelines for testing required for the safety assessment in support of the phases of clinical development of drugs were first outlined by Goldenthal (1968) and later incorporated into a 1971 FDA publication entitled *FDA Introduction to Total Drug Quality*.

In the 1970s and more so in the 1980s, other testing guidelines were prepared and were used as a basis for the design of toxicity studies for preclinical studies. In 1982, FDA's Bureau of Foods published the guidelines on *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food* (The "Red Book"). Although these guidelines were specifically directed toward the safety evaluation of food additives, they describe how FDA incorporates information about expected human exposure and chemical structure/activity relationships for food and color additives used in food. These guidelines were at times referenced as a basis for the testing of new pharmaceuticals. Starting in the early 1980s, the Organization of Economic Cooperation and Development (OECD) began to release testing guidelines that have often been used as a basis for the design of preclinical studies. Concurrent with the OECD guidelines, the FDA began to formalize the guidance documents that described the need for certain endpoints, group size, etc., as well as specific studies necessary for drug approval. Furthermore, Japanese guidelines made available from the Ministry of Health, Labor and Welfare (MHLW) also specified the requirements for testing of new

molecular entities. Generally, the Japanese requirements are similar to that of the FDA, although slight differences exist, e.g., mutagenicity testing.

Common Mistakes

There is no single right way to develop a new drug and assess its safety, but there are many wrong ways. Some of the common mistakes to avoid:

Wrong test species: The test species should be selected for (at least) the systemic toxicity studies (a rodent and nonrodent generally) must be pharmacologically responsive to the drug and have at least a similar metabolic profile.

Poor or no formulation: While the formulations used in nonclinical safety studies need not (other than for hazard/local tissue tolerance studies) be the same as in clinical studies, time should be taken to optimize both their tolerance and relative pharmacokinetic properties.

Insufficient dose: It is essential to demonstrate toxicity (and identify target organs) for toxicity in systemic toxicity studies (at least), or to make every effort to do so. With the general exception of monoclonal antibodies, all too often the high dose in such studies (and even the middle dose) is set too low. This tendency must be avoided.

The FDA has settled on a procedure for setting a safe starting dose for clinical trials in humans, and put it into a guidance, which is now largely adhered to by the other ICH countries. This procedure starts from the point of “scaling” between species based on body surface area.

Table 7 presents the FDA’s current values for scaling animal study doses to equivalent human doses.

Use of nonrepresentative test material: Studies (particularly systemic toxicity and cardiovascular safety) should be conducted with API as representative as possible of what is to be evaluated clinically. This strongly suggests the use of material from the first clinical GMP lot for the 28 day repeat dose and in vivo cardiovascular safety studies.

Failure to verify adequate exposure: It is essential to verify systemic or target organ exposure to the drug. In safety studies, toxicokinetic components serve this purpose. The most common failure here is in vivo micronucleus studies. A lack of effect in such studies is meaningless if one cannot prove test articles from the bone marrow.

Saving money while wasting time: The most precarious commodity in the drug development process is calendar time. Cost savings by skipping essential or recommended steps or by selecting vendors based purely on cost/price is almost always a mistake.

Table 7 Conversion of animal doses to human equivalent doses (HED) based on body surface area

Species	Reference body weight (kg)	Working weight range ^a (kg)	Body surface area (m ²)	To convert doses in mg/kg to mg/m ² multiply by km below:	To convert animal dose in mg/kg to HED ^b in mg/kg, either:	
					Divide animal dose by:	Multiply animal dose by:
Human	60	–	1.62	37	–	–
Child ^c	20	–	0.80	25	–	–
Mouse	0.020	0.011–0.034	0.007	3	12.3	0.081
Hamster	0.080	0.047–0.157	0.016	5	7.4	0.135
Rat	0.150	0.080–0.270	0.025	6	6.2	0.162
Ferret	0.300	0.160–0.540	0.043	7	5.3	0.189
Guinea pig	0.400	0.208–0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.9–3.0	0.15	12	3.1	0.324
Dog	10	5–17	0.50	20	1.8	0.541
Primates:						
Monkeys ^d	3	1.4–4.9	0.25	12	3.1	0.324
Marmoset	350	0.140–0.720	0.06	6	6.2	0.162
Squirrel monkey	600	0.290–0.970	0.09	7	5.3	0.189
Baboon	12	7–23	0.60	20	1.8	0.541
Micro-pig	20	10–33	0.74	27	1.4	0.730
Mini-pig	40	25–64	1.14	35	1.1	0.946

^aFor animal weights within the specified ranges, the HED for a 60 kg human is calculated using the standard kilo meter value and does not vary more than ±20% from the HED calculated using a kilo meter based on the exact animal weight

^bAssumes 60 kg human. For species not listed or for weights outside the standard ranges, human equivalent dose can be calculated from the formula:

HED = animal dose in mg/kg × 0.33 $\left(\frac{\text{animal weight in kg}}{\text{human weight in kg}} \right)$

^cThe kilo meter is provided for reference only since the healthy children rarely volunteer for Phase 1 trials

^dFor example, cynomolgus, rhesus, stump-tail, etc

Toxicity Testing of Pharmaceuticals: The General Approach

As noted previously, testing of pharmaceuticals usually proceeds in a rather fixed and orderly way. For entry into early clinical trials, testing is needed to support those trials, and the duration of the repeat dose studies generally need to mirror the duration of the clinical trial (Table 8).

As the duration of the clinical study increases, the duration of the preclinical study also is longer. It is possible, however, to initiate a single dose clinical study for some pharmaceuticals by providing the agency a single dose toxicity study in two species. These studies must include clinical pathology and histopathology as well as be fully GLP compliant. Each of the systemic toxicity studies in these guidelines must be designed and executed in a satisfactory manner. Sufficient animals must be

Table 8 General guidelines for animal toxicity studies in early development (ICH M3 (R2))

Route of administration	Duration of clinical trial	Animal study duration	Special studies
Oral or parenteral	Several days to up to 2 weeks; up to 4 weeks; up to 3 months	Two species; 2 weeks; two species; up to 4 weeks; two species; up to 3 months	For parentally administered drugs; compatibility with blood where applicable
Inhalation (general anesthetics)		Four species; 5 days (3 h/day)	
Dermal	Single application	Two species; single 24-h exposure followed by 2-week observation	Sensitization
	Single or short-term application	Two species; 4 week (intact and abraded skin)	
Ophthalmic	Single application		Eye irritation tests with graded doses
	Multiple application	One species; 3 weeks daily applications, as in clinical use One species; duration commensurate with period of drug administration	
Vaginal or rectal	Single application Multiple application	Two species; duration and number of applications determined by proposed use	Local and systematic toxicity after vaginal or rectal application in two species
Drug combinations		Two species; up to 3 months	Lethality by appropriate route, compared to components run concurrently in one species

Table 9 Numbers of animals per dose group

Study duration (per sex)	Rodents (per sex)	Nonrodents (per sex)
2–4 weeks	5–10	4
13 weeks	20	6
26 weeks	30	8
39 or 52 weeks (chronic)	NA	10

used to have confidence in finding and characterizing any adverse drug actions that may be present. These two features – dosage level and group size – are critical to study designs. Table 9 presents general guidance on the least number of animals to be used in systemic toxicity studies. These and other technical considerations for the safety assessment of pharmaceuticals are present in detail in Gad (2009).

The number of animals in each group shown in Table 9 is usually the minimal numbers required and is based on OECD guidelines. Indeed, for 4-week studies, ten rats/sex/group is often used, and this number of rats is encouraged for 2-week studies. Likewise, the number of nonrodents, e.g., dogs, generally has been three/sex/group for 2- and 4-week studies although the agency has recommended increasing this number for the treatment phase of the study.

In these studies, the usual endpoints are to be included in the protocol that is outlined in the OECD guidelines. These endpoints would include the measurement of body weights, recording of clinical observations as well as daily observations for mortality and morbidity. Furthermore, hematology and clinical chemical parameters are to be measured in pivotal studies. Although caution should be exercised about including certain measures because of either variability or uncertainty regarding interpretation, e.g., creatinine phosphokinase (CPK), isoform of this or other enzymes can provide valuable information on changes in cellular function. At necropsy, organ weights are to be measured for major organs, e.g., liver, brain, heart, etc., with histopathology of tissues. Also, ophthalmological examinations need to be done in pivotal studies, especially for rabbits and dogs, although including this endpoint in carcinogenicity is necessary for certain pharmaceutical categories.

In recent years, the FDA has encouraged sponsors to include additional animals to examine the reversibility of potential effects observed during the treatment phase of the study (“recovery”). Although this has been generally accepted in studies of 4 weeks and longer, more recently the agency has urged sponsors to include recovery animals for 2-week studies. Furthermore, additional rodents are often needed in studies for the collection of blood samples for toxicokinetic determinations.

Many of these issues should be resolved at the pre-IND meeting to ensure successful development of the pharmaceutical.

Developmental and Reproductive Toxicity Studies

The agency has a special set of concerns with reproductive toxicity, fetal/embryo toxicity, and developmental toxicity. Historically, these studies have been referred to as Segment (Seg) I, II, and III studies. The ICH has issued guidance on these

studies (ICH S5R2) and is referred to as fertility and early embryonic development (Seg I), pre- and postnatal development, including maternal function (Seg II) and embryo-fetal development (Seg III). These studies are often conducted during the Phase 2 clinical trial, but may be required for the IND if the drug represents a possible risk factor for reproductive toxicity, e.g., estrogenic- or androgen-like actions.

The first protocol for DART test is a Seg I study of rats in fertility and general reproductive performance. This Seg I study and the Seg II study are generally completed, particularly if women of childbearing potential are included in the clinical trials. The teratogenicity testing is required in two species – a rodent (rat or mouse) and a rabbit. The use of the rabbit was instituted as a result of the finding that thalidomide was a positive teratogen in the rabbit but not in the rat. On occasion, when a test article is not compatible with the rabbit, teratogenicity data in the mouse may be substituted. There also are some specific classes of therapeutics, e.g., quinolone antibiotics, where Seg II studies in primates are effectively required prior to product approval. Both should be completed before entering Phase 3 clinical trials. The more complicated Seg III DART protocol is generally commenced during Phase 3 trials and should be part of the NDA. There are differences between national guidelines (as discussed later with international considerations) regarding the conduct of these studies. The drug companies try to design their protocols to be in compliance with as many of the guidelines as possible to avoid duplication of testing while allowing the broadest possible approval and marketing of therapeutics.

Genetic Toxicity Assessment

Genetic toxicity testing generally focuses on the potential of a new drug to cause mutations (in single-cell systems) or other forms of genetic damage (disruption of chromosome replication) *in vitro* or *in vivo*. The tests, generally short in duration, often rely on *in vitro* systems and generally have a single endpoint of effect (point mutations, chromosomal damage, etc.). Protocol guidance has been provided by the ICH (S2B) with more specificity of the protocols provided by the OECD.

The FDA generally expects to see at least some such tests performed and will ask for them if the issue is not addressed. Often, the bacterial reverse mutation assay (Ames) and a study for clastogenicity are needed for the IND. If equivocal results or clear evidence of genotoxicity is observed in any of these *in vitro* studies, the sponsor is expected to perform additional studies prior to the submission of the IND to clarify the findings. An *in vivo* (rodent – usually mouse) micronucleus is generally performed under these circumstances although other *in vitro* or *in vivo* studies may be necessary, e.g., mouse lymphoma tk assay, unscheduled DNA synthesis, SHE transformation assay, etc. Positive results with the bacterial reverse mutation assay or clastogenicity testing does not often impede progress in development, although the sponsor is expected to undertake the additional studies to clarify the finding. At the time of this writing, the FDA

is considering accepting the mouse lymphoma assay in place of the in vitro clastogenicity assays. It should be noted that the Japanese regulatory authority, the MHLW, requires the mouse lymphoma tk assay in place of the chromosomal aberration study. Furthermore, there is a consideration of suggesting that the in vivo micronucleus be included with repeat dose toxicity studies, i.e., collect peripheral lymphocytes or bone marrow cells at the time of sacrifice in the toxicity study.

There are a wide variety of test protocols that are described under current OECD guidelines and are accepted by FDA. These are described below. It should be noted that ICH and FDA have a number of alternative test protocols that have recently been added to the accepted list – the comet assay, the liver unscheduled DNA synthesis (UDS) test, and a transgenic gene mutation assay performed in mice.

Fifteen common assays described by OECD and Accepted by FDA

Assays for gene mutations	In vitro	In vivo
<i>Salmonella Typhimurium</i> reverse mutation assay (Ames test, bacteria) [OECD 471]	✓	
<i>Escherichia coli</i> reverse mutation assay (bacteria) [OECD472]	✓	
Gene mutation in mammalian cells in culture [OECD 476]	✓	
<i>Drosophila</i> sex-linked recessive lethal assay (fruit fly) [OECD 477]		✓
Gene mutation in <i>Saccharomyces cerevisiae</i> (yeast) [OECD 480]	✓	
Mouse Spot test [OECD 484]		✓
Assays for chromosomal and genomic mutations		
In vitro cytogenetic assay [OECD 473]	✓	
In vivo cytogenetic assay [OECD 475]		✓
Micronucleus test [OECD 474]		✓
Dominant lethal assay [OECD 478]		✓
Heritable translocation assay [OECD 485]		✓
Mammalian germ cell cytogenetic assay [OECD 483]		✓
Assays for DNA effects		
DNA damage and repair: unscheduled DNA synthesis in vitro [OECD 482]	✓	
Mitotic recombination in <i>Saccharomyces cerevisiae</i> (yeast) [OECD 481]	✓	
In vitro sister chromatid exchange assay [OECD 479]	✓	

In certain cases, genotoxicity testing may not be necessary. Clearly, such studies have little value if the drug being developed is an oncologic, and where the drug is cytotoxic. For noncytotoxic oncologics, e.g., biotechnology products, genotoxicity studies may need to be conducted. Genotoxicity testing of antibiotics, particularly in the bacterial reverse mutation assay may have limited value. However, the FDA has requested these studies at times with the in vitro concentrations being below cytotoxic levels. Finally, for some therapeutics that is not systemically available, e.g., antacids, genotoxicity studies are not usually required.

Safety Pharmacology Studies

Over the last 10 years, there has been increasing interest on the part of the FDA, as well as other international regulatory authorities, that safety pharmacology studies be included with the IND for a Phase 1 clinical study (ICH 2001). The base set of studies are limited of cardiovascular, respiratory, and central nervous system (CNS) function, except in unusual cases there is a specific reason (usually based on a known class effect or the proposed mechanism of action of the drug) to also evaluate another organ system. Other organ systems (renal, gastrointestinal, and liver) are not ignored, but rather are not required to be evaluated until a later point in the development of the drug (generally, concurrently with Phase 3). The immune system is not included because it is covered by a separate ICH guidance (S8, promulgated in September 2005).

For the species to be used in these studies, selection of the relevant animal models or other test systems needs to be determined. Selection factors can include the pharmacodynamic response of the animal model to the pharmaceutical, pharmacokinetic profile, species, strain, gender, and age of the experimental animals, etc. The time points for the measurements should be based on pharmacodynamic and pharmacokinetic considerations. Most often, the dose levels selected for these studies are based on the maximum blood concentration of the pharmaceutical determined from other toxicity studies, i.e., the dose levels should result in a C_{max} following a single acute administration. In the respiratory and CNS studies, the rat is the preferred species although other species can be used with scientific justification. For the cardiovascular study, the dog is the preferred species although the nonhuman primate also has been used.

For the CNS safety pharmacology study, the effects should be assessed by measuring motor activity, behavioral changes, coordination, sensory/motor reflex responses, and body temperature. The functional observation battery (FOB), a modified Irwin's or other appropriate test can be used. In the respiratory safety pharmacology study, respiratory rate, tidal volume and minute volume should be evaluated. Effects of the test substance on the cardiovascular system should be assessed with heart rate and the electrocardiographic measures. Indeed, prolongation of the QT interval is of paramount importance in this study as a measure of possible torsades de pointe.

Although not usually required for Phase 1 clinical studies, other safety pharmacology studies are necessary when the mode of action of the pharmaceutical is expected to cause concern on the part of the FDA. Drugs intended for renal or gastrointestinal indications require these studies. For the renal pharmacology study, specific renal function is examined to include cytology in the urine, glomerular filtration rate, electrolyte concentrations, etc. Most often these studies are conducted with rats although dogs, nonhuman primates, and swine also have been used. In the GI pharmacology study, propulsion rate and alterations in absorption potential are examined with the studies carried out in rats.

Safety pharmacology studies may not be needed for locally applied agents, e.g., dermal agents, or when systemic exposure is demonstrated to be low. Indeed, these studies are often not needed for dermal agents that are intended for topical indications, such as acne, rosacea, etc. However, when systemic exposure is expected because of chronically damaged skin, safety pharmacology studies may be needed. In addition, safety pharmacology studies for cytotoxic agents used for the treatment of end-stage cancer patients may not be necessary. However, for cytotoxic agents with novel mechanisms of action, there may be value in conducting safety pharmacology studies. For biotechnology-derived products that have a novel therapeutic class, an extensive evaluation by safety pharmacology studies should be considered.

Toxicity Testing: Biotechnology Products

The FDA regulates biologics as described under the 1902 act, but then uses the rule-making authority granted under the Food and Drug Act to “fill in the gaps.” The Bureau of Biologics, now Center for Biologics Evaluation and Research (CBER) was at one time a little known center within the FDA that was primarily concerned with the regulation of human blood products and vaccines used for mass immunization programs. New technology created in the 1980s and certainly in the 1990s and 2000s, saw a very large increase of new therapies and development of a new industry – the biotech industry. Products, such as recombinant-DNA-produced proteins (e.g., tissue plasminogen activator), biological response modifiers (cytokinins and colony-stimulating factors), monoclonal antibodies, antisense oligonucleotides, and self-directed vaccines (raising an immune response to self-proteins such as gastrin for therapeutic reasons), began to appear on the market with limited guidance on managing the safety and efficacy of these new products. Table 10 presents the basic test requirement matrix for biotechnology-derived therapeutics.

Therefore, these new products raised a variety of new questions on the appropriateness of traditional methods of evaluating drug toxicity that generated several points-to-consider documents. Some of the safety issues that arose over the years included:

- The appropriateness of testing a human-specific peptide hormone in nonhuman species. One must either determine/demonstrate that the target human pharmacologic response is also present in the relevant animal species to develop such a model species (i.e., a humanized knock out mouse species) or develop an analog compound which evokes the target receptor response in an animal species and can be evaluated for safety in parallel with the actual therapeutic molecule. Indeed, it is the interpretation of the data and the nuances of the data that led to some rather tragic consequences, e.g., Tigenaro.
- The potential that the peptide could break down due to nonspecific metabolism resulting in products that had no therapeutic value or even a toxic fragment.

Table 10 Biotechnology-derived drugs

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase ^d DRF toxicity in rodents (intended clinical route)	R/M
Two phase ^d DRF toxicity in nonrodents (intended clinical route)	D/S/P
Genotoxicity only if appropriate (special cases – nonprotein component)	
Safety pharmacology: CV in vivo	D/S/P
Safety pharmacology: respiratory – rodent	R
Pivotal/repeat dose in rodents (14 ^c –28 via intended clinical route)	R/M
Pivotal/repeat dose in nonrodents (14 ^c –28 day via intended clinical route)	D/P/S
*Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
Antibody-based assay to select appropriate species	
To support continued clinical development	
^b Immunotoxicity	TBD
Pivotal/repeat dose in appropriate species (3/9–12 month via intended clinical route). Must also characterize antigenicity	M/D/P/S
To support marketing approval	
Reproductive toxicity – Seg I	R
Reproductive toxicity – Seg III	R

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit *TBD* to be determined

*Recommended

^bMay be required

^cLess than 14 days clinical use

^dAcute and 7-day repeat dose

- The potential sequelae to an immune response (formation of neutralizing antibodies, provoking an autoimmune or a hypersensitivity response) and pathology due to immune precipitation, etc.
- The presence of contamination with oncogenic virus DNA (depending on whether a bacterial or mammalian system was used on the synthesizing agent) or endotoxins.
- The difficulty interpreting the scientific relevance of response to supraphysiological systemic doses of potent biological response modifiers.

The last few years have shown that some of these concerns were more relevant than others. For example, the “toxic peptide fragment” concern has been shown to be without merit. The presence of potentially oncogenic virus DNA and endotoxins is a quality control concern and is not truly a toxicological problem. Regardless of the type of synthetic pathway, all proteins must be synthesized in compliance with Good Manufacturing Practices. Products must be as pure as possible, not only free of rDNA, but also free of other types of cell debris (endotoxins). Batch-to-batch consistency with regard to molecular structure must also

be demonstrated using appropriate methods. The regulatory thinking and experience, over the last 15 years, has come together in the document, "S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" prepared by the International Conferences on Harmonization. More recently, however, draft guidance from the FDA on the safety evaluation of biotechnology-derived products was issued (Hastings 2007). This new guidance applies to investigational, protein therapeutic, diagnostic, and prophylactic products derived from characterized cells through the use of expression systems, such as bacteria, yeast, insect, plant, and mammalian cells, and produced by cells in culture or by recombinant DNA technology, including transgenic plants and animals. These protein products include monoclonal antibodies, cytokines, growth factors, plasminogen activators, recombinant plasma factors, enzymes, fusion proteins, receptors, hormones, and modified toxins. However, the guidance did not cover antibiotics, allergenic extracts, heparin, vitamins, cellular blood-derived components, conventional, bacterial, or viral vaccines, DNA vaccines, or cellular and gene therapies. Many of the principles outlined above for small molecules apply to the safety evaluation of biotechnology products. While guidance generally exempts therapeutic proteins for the evaluation of safety pharmacology endpoints, recently some FDA divisions have begun to ask for such as part of the IND package.

It has also been clearly demonstrated in the testing of rDNA protein products that animals develop antibodies to foreign proteins. The safety testing of any large molecule should include the appropriate assays for determining whether the test system has developed a neutralizing antibody response. Depending on the species, route of administration, intended therapeutic use, and the development of neutralizing antibodies (which generally takes about 2 weeks), it is rare for a toxicity test on an rDNA protein to be longer than 4 weeks duration. However, if the course of therapy in humans is to be longer than 2 weeks, the formation of neutralizing antibodies must be demonstrated with a long-term testing performed. The second antigen-antibody formation concern is that a hypersensitivity response is elicited. Traditional preclinical safety assays are generally adequate to guard against this if they are 2 weeks or longer in duration, and the relevant endpoints are evaluated.

For biotechnology products, animal models that mimic the human disease may be used to demonstrate that the product is actually able to bind to the target tissue. Indeed, a number of animal models have become available over the last 15 years for various disease states. However, it is not always clear that the pharmacological activity in a rodent model behaves similarly to that in humans. When the pharmacologic activity of a biopharmaceutical is dependent upon specific drug receptor/antigen binding that is not evident in an animal species, a number of different, scientifically rational approaches may be used to obtain these data, e.g., xenograft models, transgenic models, etc. The nonhuman primate often is the animal model of choice in testing of these substances although the rabbit and dog continue to be used.

Toxicology Testing: Special Cases

There are a number of special case situations for preclinical development of pharmaceuticals that do not follow the “normal” pattern of development. These therapies include oral contraceptives, drugs for compassionate use, orphan drugs, etc. These special situations are described more completely in Gad (2009) and elsewhere and are only briefly described here.

Oral Contraceptives

These have recently been modified so that in addition to those preclinical safety tests generally required, the following are also required (Berliner 1974):

- A 3-year carcinogenicity study in beagles (this is a 1987 modification in practice from earlier FDA requirements and the 1974 publication)
- A rat reproductive (Seg II) study, including a demonstration of return to fertility.

Life-Threatening Diseases (Compassionate Use)

Drugs for life-threatening diseases are not strictly held to the sequence of testing requirements as described previously (Gad 2009) because the potential benefit on any effective therapy in these situations is so high. This special case was applied to AIDS-associated diseases and cancer. The development of more effective HIV therapies (protease inhibitors) has now made cancer therapy more the focus of these considerations. Toxicity studies in animals are required to support initial clinical trials. These studies have multiple goals:

- Determine a starting dose for clinical trials
- Identify target organ toxicity and assess recovery
- Assist in the design of clinical dosing regimens

In general, it can be assumed that most antineoplastic cytotoxic agents are highly toxic. Studies to support the clinical trial would be of 5–14 days in length, but with longer recovery periods, e.g., 4 weeks. A study in rodents is required that identifies those doses that produce either life-threatening or nonlife threatening toxicity. Using the information from this first study, a second study in nonrodents (generally the dog) is conducted to determine if the tolerable dose in rodents produces life-threatening. For antineoplastic agents, dosing would be done on the basis of mg/m² rather than mg/kg with the starting dose in the initial clinical trial generally one-tenth of that required to produce severe toxicity in rodents or one-tenth of the highest dose in nonrodents that does not cause severe irreversible toxicity.

Information on pharmacokinetic information is not usually required but including these data in the study is usually recommended. Special attention is paid to organs with high cell-division rates, bone marrow, testes, lymphoid tissue testing, and GI tract. As these agents are almost always given intravenously, special attention needs to be given relatively early in the development of intravenous irritation and blood compatibility study, studies that always apply to pharmaceuticals given by the route of administration.

While not required for the IND, the assessment of genotoxicity and developmental toxicity needs to be addressed as the drug progresses in development. As noted above for genotoxicity, it is important to establish the ratio between cytotoxicity and mutagenicity. In vivo models, e.g., the mouse micronucleus test, can be particularly important in demonstrating the lack of genotoxicity at otherwise subtoxic doses. For developmental toxicity, ICH stage C-D studies (traditionally known as Seg II studies for teratogenicity in rat and rabbits) is also necessary.

The emphasis of this discussion has been on purely cytotoxic neoplastic agents. Additional considerations must be given to cytotoxic agents that are administered under special circumstances: those that are photoactivated, delivered as liposomal emulsions, or delivered as antibody conjugates. These types of agents require additional studies. For example, a liposomal agent needs to be compared to the free agent and a blank liposomal preparation. There are also studies that may be required for a particular class of agents. For example, anthracyclines are known to be cardiotoxic, so comparison of a new anthracycline agent to previously marketed anthracyclines is expected.

In addition to antineoplastic, cytotoxic agents, there are cancer therapeutic or preventative drugs that are intended to be given on a chronic basis. This includes chemopreventatives, hormonal agents, immunomodulators, etc. The toxicity assessment studies on these more closely resemble those of more traditional pharmaceutical agents. Chronic toxicity, carcinogenicity, and full developmental toxicity (ICH A-B, C-D, E-F) assessments are required. For a more complete review, the reader is referred to DeGeorge et al. (1998). Table 11 presents a basic test requirement matrix for those drugs (other than oncology) intended for use in the treatment of life-threatening diseases.

Antibiotics and Anti-Infectives

Usually, the preclinical development of these agents follows the traditional small molecule progression. The exception to this is that for early clinical development, the duration of repeated dose toxicity studies needs to only be up to 14 days as these agents are not often prescribed for longer than 10 days (it should be noted, however, that conducting 28-day repeat dose systemic toxicity testing may be more efficient in the long term as it serves to support the full term of clinical evaluation). Genotoxicity

Table 11 Life-threatening short use^a indications

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase ^c DRF toxicity in rodents (intended route)	R/M
Two phase ^c DRF toxicity in nonrodents (intended route)	D/S/P
Genotoxicity: Bacterial mutagenicity (ames)	In vitro
^b Safety pharmacology: CV-hERG	In vitro
^c Safety pharmacology: CV in vivo	D/P/S
Pivotal/repeat dose in rodents (14–28 day oral)	R/M
Pivotal/repeat dose in nonrodents (14–28 day oral)	D/P/S
^b CYP induction/inhibition	In vitro
^b Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
To support continued clinical development	
Pivotal/repeat dose in rodents (3/6 month oral) ^d	R/M
Pivotal/repeat dose in nonrodents (3/9–12 month oral) ^d	DP/S
Species: <i>R</i> rat; <i>M</i> mouse; <i>D</i> dog; <i>S</i> pig; <i>P</i> primate; <i>B</i> rabbit; <i>TBD</i> to be determined	
^a Less than 14 days clinical use	
^b Recommended	
^c May be required	
^d If the drug is not to be used for more than 28 days over a person's life span these are not needed	
^e Acute and 7-day repeat dose	

studies and developmental toxicity studies are also necessary, with genotoxicity testing required to open the IND; see above description of the testing needs for these drugs. Also, safety pharmacology studies are required to open the IND since some of the fluoroquinolone drugs are notorious for inducing cardiovascular effects, e.g., Torsade de Pointes. Furthermore, additional safety pharmacology studies may be necessary, particularly if there is concern with renal or gastrointestinal toxicity.

Special cases exist even within this subset – because of known class effects, fluoroquinolone antibiotics require phototoxicity evaluation and more extensive cardiotoxicity evaluation prior to opening an IND and proceeding to clinical evaluation.

Special Cases

Direct to FIM Trials: Imaging Agents

Imaging agents are regulated as drugs (usually by CDER, though in cases where they are seen as “tagents” which allow tracing of injected cells or tissue therapies, by CBER) and represent a special category as per testing requirements.

Table 12 Imaging agents

Test requirement	Species
Initial clinical trial/IND requirements	
Acute toxicity in rodents (IV) – expanded acute as in Phase 0 IND guidance	R/M
Acute toxicity in nonrodents (IV) – expanded acute	D/S/P
Genotoxicity: bacterial mutagenicity	In vitro
Genotoxicity: in vitro clastogenicity (mammalian chromosome aberration)	In vitro
Genotoxicity: in vivo (mouse or rat micronucleus)	R/M
Safety pharmacology: CV in vivo (nonrodent)	D/P/S
Safety pharmacology: respiratory – rodent	R
Pivotal/repeat dose in nonrodents (14–28 day IV)	D/P/S
Develop Bioanalytical for two species (man/nonrodent)	NA
Hemolysis	In vitro
To support continued clinical development	
Reproductive toxicity – Seg I	R

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *TBD* to be determined

For these regulated by CDER (traditional imaging agents which do not need to chemically interact with the body to serve their therapeutic agent), initial clinical evaluations can be legally performed without an IND (with the limitation that such a trial be at a single academic center, have IRB review, and be conducted in a limited number of subjects – generally 30 or fewer – ANAT CFR ref).

Expanding clinical evaluation beyond the single center structure for single clinical dose requires in vitro genotoxicity (mutagenicity and clastogenicity), expanded acute in a rodent and nonrodent (along the lines outlined in the FDA exploratory IND guidance). Limited multidose clinical evaluation (pre-Phase 3) adds in a requirement to provide data to address first their safety pharmacology endpoints (CNS, respiratory and cardiovascular, though not necessarily by distinct GLP safety pharmacology studies) and 14-day repeat dose toxicity studies in a rodent and non-rodent species. Table 12 provides the test requirement scheme for imaging agents.

Gene Therapy

Principal concerns for gene therapy products are (1) that the genetic material that is inserted in the target cells in the body (is inserted only in the target cells), (2) the vector used to deliver the genetic material does not evoke adverse immune responses (because initial clinical trials of gene therapy products are limited to patient populations – not “normal” volunteers), and (3) that the treatment that does not make the target disease worse in patients or interfere with existing disease treatments. It is considered that adverse outcomes at least require protracted periods of follow up.

Translating these to actual practice, a single administration study (conducted at each of several preferably three “dose” levels) in an animal model with and without the disease of interest present (such as a mouse with and without an induced tumor

load), followed out to 90 days or more (if practicable disease-bearing animals may not last that long) past administration to be able to detect unintended immune or other adverse effects. They, “with and without” disease, also apply to treatment groups, and some form of assay must be incorporated to evaluate whether the genetic material has been transmitted (and remains present and active) to unintended tissue targets.

Cellular (Stem Cell) Therapy

Stem cells are a potential mode of therapy that not only promise great clinical utility, but also (when one considers what has been seen in the case of the closely related field of gene therapy) significant concern as to safety. Pleuripotent cells are introduced into the body of a patient – concerns are contamination, will they stay where they are put, and will they potentially change into a different cell type? Additionally, will they remain viable in the role intended? How these concerns are addressed is very much in flux. At the current time, planned nonclinical safety evaluation plans are negotiated with the FDA in advance. And because there is no way to remove or selectively inactivate the cells once they are put in place, the test program must be completed prior to the initiation of clinical studies.

1. A method must be developed and validated for verifying cell viability in vitro and in the target tissue site that the cells are being injected into both the intended rodent and nonrodent test species after cell transplantation.
2. A dose-range finding toxicity study in a suitable disease model species (such as stroke model rats for a therapy intended to treat stroke. Such a study would be non-GLP.
3. A 6-month toxicity study in rats with administration by the intended means and frequency intended to be used in patients. The study includes biodistribution evaluations for the cells. Interim sacrifice groups should be taken at 30 days and 3 months post administration. This study should be GLP in every aspect feasible.
4. A 1-year toxicity study in primates with administration by the intended means and frequency intended to be used in patients. The study includes biodistribution evaluations for the cells. Interim sacrifice groups should be taken at 30 days and 3 months post administration. This study should be GLP in every aspect feasible.

Excipients

Novel excipients, those for which there exists no DMF or evidence of use in approved pharmaceutical products (inactive components) that are to be used in formulations administered to humans must now be qualified in accordance with

Table 13 Excipients (table entries for oral agents – if for use via other, that route used for in vivo studies)

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase ^d DRF toxicity in rodents (oral)	R/M
Two phase ^d DRF toxicity in nonrodents (oral)	D/S/P
Genotoxicity: bacterial mutagenicity (ames)	In vitro
Genotoxicity: in vitro clastogenicity (CHO chromosome aberration)	In vitro
Genotoxicity: in vivo (mouse or rat micronucleus)	R/M
^a Safety pharmacology: CV-hERG	In vitro
Safety pharmacology: CV in vivo	D/S/P
Safety pharmacology: FOB/Irwin	R/M
Safety pharmacology: respiratory-rodent	R
Pivotal/repeat dose in rodents (14–28 day oral)	R/M
Pivotal/repeat dose in nonrodents (14–28 day oral)	D/S/P
^a CYP induction/inhibition	In vitro
^a Five species microsome metabolic panel	In vitro
Develop bioanalytical for three species (man/rodent/nonrodent)	NA
To support continued clinical development	
Development tox (Seg II) – rate and rabbit pilots and rat and rabbit studies	R/B
Immunotoxicity ^b	TBD
Pivotal/repeat dose in rodents (3/6 month oral) ^c	R/M
Pivotal/repeat dose in nonrodents (3/9–12 month oral) ^c	D/S/P
To support marketing approval	
Reproductive toxicity – Seg I	R
Tumorigenicity/carcinogenicity – rat	R

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *TBD* to be determined

^aRecommended

^bMay be required

^cLess than 14 days clinical use

^dAcute and 7-day repeat dose

ICH guidance. These guidance set requirements that are identical to what is required for any other New Chemical Entity (NCE). In practice, for opening an IND these requirements are generally met by (1) supplying baseline genetic toxicity data for the excipient and (2) conducting the “pivotal” (14 or 28 days) repeat dose toxicity studies using the clinical formulation. Table 13 presents the ICH guideline requirements for the development and approval of novel excipients.

Pediatric Claims and Juvenile Animal Studies

Relatively few drugs marketed in the USA (approximately 20%) have pediatric dosing information available. Clinical trials had rarely been done specifically on pediatric patients. Traditionally, dosing regimens for children have been derived empirically by

extrapolating on the basis of body weight or surface area. This approach assumes that the pediatric patient is a young adult, which simply may not be the case. There are many examples, e.g., acetaminophen, fluoroquinolones, of how adults and children differ qualitatively or quantitatively in metabolic and/or pharmacodynamic responses to pharmaceutical agents (Schacter and DeSantis 1998). In response to the pediatric initiatives, the FDA published policies and guidelines (<http://www.fda.gov/cder/pediatric>) although the focus of the initiatives had been directed toward clinical trials with limited preclinical toxicology information. In 2006, however, the agency developed a pediatric guidance that describes the timing for initiation of these studies as well as recommendations on study regimen. Although testing in juvenile animals as a basis for pediatric approvals tends to occur after the development of the adult formulation, the sponsor is required to submit an IND for undertaking a clinical trial in a pediatric population.

The FDA designated levels of postnatal human development and the approximate equivalent ages in various animal models with a comparison to the human for different organ systems provided in the guidance. The table is not completely accurate, however, because of the difference in the stages of development at birth. A rat is born quite underdeveloped when compared to a human being. Therefore, there is no consistent temporal relationship in developing the ages of animals compared with humans (Hood 2006).

In designing the juvenile toxicology study, several considerations are important and include:

- The timing of dosing in relation to the phases of growth and development in pediatric populations and juvenile animals
- The potential differences in pharmacological and toxicological profiles between mature and immature animal models
- Any established temporal developmental differences in animals relative to pediatric populations
- Juvenile animals generally undergo more dynamic development than is seen in the relatively stable adult

In these studies, juvenile rats and dogs are the preferred species although pigs, nonhuman primates, and other appropriate species have been used. The duration of testing must consider the length of the treatment period balancing the developmental age of the animal model and the proposed length of clinical treatment. Where appropriate, changes that need to be considered for the toxicology study include the developmental landmarks as well as the more standard indicators of target organ toxicity.

Exploratory INDs

The FDA has proposed a route to allow the evaluation of a single dose of a novel drug (NME) in humans at very low doses (a “microdose” or 1/100th of the intended clinical dose) with minimal preclinical evaluation. Table 14 presents the requirements for such.

Table 14 Exploratory/phase 0 IND (the “Microdose”)

Test requirement	Species
Initial clinical trial/IND requirements	
Enhanced acute toxicity in rodents (intended clinical route)	R/M
Enhanced acute toxicity in nonrodents (intended clinical route)	D/S/P
Species: <i>R</i> rat; <i>M</i> mouse; <i>D</i> dog; <i>S</i> pig <i>P</i> primate; <i>B</i> rabbit <i>TBD</i> to be determined	

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Nonclinical Safety Evaluation Studies Conducted to Support Continued Clinical Development

Once a candidate drug has proceeded through the opening of an IND or CTA and has been assessed in initial clinical studies, the focus of the nonclinical safety assessment efforts shifts to performing studies to enable longer and more extensive studies (including a wider variety of human subjects).

Much of what must be considered here comes from the ICH M3 Guidance (“Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals”) which has just (August, 2008) been revised (R2) General provisions for US FDA are in CFR 2005.

Repeat Dose Toxicity

The regulatory expectation is that a new therapeutic must be evaluated for a longer term of exposure than that to which clinical subjects are exposed, up to the limits of regulatory expectations (as displayed in Tables 15 and 16). Note that requirements are somewhat different for what is required to support clinical trials (Table 15) and what, for the same drugs would be required to support a marketing application (Table 16).

These same systematic studies must be conducted in compliance with the other expectation principles: at least three different dose groups must be included in the study, and the high dose group (at minimum) should serve to identify a target organ toxicity.

Currently, these requirements are common across the ICH conforming community nations. The sole exception is that the US FDA may require 12-month (instead of 9-month) nonrodent studies.

Developmental and Reproductive Toxicology (DART)

There are three separate considerations under DART study timing. The first is for male fertility studies (the classical segment I studies). Such studies (across ICH regions) should be conducted prior to the initiation of Phase 3 studies. It should be

Table 15 Duration of repeated dose toxicity studies to support the conduct of clinical trials in all regions

Maximum duration of clinical trial	Maximum duration of repeated dose toxicity studies to support clinical trials	
	Rodents	Nonrodents
Up to 2 weeks	2 weeks	2 weeks
Between 2 weeks and 6 months	Same as clinical trial	Same as clinical trial
>6 months	6 months	9 months ^a

^aExcept perhaps in USA**Table 16** Duration of repeated dose toxicity studies to support marketing in all regions

Duration of indicated treatment	Rodent (month)	Nonrodent (month)
Up to 2 weeks	1	1
>2 weeks to 1 month	3	3
>1–3 months	6	6
>3 months	6	9 ^a

^aExcept perhaps in the USA, where it can be 12 months

noted, however, that male reproductive organs are excavated histopathically in the repeat dose studies (typically 28-day) conducted prior to first in human studies and in all subsequent repeat dose systemic toxicity studies.

The second is for woman not of childbearing potential (that is, those who have been sterilized). Inclusion of such individuals is governed by the conduct of suitable repeat dose studies, and there are no explicit DART testing requirements.

Inclusion of women of childbearing potential is much more restricted (primarily due to developmental toxicity concerns). They may be included in short-term (up to 2 weeks of treatment) clinical trial with adequate informed consent, pregnancy testing prior to inclusion, and the use of a highly effective method of birth control. Note that no DART studies are thus conducted beforehand and that this really applies to women in traditional Phase 1 (P1) clinical studies.

With the completion of adequate developmental toxicity studies (segment II studies, and therefore also the required pilot studies before these in two species), the inclusion of up to 150 women of childbearing potential may be included in trials, having up to 3 months of dose administration of the drug. Such segment II studies must be completed prior to the inclusion of women in Phase 2 studies in the EU and Japan, but not in the USA. To all venues, female fertility (segment III) studies must be completed prior to the initiation of Phase 3 (P3) clinical studies.

If standard toxicity studies (as described under ICH S8) yield a result identifying the need for an additional study to evaluate immunotoxicity, such studies must be performed prior to the initiation of clinical studies.

Impurities, Degradants, and Residual Solvents

Impurities

The ICH *Guidance for Industry, Q3A Impurities in New Drug Substances*, published in February 2003 and Q3B(R), are intended to “provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state.” A new drug substance is not the final marketed product, but the active ingredient used in the marketed product. Impurities in new drug substances are addressed from both chemistry and safety perspective. CDER 2000 and 2009 provide the FDA equivalent guidance.

The guidance is not intended to apply to new drug substances during the clinical research stage of development (though such drugs in development must have consideration for meeting these requirements at the time of marketing approval and addresses safety concerns associated with such substances during development) nor does it cover natural product or biological process-produced drugs or extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as good manufacturing practice (GMP) issues (FDA 2005). The guidance further describes the circumstances in which impurities need to be reported, identified, and qualified.

The rationale for the reporting and control, identification, and qualification of impurities is discussed in the guidance. Organic impurities need to be summarized based on the actual and potential impurities most likely to arise during the synthesis, purification, and storage of a new drug substance, as determined by validated analytical methods (ICH 1995; ICH 1996). This discussion can be limited to those impurities that might reasonably be expected based on the knowledge of the chemical reactions and conditions involved (Ball et al. 2007).

Studies conducted to characterize the structure of impurities present in a new drug substance at a level greater than the identification threshold should be described and any impurities from any batch or degradation product from stability studies should be identified. If identification of an impurity or degradant is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. If an impurity is pharmacologically or toxicologically active, identification of the compound should be conducted even if the impurity level is below the identification threshold. Table 17 presents the thresholds for taking such actions.

The guidance also states that “qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for establishing impurity acceptance criteria that includes safety considerations. The level of any impurity that is present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. A level of a qualified impurity higher

Table 17 Thresholds for action on impurities in a drug product

Maximum daily dose ^a	Reporting threshold ^{b,c}	Identification threshold ^c	Qualification threshold ^c
≤2 g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
>2 g/day	0.03%	0.05%	0.05%

^aThe amount of drug substance administered per day

^bHigher reporting thresholds should be scientifically justified

^cLower thresholds can be appropriate if the impurity is unusually toxic

than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies. If data are unavailable to qualify the proposed acceptance criterion of an impurity, safety studies to obtain such data can be appropriate when the usual qualification thresholds are exceeded.”

Q3B(R) describes considerations for the qualification of impurities when thresholds are exceeded. If the level of impurity cannot be decreased to below the threshold, or if adequate data is not available in the scientific literature to justify safety, then additional safety testing should be considered. The studies considered appropriate to qualify an impurity depend on a number of factors, including the patient population, daily dose, and route and duration of administration. Toxicology studies are discussed briefly later in this chapter and in more detail in other chapters in this volume. Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate.

ICH Q3A states that “safety assessment studies to qualify an impurity should compare the new drug substance containing a representative amount of the new impurity with previously qualified material. Safety assessment studies using a sample of the isolated impurity can also be considered.” The latter is especially important to consider for genetic toxicology studies, and the importance of testing the isolated impurity is discussed in more detail at the end of this chapter.

Therefore, according to the guidance, if the maximum daily dose of the drug is less than 2 g/day, and the impurity intake is more than 0.15% or 1.0 mg/day, the qualification threshold has been reached, meaning safety studies need to be performed. Lower thresholds can be appropriate if the impurity is unusually toxic. In addition, the impurity needs to be reported and identified. These studies include general and genetic toxicology studies, and possibly other specific toxicology endpoints, as appropriate. Discussion of specific toxicity testing with the relevant FDA division is recommended.

If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and one to detect chromosomal aberrations, both in vitro, are considered an appropriate minimum screen.

Qualification studies for impurities are essentially bridging studies. If general toxicity studies are desirable, one or more studies should be designed to allow

comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of a degradation product. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days (always in rodents) would be considered appropriate.

The genetic toxicology studies can include a minimum screen (a study to detect point mutations and one to detect chromosome aberrations, both *in vitro*). The general toxicology studies should include one or more studies designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate (EMA 2004).

Inorganic impurities are normally detected and quantified using pharmacopeial or other appropriate procedures. The need for inclusion or exclusion of inorganic impurities in a new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopeia standards or known safety data. The control of residues of the solvents used in the manufacturing process for a new drug substance should be discussed and presented according to ICH Q3C.

A registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities. Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response of an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application. Analytical results should be provided in an application for all batches of a new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. The application should also contain a table that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used. Any impurity at a level greater than the reporting threshold and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Table 18 is an illustration of reporting impurity results for the identification and qualification in an application.

The guidance also states that when analytical procedures change, results provided in the application should be linked to the procedure used, with appropriate validation information provided, including representative chromatograms of representative batches. The applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested. Table 19 presents an example of how such values might be derived (or “rounded up”) and reported.

The ICH Q3A guidance also states that the specification for a new drug substance should include a list of impurities. Individual impurities with specific acceptance

Table 18 Threshold for degradation products in new drug products

Maximum daily dose ^a	Threshold ^{b,c}
Reporting thresholds	
≤ 1 g	0.1%
>1 g	0.05%
Identification thresholds	
<1 mg	1.0% or 5 mg TDI, whichever is lower
1–10 mg	0.5% or 20 mg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 mg	0.10%
Qualification thresholds	
<10 mg	1.0% or 50 mg TDI, whichever is lower
10–100 mg	0.5% or 200 mg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

^aThe amount of drug substance administered per day

^bThresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic

^cHigher thresholds should be scientifically justified

criteria included in the specification for a new drug substance are referred to as specified impurities. Specified impurities can be identified or unidentified. A rationale for the inclusion or exclusion of impurities in a specification should be presented.

“Acceptance criteria should be set no higher than the level that can be justified by safety data and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of a new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated” (ICH Q6A 2000 and ICH Q6B 1999).

ICH *Q3B(R) Impurities in New Drug Products* was published in November 2003 and is intended to provide guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state. A new drug product is a finished dosage form, for example, a tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. The Q3B(R) guidance complements the ICH guidance *Q3A Impurities in New Drug Substances*, which should be consulted for basic principles along with ICH *Q3C Impurities: Residual Solvents*, when appropriate.

Q3A addresses only those impurities in new drug products classified as degradation products of the drug substance, or reaction products of the drug substance with an

Table 19 Illustration of reporting degradation product results for identification and qualification in an application

Raw result (%)	Action			
	Reported result (%) (reporting threshold = 0.1%)	Total daily intake (TDI) of the degradation product (rounded result in mg)	Identification threshold 0.2%	Qualification threshold 200 µg TDI (equivalent to 0.4%)
50 maximum daily dose				
0.04	Not reported	20	None	None
0.2143	0.2	100	None	None
0.349	0.3	150	Yes	None
0.550	0.6	300	Yes	Yes
Raw result (%)	Action			
	Reported result (%) (reporting threshold = 0.05%)	Total daily intake (TDI) of the degradation product (rounded result in mg)	Identification threshold 2 mg TDI (equivalent to 0.11%)	Qualification threshold 3 mg TDI (equivalent to 0.16%)
1.9 g maximum daily dose				
0.049	Not reported	1	None	None
0.079	0.08	2	None	None
0.183	0.18	3	Yes	None ^{a,b}
0.192	0.19	4	Yes	Yes ^a

^aAfter identification, if the response factor is determined to differ significantly from the original assumptions, it can be appropriate to remeasure the actual amount of the degradation product present and reevaluate against the qualification threshold (see Attachment 1)

^bAlthough the reported result of 0.18% exceeds the calculated threshold value of 0.16%, in this case the action is acceptable since the TDI (when rounded) does not exceed 3 mg. Chromatograms with peaks labeled (or equivalent data if other analytical procedures were used) from representative batches, including chromatograms from analytical procedure validation studies and from long-term and accelerated stability studies, should be provided. The applicant should ensure that complete degradation product profiles (e.g., chromatograms) of individual batches are available, if requested

excipient and/or immediate container closure system (collectively referred to as *degradation products*). Generally, impurities present in a new drug substance need not be monitored or specified in new drug product unless they are also degradation products. This guidance does not address impurities arising from excipients present in a new drug product or extracted or leached from the container closure system. This guidance also does not apply to new drug products used during the clinical research stages of development. It also does not cover the same types of products as in Q3A(R): biological/biotechnological, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and associated semisynthetic products, herbal products, and crude products of animal or plant origin. Also excluded from this guidance are extraneous contaminants that should not occur in new drug products and are more appropriately addressed as GMP issues, polymorphic forms, and enantiomeric impurities. Photo degradants are covered by a separate guidance (ICH 1996).

Qualification of an impurity for a new drug substance has similar concerns as Q3A. The main differences are the reporting, identification, and qualification thresholds (Table 27). The thresholds are basically higher than they were in Q3A; however, there are more categories for dosages. If the qualification thresholds given in Table 27 are exceeded and data are unavailable to qualify the proposed acceptance criterion of a degradation product, additional studies to obtain such data may be appropriate.

Residual Solvents

ICH Q3C is intended to provide guidance for recommending acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guidance recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. A complete list of the solvents included in this guidance is provided in a companion document entitled *ICH Q3C-Tables and List* which can be found at the ICH or FDA Web site. The list is not exhaustive, and other solvents may be used and later added to the list.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield or determine characteristics, such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guidance does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

As there are no therapeutic benefits from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (carcinogens), such as benzene and carbon tetrachloride (Class 1 solvents, see Table 1 in ICH 1997), should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity), such as acetonitrile and chlorobenzene (Class 2 solvents), should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents, such as acetic acid and acetone (Class 3 solvents), should be used where practical.

This guidance does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to previously existing marketed drug products.

The guidance applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short-term (30 days or less) or topical application. Justification for these levels should be made on a case-by-case basis and discussed with the appropriate FDA division.

The limits of residual solvents may include a value for the Permitted Daily Exposure (PDE), which is the maximum acceptable intake per day of residual solvent in pharmaceutical products. These limits vary depending on the class.

For solvents where quantities are limited to set values in pharmaceutical products because of their inherent toxicity, the Class 2 list (Table 2) within the ICH Q3H (guidance) should be consulted. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm.

For solvents with low toxic potential, solvents in Class 3 (Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg/day or less (corresponding to 5,000 ppm or 0.5% under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and GMPs.

For solvents for which no adequate toxicological data were found, the solvents listed may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were previously found for these. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Acceptable exposure levels in this guidance for Class 2 solvents were established by the calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (*Pharmacopeial Forum*, Nov–Dec 1989), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (EHC 170, WHO, 1994). These methods are similar to those used by the US EPA (IRIS) and the US FDA (Red Book) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values provided in the lists of the ICH Q3C document.

$$\frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{PDE} = \text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}} \quad (1)$$

PDE is derived from the NOEL or the LOEL in the most relevant animal study as follows:

The PDE is derived preferably from an NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of *uncertainty factors* used in EHC (EHC 170, WHO, Geneva, 1994), and *modifying factors* or *safety factors* in *Pharmacopeial Forum*. The assumption of 100% systemic exposure is used in all calculations regardless of the route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species.

F1 = 5 for extrapolation from rats to humans.

F1 = 12 for extrapolation from mice to humans.

F1 = 2 for extrapolation from dogs to humans.

F1 = 2.5 for extrapolation from rabbits to humans.

F1 = 3 for extrapolation from monkeys to humans.

F1 = 10 for extrapolation from other animals to humans.

F1 takes into account the comparative surface area:body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.6}$$

in which M = body mass, and the constant k has been taken to be 10. The body weights used in the equation are those shown below in the included table.

F2 = A factor of 10 to account for variability between individuals.

A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this guidance.

F3 = A variable factor to account for toxicity studies of short-term exposure.

F3 = 1 for studies that last at least one half-lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys).

F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.

F3 = 2 for a 6-month study in rodents, or a 3.5-year study in nonrodents.

F3 = 5 for a 3-month study in rodents, or a 2-year study in nonrodents.

F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

F4 = A factor that may be applied in cases of severe toxicity (e.g., nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity). In studies of reproductive toxicity, the following factors are used:

F4 = 1 for fetal toxicity associated with maternal toxicity.

F4 = 5 for fetal toxicity without maternal toxicity.

F4 = 5 for a teratogenic effect with maternal toxicity.

F4 = 10 for a teratogenic effect without maternal toxicity.

F5 = A variable factor that may be applied if the NOEL was not established.

Table 20 Amount of residual solvent per day at maximum clinical dose (mg/day) of drug (example to be filled in)

Residual solvent	Concentration in drug product	Potential maximum clinical exposure (mg/day)	Reporting threshold (0.05%)	Qualification threshold (0.5%)
Name	in ppm		in mg/day	in mg/day

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg/kg/day. The PDE for acetonitrile in this study is calculated as follows:

$$\frac{50.7\text{mgkg}^{-1}\text{day}^{-1} \times 50\text{kg}}{\text{PDE} = 12 \times 10 \times 5 \times 1 \times 1 = 4.22\text{mgday}^{-1}}$$

In this example,

- F1 = 12 to account for the extrapolation from mice to humans.
- F2 = 10 to account for differences between individual humans.
- F3 = 5 because the duration of the study was only 13 weeks.
- F4 = 1 because no severe toxicity was encountered.
- F5 = 1 because the NOEL was determined.

The results would then be presented in a table such as Table 20.

Extractables and Leachables

Leachables are chemical entities, either organic or inorganic, that migrate from pharmaceutical container closure system components into a drug product formulation. Since patients can be exposed to leachables during normal use of a drug product, leachables are of potential safety concern (Norwood 2007; Norwood et al. 2007; Osterberg 2005a, b). Extractables are compounds that are forced out

of container closure system materials and components under laboratory experimental conditions. All extractables from a given pharmaceutical container closure system and its components are, therefore, potential leachables in a drug product incorporating the same container closure system components. Regulatory concern for regarding leachables and extractables is directly related to the potential for contamination and/or interaction of the drug product formulation with the container closure system, with the greatest concern focused on Orally Inhaled and Nasal Drug Products (OINDP), which include Metered Dose Inhalers (MDIs), Dry Powder Inhalers (DPIs), inhalation solutions, suspensions and sprays, and nasal sprays (Norwood et al. 2007; CDER 1998). Controlled extraction studies are an extremely important part of the pharmaceutical development process for OINDP, and should be performed on critical components as identified by the manufacturer and regulatory authority. As stated in the PQRI L&E Recommendations: “A controlled extraction study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container closure system. The purpose of a controlled extraction study is to systemically and rationally identify and quantify potential leachables, i.e., extractables, to the extent practicable, and within certain defined analytical threshold parameters.”

Controlled extraction studies result in extractables profiles of OINDP components. Extractables profiles contain information which allows the identification, to the extent possible, and quantitation of individual extractables from a given component, and therefore an early indication of potential leachables of concern. Controlled extraction studies generally establish a basis for the development and validation of routine quality control methods for drug product leachables, and finally allow for the correlation of extractables and leachables profiles. Although information on component composition from suppliers is very useful, helping to inform component selection and guide controlled extraction studies, such knowledge does not provide a complete extractables profile and therefore does not alleviate the requirement for controlled extraction studies no matter how “complete” the information might appear to be.

- Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.
- Controlled Extraction Studies should incorporate multiple extraction techniques.
- Controlled Extraction Studies should include careful sample preparation based on the knowledge of analytical techniques used.
- Controlled Extraction Studies should employ multiple analytical techniques.
- Controlled Extraction Studies should include a defined and systematic process for the identification of individual extractables.
- Controlled Extraction Study “definitive” extraction techniques and methods should be optimized.
- During the Controlled Extraction Studies, sponsors should revisit supplier information describing component information.

- Controlled Extraction Studies should be guided by Analytical Evaluation Thresholds (AET) that are based on an accepted safety concern threshold.
- Qualitative and quantitative extractables profiles should be discussed with and reviewed by toxicologists so that any potential safety concerns regarding individual extractables, i.e., potential leachables, are identified early in the development process.
- Polynuclear aromatics (PNAs), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are “special case” compounds, requiring the evaluation by specific analytical techniques and technology-defined thresholds.

The characterization and control of leachables and extractables represents possibly the most significant challenge facing a pharmaceutical development team responsible for the development, registration, and manufacture of an OINDP. Indeed, detecting, identifying, and quantifying organic leachables is a formidable task. In contrast to drug substance or excipient-related impurities, organic leachables can represent a diversity of chemical structures and compound classes, and are potentially present at widely varying concentrations in any particular OINDP. Additionally, the information available to a pharmaceutical development team on container closure system component composition and processing, which is provided by the component supplier, is often incomplete. In some cases, the supplier may provide no information. Thus, when an extractables study is first undertaken, the development team may only have a limited idea of what to look for, and what extraction techniques and analytical methods to use for the identification and assessment of potential leachables.

Residual Metals and Metal Catalysts

In early 2008, the EMEA promulgated a standard for metals as impurities in pharmaceuticals (EMEA 2008). They organized metals of concern into categories, as presented in Table 21.

If synthetic processes of pharmaceutical substances are known or suspected to lead to the presence of metal residues due to the use of a specific metal catalyst or metal reagent, a concentration limit and validated test for residues of each specific metal should be set. All concentration limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. Since the use of metal catalysts or metal reagents during synthesis is restricted to validated and controlled chemical reactions, the limitation of their residues in pharmaceutical substances itself is normally sufficient. A limit for a metal residue in the pharmaceutical substance may, however, be replaced by a limit for that metal residue in the final medicinal product, as described below.

Table 21 Class exposure and concentration limits for individual metal catalysts and metal reagents

Classification	Oral exposure		Parenteral exposure		Inhalation exposure ^a
	PDE (mg/day)	Concentration (ppm)	PDE (mg/day)	Concentration (ppm)	PDE (ng/day)
Class 1A: Pt, Pd	100	10	10	1	Pt:70 ^a
Class 1B: Ir, Rh, Ru, Os	100 ^b	10 ^b	10 ^b	1 ^b	
Class 1C: Mo, Ni, Cr, V metals of significant safety concern	250	25	25	2.5	Ni: 100 Cr (VI): 10
Class 2: Cu, Mn metals with low safety concern	2,500	250	250	25	
Class 3: Fe, Zn metals with minimal safety concern	13,000	1,300	1,300	130	

^aPt as hexachloroplatinic acid^bSubclass limit: the total amount of listed metals should not exceed the directed limit

For pharmaceutical products administered via the oral, parenteral, or inhalation route of administration, two options are available when setting a concentration limit for a metal residue.

Option 1: For each metal, the concentration limit in parts per million (ppm) as stated in Table 1 can be used. The concentration limits in Table 21 have been calculated using (2) below by assuming a daily dose of 10 g of the drug product.

$$\text{Concentration ppm} = \frac{\text{PDE } (\mu\text{g/day})}{\text{daily dose (g/day)}} \quad (2)$$

If all pharmaceutical substances in a drug product meet the option 1 concentration limit for all metals potentially present, then all these substances may be used in any proportion in the drug product as long as the daily dose of the drug product does not exceed 10 g/day. When the daily dose of the drug product is greater than 10 g/day, Option 2 should be applied.

Option 2a: The PDE in terms of mg/day as stated in Table 21 can be used together with the actual daily dose of a pharmaceutical substance in the drug product to calculate the concentration of residual metal allowed in that pharmaceutical substance.

Option 2b: Alternatively, it is not considered necessary for each pharmaceutical substance to comply with the limits given in Option 1 or the calculated limits using Option 2a.

The PDE in terms of mg/day as stated in Table 21 can also be used with the known maximum daily dose of the drug product to determine the concentration of a metal residue originating from any of the pharmaceutical substances in the drug

product (not the substance). This approach is considered acceptable provided that it has been demonstrated that the metal residue has been reduced to the practical minimum in every substance. This approach implies that the maximum levels of a metal in certain substances may be higher than the option 1 or option 2a limit, but that this should then be compensated by lower maximum levels in the other substances.

For pharmaceutical products applied via other routes of administration, the concentration limits should be set in consideration of the route of administration.

Without proper justification, parenteral limits/PDEs should be used for pharmaceutical substances that are administered by other routes of administration, including inhalation. Oral limits/PDEs may be applied if the absorption by other routes of administration is not likely to exceed the absorption following oral administration. For example, for cutaneous administration, oral concentration limits/PDEs are considered acceptable.

Platinum salts have been shown to be allergenic, with hexachloroplatinic acid being clearly the most allergenic. Consequently, a specific limit for inhalation exposure of this molecule has been set at 70 ng/day (see monograph). Chromium VI and nickel, when inhaled, have been associated with carcinogenicity. Therefore, specific limits for inhalation exposure have been set for chromium VI at 10 ng/day and for nickel at 100 ng/day.

For pharmaceutical products used for short-term and for life-saving indications, as the PDEs and concentration limits mentioned in this guideline are based on chronic use, higher PDEs and concentration limits may be acceptable in cases of short-term use (30 days or less). For instance, this may be applicable to contrasting agents, antidotes, or products for diagnostic use. This may, however, only be applied if neither an Option 1 nor an Option 2 limit is feasible.

Specific risk-benefit considerations, such as compounds used for life-saving indications, may also warrant the use of higher limits. Justifications should be made on a case-by-case basis.

Safety Assessment of Metabolites (Metabolites in Safety Testing – MIST)

Generally, measurements of circulating concentrations of a parent drug in animals are used as an index of systemic exposure in humans. Quantitative and qualitative differences in metabolite profiles are important when comparing exposure and safety of a drug in a nonclinical species relative to humans during risk assessment. Based on data obtained from in vitro and vivo metabolism studies, when the metabolic profile of a parent drug is similar qualitatively and quantitatively across species, we can generally assume that potential clinical risks of the parent drug and its metabolites have been adequately characterized during standard nonclinical safety evaluations. However, metabolic profiles and metabolite concentrations can vary across species, and there are cases when clinically relevant metabolites have not

been identified or adequately evaluated during nonclinical safety studies. This may be because the metabolite being formed in humans was absent in the animal test species (unique human metabolite) or because the metabolite was present at much higher levels in humans (major metabolite) than in the species used drug standard toxicity testing.

The FDA and ICH recommends that – and this guidance encourages – attempts be made to identify as early as possible during the drug development process differences in drug metabolism in animals used in nonclinical safety assessments compared to humans. It is especially important to identify metabolites that may be unique to humans. The discovery of unique or major human metabolites late in drug development can cause development delays and could have possible implications for marketing approval. Early identification of unique or major metabolites allows for timely assessment of potential safety issues.

Generally, it is recommended that metabolites identified in human plasma that account for greater than 10% of drug-related material (administered dose or systemic exposure whichever is less) be considered for safety assessment. The rationale for setting the level at greater than 10% for characterization of metabolites reflects consistency with other FDA and EPA regulatory guidance (US Food and Drug Administration 2005 and 2008; US Environmental Protection Agency 1998) and is supported by actual cases, described below, in which it has been determined that the toxicity of a drug could be attributed to one or more metabolites present at greater than 10% of the administered dose. Of the cases that follow, the last two are examples of a situation when a metabolite present at less than 10 % caused toxicity. As a result, depending on the situation, some metabolites present at less than 10% should be tested.

The objectives of standard nonclinical safety studies are to evaluate the general toxicity profile of a drug and its metabolites in rodent and nonrodent animal species and to assess the potential for genotoxicity in support of Phase 1 safety and tolerability studies in humans. Metabolism studies are generally performed through a combination of in vitro studies using animal and human tissues and in vivo studies in animals. The in vitro studies are generally conducted prior to the in vivo studies and provide an initial comparative metabolic profile. Results from these studies can assist in the selection of the appropriate animal species for toxicological assessments, should qualitative interspecies differences in metabolism be detected.

Identifying a major metabolite in animals that does not exist in humans can mean that toxicity observed in that animal species may not be relevant to humans. Conversely, identifying a human metabolite during the clinical development that did not form at appreciable levels in animals would raise safety concerns because it probably was not evaluated in the nonclinical studies to inadequate exposure. Additionally, when a potentially clinically relevant toxicity is observed during standard nonclinical studies, it is prudent to determine if metabolites contribute to that finding. In such cases, we recommend that the

metabolites be synthesized and directly administered to the appropriate animal species for further pharmacological/toxicological evaluation. When qualitative and/or quantitative species differences in metabolite profiles are discovered, we also recommend the investigation of different routes of administration or the use of alternative animal species for safety assessments. Discovery of such a metabolite could delay development until the relationship between metabolite exposure and toxicity (if any) is understood.

In vitro studies using liver slices, microsomes, or hepatocytes from animals and humans to identify the drug metabolic profile are generally conducted before the initiation of clinical trials. It is also important to try to determine whether the concomitant use of drugs results in the inhibition or the induction of common metabolic pathways. In vivo metabolic profiles in nonclinical test species are generally available early in drug development, and their results may reveal significant quantitative and/or qualitative differences in metabolism across species. However, a unique metabolite may only be recognized after the completion of in vivo metabolic profiling in humans. Therefore, we recommend the in vivo metabolic evaluation in humans be performed as early as feasible.

In general, systemic exposure to metabolites varies among species, and it is uncommon for humans to form unique metabolites. Therefore, the identification of major human metabolites at levels higher than those measured in the test species used for toxicological assessment is of serious concern. For metabolites detected in humans as well as in nonclinical species (although at lower levels in the latter), adequacy of exposure should be considered on a case-by-case basis. Generally, systemic exposure is assessed by measuring the concentration of the compound in serum or plasma. However, when measurements cannot be made in plasma for any one or a number of reasons, measurements can be made in other biological matrices such as urine, feces, or bile. Noncirculating metabolites (i.e., excreted in bile, urine) are sometimes identified before clinical trials, but are not usually monitored. It is quite likely that excreted metabolite levels may be more appropriate metric in many instances. For example, if Phase 2 conjugation products of a metabolite are present in the excreta, it can be assumed that systemic exposure to the metabolite has occurred. We recommended consulting the ICH Q3A guidance with regard to the development of analytical methods for measuring metabolites in selected matrices. If the systemic exposure in nonclinical species is equivalent to human exposure when measured in plasma and/or excreta, levels may be considered sufficient and alleviate the need for additional toxicity testing. We encourage contacting the agency early in drug development to discuss these issues.

Early identification of unique human or major metabolites can provide clear justification for nonclinical testing in animals, assist in planning and interpreting clinical studies, and prevent delays in drugs development. Sponsors are encouraged to conduct in vitro studies to identify and characterize unique human or major metabolites early in drug development. If toxicity studies of human metabolites are warranted, we recommend studies be completed and the study

reports be submitted to the agency before beginning large-scale Phase 3 trials. In some cases, it may be appropriate for these nonclinical safety studies with unique human metabolites to be conducted before Phase 3 studies; for example, (1) if the metabolite belongs to a chemical class with known toxicity; (2) if the metabolite has positive structural alerts for genotoxicity, carcinogenicity, or reproductive toxicity; or (3) if clinical findings suggest the metabolite or related compounds have indicated special clinical safety concerns, such as QT prolongation.

To optimize and expedite the development of drugs for serious or life-threatening diseases that lack an approved effective therapy, the number of nonclinical studies for the unique or major human metabolites may be limited on a case-by-case basis. We recommend sponsors contact the relevant review division to discuss such situation.

Local Tissue Tolerance

Local tissue tolerance of the intended clinical formulation to a parenteral route should be evaluated prior to the initiation of P3 studies. Such studies are specified both in relevant pharmacopeia (such as the USP) and in M3 (R2).

Nonclinical Abuse Liability

The ICH M3 (R2) explicitly states the need for nonclinical abuse liability evaluation for the drugs distributed to the brain and produce CNS activity, regardless of therapeutic indication.

If there is suspected abuse potential, one must evaluate the drug discrimination, self-administration of the compound, and the assessment of the dependence and/or withdrawal.

The use of a dose that produces a plasma concentration that is several folds above the highest intended clinical exposure is considered appropriate in these studies.

Drug Registration in Japan

Drug (and device) development and marketing approval in Japan are governed by the Pharmaceutical Affairs Law (PAL). Nonclinical study requirements conform to ICH requirements, with GLP standards for nonclinical studies being governed by the August 2008 revision of article 14, paragraph 3 of the PAL (and conforming to OECD-GLPs).

Drugs in China; Pharmacology and Toxicology Study Information

Requirements for drug registration in China generally conform to ICH and include:

- Summary of pharmacology and toxicology study
- Primary pharmacodynamics study and literature
- General pharmacology study and literature
- Acute/Single dose toxicity study and literature
- Repeated dose toxicity study and literature
- Special safety study and literature of hypersensitive (topical, systemic, and phototoxicity), hemolytic, and topical irritative (blood vessel, skin, mucous membrane, and muscle) reaction related to topical systemic use of the drugs
- A specific study and relevant literature on pharmacodynamics, toxicity, and pharmacokinetics change caused by the interactions among multiple components in the combination products
- Study and literature of genotoxicity test
- Study and literature of reproductive toxicity
- Study and literature of carcinogenicity test
- Study and literature of drug dependence
- Study and literature of preclinical pharmacokinetics.

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Supporting Marketing Applications

Attrition of the therapeutic candidates getting to this point is quite high with perhaps only one of every 200 compounds designated as candidates proceeding beyond Phase 1. While there may well be studies, which were desirable before but deferred (CYP inhibition and induction, identification of major metabolites, abuse liability potential, and such).

The test sets immediately required here are much more limited than they once were. The two main formats for applications for marketing approvals are the New Drug Application (NDA), which can come in four different forms, 505(b)s which are traditional approvals for NCEs, 505(b2)s for already approved drugs for generic drugs, and Biological License Application (BLA) used for a biotechnology derived product Abbreviated New Drug Approval (ANDAs). Most significant nonclinical safety is completed before contemplation of moving to make an application.

Non-Traditional (Other than NDA/505b (1)) Approval Routes and Requirements

Innovative new molecules New Molecular Entities (NME) are approved for market under the safety assessment process described in the body of this text. There are, in such processes, a range or variations which have also been described.

There are, however, two other approaches by which a drug may achieve marketing approval by other forms of NDAs, and for these; the 505 (b) (2) and the ANDA. The nonclinical safety assessment requirements are truncated. For both of these, there are two initial requirements. (1) That the active ingredient (or ingredients) be already approved for market in a traditional NDA and (2) that all the inactive ingredients present in the drug product be covered by the FDA's inactive ingredient database (and as such, have already been included in an approved marketed drug).

For the ANDA, there is no additional nonclinical safety assessment requirement as such a product must be of the same formulation as the off patent approved NME. It is only required that the product be bioequivalent, that is, meet guideline requirements as to similarity of pharmacokinetics. It should be noted that this route is

restricted to small molecules; there is no approval route in the USA for generic biotherapeutics. Table 22 presents the requirements for ANDA nonclinical assessment.

The 505 (b) (2) is, however, different. First, it is not strictly required that there is patent expiration for the innovator NME. Second, the route and/or formulation must be different from that of the approved NME; therefore, bioequivalence is not required or relevant. Third, such a product may be biologic (such as an alternative insulin product).

There is a modest nonclinical safety assessment requirement to support the filing of an IND and therefore before going into humans, at least a single repeat dose (typically 30 days in duration though 90 is sometimes specialized) must be performed to establish safety (see Table 23). Such a study is typically performed in a nonrodent species, such as the dog, pig, or primate (almost always dog or pig). It is not uncommon that this study, plus adequate information obtained from the literature, is sufficient to support marketing approval as long as the formulation (which must be the same as used clinically) and impurity profile remain unchanged.

Table 22 ANDA (abbreviated new drug application – for a generic drug)

Test requirement	Species
Initial clinical trial/IND requirements	
Acute toxicity in nonrodents (intended route)	D/S/P
Pivotal/repeat dose in nonrodents (28 day bioequivalency by intended clinical route)	D/S/P
Develop Bioanalytical for 2 species (man/nonrodent) To support marketing approval	NA
In Silico and Human bioequivalence	
Species: <i>R</i> rat; <i>M</i> mouse; <i>D</i> dog; <i>S</i> pig; <i>P</i> primate; <i>B</i> rabbit; <i>TBD</i> to be determined	
^a Recommended	

Table 23 505b(2) registrations

Test requirement	Species
Initial clinical trial/IND requirements	
Acute toxicity in rodents (Intended clinical route) ^a	R/M
Acute toxicity in nonrodents (Intended clinical route) ^a	D/S/P
^a Safety pharmacology: CV-hERG	In vitro
Pivotal/repeat dose in nonrodents (28 days via intended clinical route) ^b	D/S/P
Develop Bioanalytical for 3 species (man/rodent/nonrodent)	NA
Species: <i>R</i> rat; <i>M</i> mouse; <i>D</i> dog; <i>S</i> pig <i>P</i> primate; <i>B</i> rabbit; <i>TBD</i> to be determined	
^a Recommended	
^b 90 days may be required	

Carcinogenicity

If treatment is to exceed 3 months, then an evaluation of the carcinogenicity of the drug must be conducted prior to marketing applications unless there is a waiver. Drugs which are strictly genotoxic are automatically waived, and it is common to set waivers for such testing on drugs which are proteins (and have not shown any indication of aprenoplastic lesions in repeat dose studies performed to date) or for compounds for use in a patient population which is not expected to have more than 5 years survival.

Pre- and Post-natal Development

These studies, almost always conducted in rodents, are only required (according to ICH M3 (R2)) as part of the marketing application package unless there is an identified cause for concern. They may be conducted earlier to meet the needs of other than the US jurisdiction or if the subject drug is specifically for use in pregnant women.

Pediatric Population Studies

Not required unless the drug is specifically intended for use in pediatric populations (that is humans under the age of 18) or pediatric use labeling is desired or required: ICH changed the requirement to (1) if a consideration, the accumulated adult repeat dose toxicity studies (of appropriate length), core safety pharmacology, and the standard package of genotoxicity tests indicate a potential cause for concern, then (2) a single rodent species pediatric study should be performed. The requirement for a nonrodent pediatric safety study has been dropped.

Special Cases

There are some special studies the need for which may be triggered by either clinical or nonclinical safety findings during the course of development. These indicate the photocarcinogenicity study and the developmental neurotoxicology studies. The need for these is almost always specified by regulatory authorities prior to the initiation of Phase 3 studies.

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Special Therapeutic Category and Route of Administration Cases

Within the regulatory systems of the USA, EU, and Japan, the fixed “general case” approach to nonclinical safety assessment breaks down most frequently (in predictable manner) in the cases of 1; a number of specific therapeutic claims or 2; of (intended drug) administration by routes other than oral and intravenous.

Specific Therapeutic Classes

There are a variety of therapeutic claim classes, where the nonclinical safety assessment requirements are markedly different from those of the general case as laid out in M3 (R2) (ICH 2008) and in this text to date. These must each be considered on a therapeutic class basis.

Oncology Drugs

Both FDA and ICH have stated that they are working on specific guidance for this class (which currently constitutes a third of all new drugs going into development). A preliminary version of this has just become available. Concepts in it were previously presented in the 1998 paper by DeGeorge et al.

Most small molecule anticancer drugs (biologic entities are considered separately) have some form of selective cytotoxicity as a mechanism. As a starting place, such drugs are not required to have genotoxicity testing prior to first in human testing (or indeed prior to any phase of clinical testing) is not required if clinical evaluation is to be performed in cancer patients only (ICH 2008).

Separate safety pharmacology evaluation prior to first in human studies if the clinical evaluation is to be performed in cancer patients, and these endpoints are evaluated in the repeat dose studies.

The regimen (dosing pattern) of animals in repeat dose studies should mirror what is to be done (or is being done if past initial clinical studies) in patients.

Table 24 Oncology agents (cytotoxic)

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase DRF toxicity in rodents (IV) ^c	R/M
Two phase DRF toxicity in nonrodents (IV) ^c	D/S/P
Safety pharmacology: CV-hERG ^{a, b}	In vitro
Pivotal/repeat dose in rodents (14–28 day IV)	R/M
Pivotal/repeat dose in nonrodents (14–28 day IV)	D/S/P
*CYP induction/inhibition	In vitro
*Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
To support continued clinical development	
Pivotal/repeat dose in rodents (3/6-month oral)	R/M
Pivotal/repeat dose in nonrodents (3/9–12-month oral)	D/S/P
Safety pharmacology: CV	D/P/S
Safety pharmacology: respiratory/pulmonary	R

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *TBD* To be determined

^aRecommended

^b May be required

^cAcute and 7-day repeat dose phases

That is, it should reflect (usually) the intermittent (one or two doses a week, for example) nature of clinical dosing. Such drugs fall into three categories, cytotoxic drugs (for which Table 24 presents the testing scheme), specific receptor targeting drugs (Table 25) and protein drugs (monoclonal antibodies, for which testing requirements are presented in a separate section).

As this volume is being completed, a draft of the ICH guidance on nonclinical assessment of oncology drugs has become available. This is summarized here.

Nonclinical studies to support safety evaluation and pharmacology (description of mechanism of action).

Prior to FIM studies, preliminary characterization of the mechanism(s) of action, resistance, and schedule dependencies as well as antitumor activity in vivo should have been made. As appropriate, these properties should be further investigated in parallel with Phase II and III studies.

These studies can provide preclinical proof of principle, guide schedules, and dose-escalation schemes, provide information for the selection of test species, aid in starting dose selection, and in some cases justify pharmaceutical combination where clinical information cannot be obtained.

Secondary pharmacodynamic or off target effects should be investigated as appropriate.

Careful consideration should be given to whether these pharmaceuticals may also act as tumor promoters, enhance tumor growth, or interfere with effective therapy. An evaluation of the pharmaceutical effects on these parameters is thus essential. In vitro and in vivo data (xenograft, transgenic models, etc.) with or

Table 25 Oncology agents (protein-specific receptor targeted molecules)

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase DRF toxicity in rodents (IV) ^d	R/M
Two phase DRF toxicity in nonrodents (IV) ^d	D/S/P
Safety pharmacology CV in vitro	D/S/P
Safety pharmacology FOB/irwin	R/M
Safety pharmacology: respiratory – rodent	R
Pivotal/repeat dose in rodents (14–28 day IV)	R/M
Pivotal/repeat dose in nonrodents (14–28 day IV)	D/S/P
^a CYP induction/inhibition	In vitro
^a Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
To support continued clinical development	
Antigenicity (relevant species/model)	M/P
Developmental Tox (Seg II) – rat and rabbit pilots and rat and rabbit studies ^b	R/B
Immunotoxicity ^b	M/P
Pivotal/repeat dose in nonrodents (3/6-month oral) ^c	D/S/P
To support marketing approval	
Reproductive toxicity – Seg I	R
Reproductive toxicity – Seg III	R

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *TBD* to be determined

^aRecommended

^bMay be required

^cNot required if drug is for less than 14 days clinical use

^dAcute and 7-day repeat dose

without concomitant chemotherapy, may provide valuable insight into the possible adverse consequences of these products, and such information should be provided to support the initial clinical trial. Appropriate in vitro and in vivo models should be selected based on the target and mechanism of action. Without a clear understanding that the cell line characteristics are related to the pharmacology of the drug, it is not required that the same tumor types/models intended for clinical evaluation be studied in these models.

The primary aims of the in vitro studies are to obtain mechanistic information about the test substance and characterize the activity profile.

Activity Profile and Mechanism of Action

If a specific target structure is indicated, cell lines expressing different levels of this structure should be studied, if possible. The use of well-characterized cell lines as regards genotype and biochemistry is encouraged.

Mechanism(s) of Resistance

In parallel with the characterization of the mechanism(s) of action, the corresponding profile with respect to possible mechanism(s) of resistance can be obtained. Investigation of the possible indication of resistance by long-term exposure of cell lines to a new drug and further characterization of mechanism(s) of resistance are encouraged.

The primary aims of in vivo studies are to obtain further information with respect to antitumor activity, therapeutic index, and schedule dependency.

Studies in animals are usually carried out in rodents, mainly in mice, giving due consideration, when possible, to likely differences to man in pharmacokinetics/dynamics. The selection of a suitable animal model (including species, strain, and tumor type) depends on the properties and proposed therapeutic indications of the anticancer drug and the available information about the response of different tumor cell lines. Suitable criteria for the evaluation of antitumor activity include tumor growth, survival time, and degree of remission or cure.

Safety Pharmacology

As assessment of vital organ function, including cardiovascular, respiratory, and central nervous system could be included in the assessment of general toxicology prior to FIM studies. Safety pharmacology studies may not be needed for the treatment of patients with late stage or advanced cancers. In case of concern appropriate safety pharmacology studies, core battery and/or follow up or supplemental studies should be considered (ICH S7A).

Pharmokinetics/Toxicokinetics, Including ADME

The evaluation of limited kinetic parameters, e.g., peak plasma levels and AUC, in the animal species used for nonclinical studies may facilitate dose escalation during FIM studies. Further information on ADME in animals should normally be generated in parallel with clinical development (ICH 1994).

Systemic Toxicology

The primary objective of FIM clinical trials in patients with cancer is to determine a maximum tolerated dose (MTD) and dose limiting toxicity (DLT). General toxicology studies should be conducted to determine target organ toxicity. If possible, however, the determination of no observed adverse effect level (NOAEL) or no effect level (NOEL) is not essential. Toxicology studies should be designed to

Table 26 Example study schedules for drugs and biopharmaceuticals to support initial clinical trials

Clinical schedule	Nonclinical study schedule ^{a,b}
Once every 3 weeks	Single dose study
Daily for 3 days every 3 weeks	Daily for 3 days
Daily for 5 days every 3 weeks	Daily for 5 days
Daily for 5–7 days, alternating weeks	Daily for 5–7 days, alternating weeks (2 dose cycles)
Once every 2 weeks	Two doses 14 days apart
Once a week for 3 weeks, 1 week off	Once a week for 3 weeks
Twice or three times a week	Daily for 28 days
Continuous daily	Daily for 28 days
Continuous weekly	Once a week × 4 doses

^aSchedules described in table do not specify recovery periods, which should be incorporated into the study design. Timing of recovery sacrifices should be scientifically justified on the basis of either time for drug clearance, or other important criteria

^bNonclinical schedule includes rodents and nonrodents

support the clinical schedule as outlined in Table 26 above. Evaluation of recovery, effects of accumulation, and delayed toxicity should also be considered. Nonetheless, for nonrodent studies, dose groups should consist of at least three animals/sex/group, with the addition of two animals/sex/group for recovery in control and high dose groups. Both sexes should generally be used or justification should be given for specific omissions. To support FIM clinical trial at least one nonclinical study should incorporate a recovery period at the end of the study to assess for the reversibility of toxicity findings or the potential that toxicity continues to progress after the cessation of drug treatment. For continued clinical development, additional toxicology studies that incorporated the principles discussed in this paragraph should be conducted.

Toxicokinetic evaluation should be conducted as appropriate. Knowledge of relevant physiological, biochemical, and kinetic differences between humans and animal models can help determine the most appropriate species to be used.

Reproductive toxicology studies are not required prior to clinical trials. The general expectation is that the reproductive toxicology assessment be available when the marketing application is submitted. In certain patient populations (e.g., adjuvant setting), these studies should be provided prior to submitting phase III trials (ICH 2005).

For small molecule drugs, embryofetal development toxicity studies and peri-postnatal studies are required with the exception of traditional cytotoxic drugs.

Generally, no fertility study is needed but additional endpoints should be included in the repeat dose toxicity study(ies). However, when a therapy is essentially curative and the study is warranted by the patient population a more complete assessment of fertility should be conducted.

Embryofetal toxicology studies are typically conducted in two species. IN bases where embryo-fetal developmental toxicity study is unambiguously positive for teratogenesis, a confirmatory study in second species is usually not necessary.

Drugs that target rapidly dividing cells (e.g., GI, bone marrow) as assessed in generally toxicology studies, and are positive in genetic toxicology assays are assumed to be developmental toxicants, and therefore developmental toxicity studies do not need to be conducted. However, for this class of compounds, little information exists as to risks to the fetus from treating males. Thus, in the absence of such information, appropriate studies should be provided (mating treated males to untreated dams).

Genotoxicity studies are not necessary to support clinical trials for therapeutics intended to treat patients with late stage or advanced cancer. If a drug is clearly positive in vitro and in vivo study would not be needed. Genotoxicity studies should be performed to support a marketing application.

Carcinogenicity studies are usually not necessary to support marketing for therapeutics intended to treat patients with late stage or advanced cancer. The need for carcinogenicity assessment for anticancer pharmaceuticals is described in ICH S9 guidance.

For anticancer pharmaceuticals, the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential and support marketing. In general, additional studies defined in the ICH S8 guidance are generally not needed for pharmaceuticals intended to treat patients with late stage or advanced cancers. The concepts outlined in ICH S8 should be taken into consideration; however, the additional studies are usually not necessary given that the general toxicology evaluation is sufficient to evaluate the immunotoxicity of anticancer agents.

Special Considerations for Biopharmaceutical Studies

Unless otherwise described the principles outlined in ICH S6, 1997 and the same considerations above apply to biopharmaceuticals used to treat cancer.

Assessment of pharmacological activity, target distribution, and binding affinity are important in the selection of a relevant test species for toxicity testing for biopharmaceuticals. These data should be provided prior to the initiation of clinical trials.

Mass balance and excretion studies are not needed for chemically synthesized peptide drugs or biological products used to treat cancer.

In those cases, where there is sufficient public information to scientifically justify a class effect, mechanistic studies as outlined in ICH S6 may obviate the need for conducting full reproductive and developmental toxicity evaluation of biopharmaceuticals used to treat cancer.

For biotechnology-derived oncology products, genotoxicity and carcinogenicity studies are not needed.

Nonclinical Data Evaluation to Support Clinical Trial Design

Start Dose for First Administration in Human

The goal of the start dose is to administer a pharmacologically active dose that is reasonably safe to use. This safety of the dose is determined from toxicology studies in the most sensitive species. The start dose should be scientifically justified and may employ various approaches. In case of compounds exhibiting low general toxicity, it should be considered to set the starting dose in Phase I clinical trials on the bases of expected pharmacologically active dose. For anticancer small molecular weight drugs, the first-in-human maximal starting dose is usually determined from the appropriate general toxicology studies. A common approach is to set a start dose at 1/10 the STD 10 in rodents. If the nonrodent is more sensitive species than the rodent, the HNSTD is considered an appropriate start dose. The HNSTD is defined as the dose level below that in which observations of lethality, life-threatening toxicities or irreversible findings were observed. This approach may continue to be followed. Doses that cause excessive lethality are not appropriate to select the safe start dose. For the most systematically administered therapeutics, this conversion should be based on the normalization of doses to body surface area. Although body surface area conversion is the standard way to approximate equivalent exposure if no further information is available, in some cases extrapolating doses based on other parameters may be more appropriate.

In certain circumstances, determined case-by-case, alternative approaches may be acceptable (e.g., cytotoxic drugs). In those cases, a repeat dose toxicity study appropriate during two rodent species may be sufficient.

Dose Escalation and the Highest Dose in a Clinical Trial

In general, nonclinical data do not limit the dose escalation or highest dose investigated in a clinical trial for cancer patients. When a steep dose-responsive curve is observed in nonclinical toxicology studies, or no preceding marker of toxicity is available, a slower escalation should be considered.

Duration and Schedule of Toxicology Studies to Support Initial Clinical Trials

Since different dosing schedules may be utilized in initial clinical trials, the design of nonclinical studies should be appropriately chosen. See Table 26, for example, study designs and durations that may be used for drugs or biopharmaceuticals.

If a more intense schedule (e.g., going from weekly to 3× weekly) than those used in the toxicology studies used to support the initial clinical trial that is to be used clinically, an appropriate toxicology study in a single species could suffice to support this new schedule and be limited to include clinical signs and clinical chemistry at a minimum.

Duration of Toxicology Studies to Support Continued Development

In order to support continued development of a drug for patients with advanced disease, results from repeat dose studies of up to 3 months duration or 3–4 cycles, as appropriate, should be provided prior to the initiation Phase 3 studies. For most small molecular weight pharmaceuticals, these studies would be sufficient to support product registration. Long-term studies may be required in certain circumstances, on a case-by-case basis, to be provided at any phase in development. In Japan, if the indication is for a population without advanced disease, a more extensive evaluation (e.g., 6-month studies in two species) should be conducted. In the case of biologic therapeutics, studies of 6 months duration in a relevant animal species are necessary prior to the completion of the pivotal registration studies.

Combinations of Pharmaceuticals

Pharmaceuticals planned to be used in combination should be well studied individually in separate general toxicology evaluations. Data to support a pharmacologic rationale and an assessment for the potential for drug–drug interaction for the combination should be provided prior to starting the clinical study. Based on this information, a determination is made whether or not a toxicity study should be conducted. In general, however, toxicology studies investigating the safety of combination of pharmaceuticals intended to treat patients with advanced cancer are not needed.

Studies in Pediatric Populations

The general paradigm that exists for most pharmaceuticals that are investigated in pediatric patients is first to define an MTD in adult populations and to assess some

fraction of that dose in initial pediatric studies. Studies in juvenile animals are not usually needed to support the inclusion of pediatric populations for the treatment of cancer. The requirements outlined elsewhere in this document also apply to this population. Conduct of studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended pediatric age group.

Special Considerations for Biologics

The principles described in ICH S6 for dose schedule apply for oncology. However, a dose schedule of weekly X5 for products with a long-half administered on an intermittent schedule is usually sufficient to provide support for phase I clinical trials. Similar to small molecule doses on a continuous daily basis would be expected to be dosed daily in a nonclinical study as outlined in Table 27.

For nonagonist biologics, the starting dose should be based on the same principles as described above for small molecules. For agonist antibodies, however, a minimally biologic active dose should be considered.

Conjugated Agents

Conjugated agents are pharmaceuticals covalently bound to carrier molecules, such as to protein, lipids, or sugars. The safety assessment of the conjugated material is the primary concern. The safety of the unconjugated material, including the linker used should have a more limited evaluation. Stability of the conjugate in the test species and human plasma should be provided. A pharmacokinetic evaluation should assess both the conjugated and the unconjugated compound.

Liposomal Formulated Products

The safety assessment should include a complete evaluation of the drug product and a more limited evaluation of the unencapsulated drug and carrier. The special case of nanoparticle formulations is under development, but generally requires specific evaluation of the nanoparticle delivery system materials separately, at least for systemic toxicity. This can generally be done with separate groups added to the systemic (repeat dose) toxicity studies, with specific attention to potential immune system effects.

Table 27 Timing of nonclinical studies in relation to clinical development in patients (for small molecules)

Nonclinical studies	Prior to first administration	During clinical development	Marketing application approval
Primary Pharmacodynamics	Preliminary characterization of antitumor activity	Follow-up and supplemental studies	Submitted with filing
Safety Pharmacology	Preliminary characteristics	Follow-up/supplemental, as appropriate	Submitted with filing
Pharmacokinetics	Preliminary characterization	Evaluation of ADME	Submitted with filing
General Toxicology including toxicokinetics	Up to 28 days in two species	Options: Option 1—3-month studies in two species rodent and nonrodent provided prior to initiating phase III studies. Option 2—6-month studies in two species rodent and nonrodent following new M3 guidance	Rationale: Option 1—Over last 10 years the utility of 6-month studies has not been demonstrated—6-month studies submitted with filing have not impacted clinical development in Oncology Option 2 and 3—current experience with all drug classes ICH battery submitted with filing, as appropriate Submitted with filing
See data need in footnote			
Genotoxicity	Not needed	Not needed	
Reproduction Toxicology	Not needed	Prior to long-term clinical trials—pending M3-specific studies needed are in the text	
Carcinogenicity	Not needed	Not needed	May be needed under certain circumstances and/or cause for concern—may be postapproval—see SIA
Immunotoxicity	Not needed	Deferred discussion	

Data need—finding in 6/9-month studies that impacted on clinical development that were not observed in 3-month studies

Evaluation of Drug Metabolites

In some cases, metabolites have been identified in humans that have not been qualified in safety studies. For these drugs, a separate general toxicology evaluation may not be necessary for patients with late stage or advanced cancer as the metabolite is not likely to contribute significantly to the overall toxicity profile and the human safety would have to be assessed in phase I clinical trials. If the parent compound is considered positive in an evaluation for embryo-fetal and reproductive toxicity, in vitro and in vivo for genetic toxicity, or in carcinogenicity studies (if necessary), then separate studies for the disproportionate metabolite may not be needed in any cancer indication.

Evaluation of Impurities

It is recognized that impurities are not expected to have any therapeutic benefit, that impurity standard have been based on a negligible risk (e.g., an increase in lifetime risk of cancer of one in 10^5 or 10^6 for genotoxic impurities), and that such standards may not be appropriate for antineoplastic drugs intended to treat advanced stage patients. The limits on impurities in other ICH guidance may be exceeded as justified on a case-by-case basis.

Other Life-Threatening Chronic Diseases

These situations are diseases, such as ALS and other orphan diseases for which the patients are expected to die within 5 years. In these cases, the same points of variation that apply are cited above, under oncology drugs. Table 28 presents the basic test requirements for such drugs. It should be noted that as these agents are first clinically evaluated in patients, positive genotoxicity findings do not preclude advancing into clinical trials.

Imaging Agents

As presented in Chapter “IND Enabling Toxicology Programs,” initial single dose evaluation of imaging agents in the USA does not require a regulatory filing (IND) beforehand. Rather one must perform such (in no more than 30 subjects) at one of a number of designated academic medical centers with the approval of specific IRBs. Such IRBs more flexible in what nonclinical safety

Table 28 HIV/ALS

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase DRF toxicity in rodents (intended clinical route) ^d	R/M
Two phase DRF toxicity in nonrodents (intended clinical route) ^d	D/S/P
Genotoxicity: Bacterial mutagenicity (ames)	In vitro
Genotoxicity: In vitro clastogenicity (mammalian chromosome aberration)	In vitro
^a Safety pharmacology CV-hERG	In vitro
Safety pharmacology: CV in vivo	D/S/P
Safety pharmacology: FOB/Irwin	R/M
Safety pharmacology: respiratory – rodent	R
Pivotal repeat/dose in rodents (14–28 day intended clinical route)	R/M
Pivotal/repeat dose in nonrodents (14–28 day intended clinical route)	D/S/P
^a CYP induction/inhibition	In vitro
^a Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
If route other than oral – local tissue irritation ^b	
To support marketing approval	
Developmental tox (Seg II) – rat and rabbit pilots and rat and rabbit studies	R/B
Immunotoxicity (required)	TBD
Pivotal/repeat dose in rodents (3/6-month Intended clinical route) ^c	R/M
Pivotal/repeat dose in nonrodents (3/9–12-month intended clinical route) ^c	D/S/P
To support marketing approval	
Reproductive toxicity – Seg I ^b	R
Reproductive toxicity – Seg III ^b	R
Tumorigenicity/carcinogenicity – rat	R
Tumorigenicity/carcinogenicity – mouse	M
Species: <i>R</i> rat; <i>M</i> mouse <i>D</i> dog; <i>S</i> pig; <i>P</i> primate; <i>B</i> rabbit; <i>TBD</i> to be determined	
^a Recommended	
^b May be required	
^c Not required if less than 14 days clinical use	
^d Acute and 7-day repeat dose	

evaluation work is required beforehand. Usually, this means expanded acute studies (in rodents and nonrodents), genetic toxicology, and some form of cardiovascular safety evaluation.

Subsequent to the initial single dose studies, an IND or equivalent must be filed and opened and requires M3 (R2) compliant nonclinical safety testing. A frequent complication defines how often and how many times an agent may generally be used in any single individual. This determination is essential to establish what nonclinical testing is required. Table 12, previously presented, summarized the nonclinical safety testing requirements for imaging agents.

Antibiotics

Antibiotics represent a special case largely arising from their intended regimen of use. A typical course of therapy is either 7 or 10 days of administration (most commonly once a day by either the oral or a parenteral route). As such, they are never intended for use in any one patient for more than a few courses of therapy and thus initial 28-day repeat dose studies are generally sufficient not only to support the opening of the clinical evaluations, but also to carry the drug all the way to a marketing application. Long (than 28 day) term repeat dose studies and carcinogenicity studies are not generally required.

Additionally, it is important to establish that the frequency of administration to patients serves to maintain effective systemic levels of the antibiotic in the patient over the entire 7–10 day course of therapy, and that after the completion of such therapy, the antibiotic is effectively eliminated from the patients system after the treatment is completed. Otherwise, the general case approaches as presented in Fig. 1.

Vaccines

Vaccines are intended to establish an immune system response to some form of challenge – most commonly a virus, but also possibly a bacterial or parasite, and as such, the regimen of administration consists of two or three administrations separated by a long enough period for the response to take the intended infective agent. Most commonly, this period is a month or longer.

Additionally, while the primary active component is biologically derived, vaccines contain a unique use specific component when also administered an adjunct, an immune response booster. Currently, allowable adjuvants are limited (primarily) to aluminum-containing compounds.

The resulting required program is presented in Table 29. Note that immunogenicity (that is, antibody levels) and not toxicokinetics must be monitored through the course of systemic administration studies.

Table 29 Prophylactic vaccines (therapeutic vaccines must be designed on a case-by-case basis, and may include studies in disease model animals)

Test requirement	Species
Initial clinical trial/IND requirements	
Acute toxicity in rodents (by intended route)	R/M
Acute toxicity in nonrodents (by intended route)	D/S/P/R
Pivotal/repeat dose in rodents (by intended route, two or three administrations separated by 14 days to a month giving a total study length of 2–3 months)	R/M
Pivotal/repeat dose in nonrodents (by intended route, two or three administrations separated by 14 days to a month giving a total study length of 2–3 months)	D/S/P/R
To support continued clinical development and to support marketing approval	
Immunotoxicity ^a	TBD

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *TBD* to be determined

All studies described above must be performed by GLP

^aMay be required

Routes and Regimens Other than Oral and Daily

The majority of drugs are administered by the oral route, with the second largest category being by intravenous administration. For this reason, the general case is presented for an orally administered drug, specifically for the one on a daily basis over a chronic (greater than 3–6 months) period.

But neither of these situations (oral administration or regular daily administration) are universally the case. There are many other possibilities for both of these. For routes, Table 30 presents a summary list of most (but not all) of the possibilities.

Tables 31 and 32 summarize the basic testing requirements for topical agents (Table 31) and agents intended for administration by routes other than oral and topical (Table 32).

Combination Products

Recent years have seen a vast increase in the number of new therapeutic products in a separate category, which are not purely drug, device or biologic, but rather a combination of two or more of these. Classical examples are implanted drug delivery systems (whose primary function is drug delivery) and drug-impregnated devices (in which drug delivery is an adjunct to the device function). Congress first acknowledged the need for specific regulation of such combination products in the 1990 Safe Medical Device Act (Chapekar 1996; Gopalaswamy and Gopalaswamy 2008; March 1998; Siegel 2008).

Table 30 Potential routes of administration

<i>Oral routes</i> ⁵
Oral (PO) ^a
Inhalation ^a
Sublingual
Buccal
<i>Place into a natural orifice in the body other than the mouth</i>
Intranasal
Intraauricular
Rectal
Intravaginal
Intrauterine
Intraurethral
<i>Parenteral (injected into the body or placed under the skin)</i>
Intravenous (IV) ^a
Subcutaneous (SC) ^a
Intramuscular (IM) ^a
Intraarterial
Intradermal (ID) ^a
Intralesional
Epidural
Intrathecal
Intracardial
Intracardial
Intraventricular
Intraocular
Intraperitoneal (IP) ^a
<i>Topical routes</i>
Cutaneous ^a
Transdermal (also called percutaneous) ^a
Ophthalmic ^a

^aCommonly used in safety assessment

Historical Background

The history of this category includes a variety of product types, dating at least from the perfection of the hypodermic needle (1855). There are many modern examples of implanted delivery systems, such as the insulin pump (1980). One fundamental driving force for delivery systems has been the growth of new pharmaceutical products, especially since the dramatic expansion of drug research after 1945.

That research has led to the synthesis and testing of millions of compounds for pharmacological and antimicrobial properties. Indeed, today much of that development is performed in automated computer-controlled systems, leading to an even greater acceleration of the process. The continued emergence of a stream of novel and more complex combination products has blurred any distinguishing lines of

Table 31 Topical agents

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase DRF toxicity in rodents ^d	R/M
Two phase DRF toxicity in nonrodents ^d	D/S/P
Genotoxicity: bacterial mutagenicity (ames)	In vitro
Genotoxicity: in vitro clastogenicity (mammalian chromosome aberration)	In vitro
Genotoxicity: in vivo (mouse or rat micronucleus)	R/M
^a Safety pharmacology: CV-hERG	In vitro
Safety pharmacology: CV in vivo	D/S/P
Safety pharmacology: FOB/Irwin ^b	R/M
Safety pharmacology: respiratory – rodent ^b	R
Pivotal/repeat dose in rodents (14–28 day intended route ^c)	R/M
Pivotal/repeat dose in nonrodents (14–28 day intended route ^c)	D/S/P
^a CYP induction/inhibition	In vitro
^a Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
Local Irritation ^c (clinical formulation)	R
For dermal – sensitization	G or M
For dermal – 3T3 phototox screen	In vitro
To support continued clinical development	
Developmental tox (Seg II)	R/B
Immunotoxicity ^c (if immune modulatory claim or there are finding in 14/28 dog studies)	TBD
Pivotal/repeat dose in rodents (3/6-month oral) ^c	R/M
Pivotal/repeat dose in nonrodents (3/9–12-month oral) ^c	D/S/P
To support marketing approval	
Reproductive toxicity – Seg I	R
Reproductive toxicity – Seg III	R
Tumorigenicity/carcinogenicity – rat ^b	R
Tumorigenicity/carcinogenicity – mouse ^b	M

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *G* guinea pig; *TBD* to be determined

^aRecommended

^bMay be required

^cNot required if less than 14 days clinical use

^dAcute and 7-day repeat dose

regulatory authority and has complicated product designation and regulation. The issue of products combining a device and a drug, such as an asthma inhaler, has received considerable scrutiny over the past several years. But products combining a device and a biologic, such as organ replacement or assist devices, have received less attention. Recent trends, however, suggest that device and biologic combination products are quickly moving into the spotlight.

Table 32 Non-oral/non-topical route

Test requirement	Species
Initial clinical trial/IND requirements	
Two phase DRF toxicity in rodents (intended clinical route) ^d	R/M
Two phase DRF toxicity in nonrodents (intended clinical route) ^d	D/S/P
Genotoxicity: bacterial mutagenicity (ames)	In vitro
Genotoxicity: in vitro clastogenicity (mammalian chromosome aberration)	In vitro
Genotoxicity: in vivo (mouse or rat micronucleus)	R/M
^a Safety pharmacology: CV-hERG	In vitro
Safety pharmacology: CV in vivo	D/S/P
Safety pharmacology: FOB/irwin	R/M
Safety pharmacology: respiratory – rodent	R
Pivotal/repeat dose in rodents (14–28 day) (intended clinical route)	R/M
Pivotal/repeat dose in nonrodents (14–28 day) (intended clinical route)	D/S/P
^a CYP induction/inhibition	In vitro
^a Five species microsome metabolic panel	In vitro
Develop Bioanalytical for three species (man/rodent/nonrodent)	NA
Local Irritation (venous/muscle – clinical formulation) redo as formulation changes ^b	B
To support continued clinical development	
Developmental tox (Seg II) – rat and rabbit pilots and rat and rabbit studies	R/B
Hemolysis (clinical formulation) ^b	In vitro
Immunotoxicity ^b	TBD
Pivotal/repeat dose in rodents (3/6-month oral) ^c	R/M
Pivotal/repeat dose in nonrodents (3/9–12-month oral) ^c	D/S/P
To support marketing approval	
Reproductive toxicity – Seg I	R
Reproductive toxicity – Seg III	R
Tumorigenicity/carcinogenicity – rat ^c	R
Tumorigenicity/Carcinogenicity – mouse ^c	M

Species: *R* rat; *M* mouse; *D* dog; *S* pig; *P* primate; *B* rabbit; *TBD* to be determined

^aRecommended

^bMay be required

^cNot required if less than 14 days clinical use

^dAcute and 7-day repeat dose

Even less than drug and device combinations, device and biologic products – which include, among other things, cellular and tissue implants, infused or encapsulated cells, artificial and replacement organs, heart valves and pumps, and cardiac, neural, and neuromuscular stimulation devices – do not fit neatly into existing regulatory paradigms. For example, as part of the question of regulation, FDA must take into account the possibility of tissue contamination and other hazards involved in using animal-derived tissues.

What has resulted to date is a developing regulatory process. The written guidelines are fixed, but the day-to-day process is in flux.

Device regulation designation is by principal mode of action (PMOA), which is generally straightforward but can become less clear as precedents accumulate and technology becomes more complex.

Although both extracorporeal and peritoneal dialysis systems are regulated as devices, dialysate concentrate for use with the former is a device but prepackaged dialysate for use with the latter is a drug. Sometimes, consistency was elusive even when there was no combination, but just a single product. For example, *in vitro* diagnostics for detecting antibodies to HIV are regulated as biologics when they are used for screening the blood supply, but as medical devices when used for diagnostic or other screening purposes. When the FDA decides quickly and unequivocally on the regulatory status of a product, whether it was deemed a single product or was in combination with another product, there was relatively little opportunity for objection to the agency's decisions about how to regulate combination products and products whose status was uncertain. In the case of blood devices, the EU has affirmed this process (Anon 2000).

In the Safe Medical Devices Act of 1990 (SMDA), Congress took these issues in hand and amended the Federal Food, Drug and Cosmetic Act (FDCA) to make it easier for the FDA to regulate combination products in a rational fashion. The new provisions altered the substantive provisions of the FDCA only in minor respects. The main thrust of the new law was managerial, directing the FDA to make decisions about which Center would have "primary jurisdiction" over a combination product, based on the agency's understanding of the PMOA of the product.

For these products, Center jurisdiction turns on the PMOA. If the PMOA is that of a drug, then Center for Drug Evaluation and Research (CDER) has primary jurisdiction; if it is that of a device, jurisdiction is with CDRH; if that of a biological product, the Center for Biologics Evaluation and Research (CBER) has this jurisdiction. As the statute prescribed, the regulations go on to state that the Center with primary jurisdiction may consult with other agency components.

Although neither the statute nor the regulations explain what "primary jurisdiction" means, it seems clear that the FDA intends it to mean that the Center that has primary jurisdiction will review the combination product and ordinarily give it just one approval, that is, an NDA, PMA, or biologic license application (BLA) as appropriate. Section 3.4 (b) makes it clear, however, that the FDA's designation of one agency component as having primary jurisdiction does not preclude, in appropriate cases, the requirement for separate application, e.g., a 510(k) and a BLA. When separate applications are required, both can be reviewed by the lead Center, but "exceptional" cases may involve a second application to be reviewed by a different Center. To facilitate this, the agency published new delegations giving officials in each of the three Centers the authority to clear devices and to

approve devices, drugs, biologics, or any combination of two or more of them (FDA, 1991).

Contemporaneous with publication of the new regulations, the FDA made public three new Intercenter Agreements between CDRH and CBER, CDRH and CDER, and CDER and CBER. They describe the allocations of responsibility for numerous categories of specific products, both combination and noncombination. According to the regulations, these Intercenter agreements are not binding; they are intended to “provide useful guidance to the public” and, as a practical matter, to FDA staff as well.

The Intercenter Agreements are a treasure trove of information. In addition to explicit guidance about which Center has the lead with respect to particular products and whether one Center or two work on particular issues, they contain information and hints about whether the FDA believes that it can regulate certain products at all, and if so, how.

The regulations and Intercenter Agreements, however, do not answer every question, and the regulations recognize a role for the sponsor in cases of uncertainty. When the identity of the Center with primary jurisdiction is unclear or in dispute, or a sponsor believes that its combination product is not covered by the Intercenter Agreements, a sponsor can request a designation from the FDA’s product jurisdiction officer. A sponsor “should” file a request for designation with the product jurisdiction officer before submitting its application for marketing approval or an investigational notice. In practice, though, disputes or lack of clarity may not become evident until well into the review process, and it seems likely that the FDA would, if necessary, entertain requests for designation submitted at a later time.

Section 3.7(c) of the regulations lists the information to be included in the request, all of which must fit on 15 pages or less, including the identity of the sponsor, detailed information on the product, where the developmental work stands, the product’s known modes of action and its primary mode of action, and, importantly, the sponsor’s recommendation for which Center should have primary jurisdiction and the reasons for the recommendation.

The FDA promises to check the request for designation for completeness within five working days of receipt, and to issue a letter of designation within 60 days of receipt of a complete request. If the FDA does not meet the 60-day time limit, then the sponsor’s recommendation for the appropriate lead Center is honored.

The agency’s letter of designation can be changed only with the sponsor’s written consent, or, if the sponsor does not consent, “to protect the public health or for other compelling reasons.” A sponsor must be given prior notice of any proposed nonconsensual change, and must be given an opportunity to object in writing and at a “timely” meeting with the product jurisdiction officer and appropriate Center officials.

The Center for Devices and Radiological Health (CDRH) designates the Center for major policy development and the promulgation and interpretation of procedural regulations for medical devices under the Act. The CDRH regulates all

medical devices inclusive of radiation-related device, that are not assigned categorically or specifically to CDER. In addition, CDRH independently administers the following activities (references to “Sections” are the provisions of the Act):

- (a) Small business assistance programs under Section 10 of the amendments (See PL 94–295). Both CDER and CDRH identify any unique problems relating to medical device regulation for small business
- (b) Registration and listing under Section 510, including some CDER-administered device applications. The CDER receives printouts and other assistance, as requested
- (c) Color additives under Section 706, with review by CDER, as appropriate
- (d) Good Manufacturing Practices (GMPs) Advisory Committee. Under Section 520(f) (3), CDER regularly receives notices of all meetings, with participation by CDER, as appropriate
- (e) Medical Device Reporting. The manufacturers, distributors, importers, and users of all devices, including those regulated by CDER, shall report to CDRH under Section 519 of the Act as required. The CDRH provides monthly reports and special reports as needed by CDER for investigation and follow-up of those medical devices regulated by CDER

Device incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function.

Examples

Bone cement containing antimicrobial agent
Cardiac pacemaker lead with steroid-coated tip
Condom, diaphragm, or cervical cap with contraceptive or antimicrobial agent (including virucidal) agent
Dental device with fluoride
Dental wood wedge with hemostatic agent
Percutaneous cuff (e.g., for a catheter or orthopedic pin) coated/impregnated with antimicrobial agent
Skin closure or bandage with antimicrobial agent
Surgical or barrier drape with antimicrobial agent
Tissue graft with antimicrobial or other drug agent
Urinary and vascular catheter coated/impregnated with antimicrobial agent
Wound dressing with antimicrobial agent.

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Device Safety Evaluation

Introduction

To an even greater extent than is the case with pharmaceuticals, the regulatory nonclinical safety assessment requirement (called, for devices, biocompatibility evaluation) has become globally harmonized. The primary guidance for the USA, EU, and Japan and associated countries have formally become the ISO 10993 standards, with each having reference to their own regulations only in special cases. The remainder of the world has chosen to follow suit, making adherence of testing to support a submission primarily by reference to the International Standards Organization (ISO).

Regulatory Definition of Medical Devices

The definition of a medical device in the USA (with which there is fundamental international concurrence) is, according to Section 201(h) of the Food, Drug, and Cosmetic Act, “as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part or accessory,” which is:

- Recognized in the official National Formulary (NF), or the United States Pharmacopeia (USP), or any supplement to them
- Intended for use in the diagnosis of disease or other condition, or in the cure, mitigation, treatment, or prevention of disease, in man or animals, or
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is dependent upon being metabolized for the achievement of any of its principal intended purposes (CDRH 1992)

The First guidance as to nonclinical testing requirements for devices was provided by the USP (Table 33).

Table 33 USP classification of plastics

Plastic classes ^a						Tests to be conducted			
I	II	III	IV	V	VI	Test material	Animal	Dose	Procedures ^b
X	X	X	X	X	X	Extract of sample in NaCl injection	Mouse	50 mL/kg	A (iv)
X	X	X	X	X	X		Rabbit	0.2 mL/animal at each of 10 sites	B
	X	X	X	X	X	Extract of sample in 1:20 solution of alcohol in NaCl injection	Mouse	50 mL/kg	A (iv)
	X	X	X	X	X		Rabbit	0.2 mL/animal at each of 10 sites	B
		X		X	X	Extract of sample in Polyethylene Glycol 400	Mouse	10 g/kg	A (ip)
				X	X		Rabbit	0.2 mL/animal at each of ten sites	B
		X	X	X	X	Extract of sample in vegetable oil	Mouse	50 mL/kg	A (ip)
			X	X	X		Rabbit	0.2 mL/animal at each of ten sites	B
			X		X	Implant strips of sample	Rabbit	Four strips/animal	C

^aTests required for each class are indicated by an “X” in appropriate columns

^bA represents (ip vs. iv) – systemic injection test (intraperitoneal or intravenous); B represents intracutaneous; C represents implantation test

In practice, diagnostics which rely on in vitro evaluation of samples collected from patients (plasma, serum, blood, urine, feces, and so on) and analyzed external to the body are regulated as devices. But as there is no actual patient contact, there is also neither safety concern (arising from the diagnostic itself) nor nonclinical evaluation of same. This also applies to imaging devices which operate external to the body (X-rays, MRI, and CAT scan devices) to the extent that there is no nonclinical biocompatibility assessment.

International Standards Organization

The basic guidance (and regulation) of biocompatibility evaluation arises not from a governmental body, but rather from ISO, anongovernmental organization (NGO). The primary definition of what nonclinical testing is required to support going forward to evaluate a device in human beings (in the USA, via the mechanism of an Investigational Device Exemption, or IDE) or to marketing approval of a device (in the USA via either a 510(k), 513(f), or PMA) is to be found in ISO 10993-1:1997, Biological evaluation of medical devices – Part 1: Evaluation and Testing. This guidance calls for an initial determination of what the nature of patient body contact will be:

- Surface Devices
 - Skin contact
 - Mucous membrane
 - Breached surface
- External Communicating Devices
 - Blood path indirect
 - Tissue/bone communicating
 - Blood path direct (circulating)
- Implant Devices
 - Bone/tissue
 - Blood

This is followed by a determination of the cumulative duration of such contact (characterized as limited, prolonged, or permanent):

- Limited exposure (<24 h)
- Prolonged or repeated exposure (24 h to 30 days)
- Permanent contact (>30 days)

One then refers to a test selection grid, presented in Tables 1 and 2, to determine what testing or data are required.

It should be noted that since 2002, ISO has added a number of additional guidances (to the ISO 10993 series) which describe testing that is not called out in the tables incorporated into 10993-1. Of these new requirements, parts 13–19 are chemical and analytical in nature. Part 20 (Principles and methods for immunotoxicology testing of medical devices), however, does describe immunotoxicity evaluations required in some cases. The full set of guidance (called Standards by ISO) for the biological evaluation of medical devices is, as of November of 2007:

- Part 1: Evaluation and testing
- Part 2: Animal welfare requirements
- Part 3: Tests for genotoxicity, carcinogenicity, and reproductive toxicity
- Part 4: Selection of tests for interactions with blood
- Part 5: Tests for cytotoxicity: in vitro methods
- Part 6: Tests for local effects after implantation
- Part 7: Ethylene oxide sterilization residuals
- Part 8: Withdrawn
- Part 9: Framework for the identification and quantification of potential degradation products
- Part 10: Tests for irritation and sensitization
- Part 11: Tests for systemic toxicity
- Part 12: Sample preparation and reference materials
- Part 13: Identification and quantification of degradation products from polymers

- Part 14: Identification and quantification of degradation products from ceramics
- Part 15: Identification and quantification of degradation products from metals and alloys
- Part 16: Toxicokinetic study design for degradation products and leachables
- Part 17: Establishment of allowable limits for leachable substances
- Part 18: Chemical characterization of materials
- Part 19: Physicochemical, mechanical, and morphological characterization
- Part 20: Principles and methods for immunotoxicology testing of medical devices

Additionally, it should be noted that there is also ISO guidance for device risk assessment (based primarily on data from the above standards – EN 14971).

Tables 34 and 35 present the basic ISO test requirement schemes for device nonclinical biocompatibility evaluation (as presented in ISO 10993-1)

USFDA

FDA regulation of medical devices rests primarily on five statutes:

- Food Drug and Cosmetic Act (FDCA) of 1938
- Medical Device Amendments (to the FDCA) of 1976
- Safe Medical Devices Act of 1990
- Medical Device Amendments (to the FDCA) of 1992
- Medical Device User Fee and Modernization Act of 2002

While the FDA generally adheres to (and accepts as sufficient testing done in accordance with the) ISO 10993 standards, it does have its own guidance which is slightly different and occasionally requires the modification of testing requirements and plans. This is the G95-1 (“Blue Book”) Memorandum. In May 1995, the Office of Device Evaluation (ODE) adopted General Program Memorandum G95-1, an FDA-modified version of International Standard ISO 10993, “Biological Evaluation of Medical Devices Part I” and specifically requires individual organ or system toxicity evaluation. Table 36 forms the core of the G95-1.

Specific additional or clarifying points include:

1. For those devices with possible leachables or degradation products, e.g. absorbable surfaces, hemostatic agents, etc., testing for pharmacokinetics may be required.
2. Reproductive and developmental toxicity tests may be required for certain materials used for specialized indications.
3. Considerations should be given to long-term biological tests where indicated in the table taking into account the nature and mobility of the ingredients in the materials used to fabricate the device.

To meet these test requirements, a typical test matrix set for an implantable device is presented in Table 37.

Table 34 Initial evaluation tests for consideration

Medical device categorization by		Biological effect									
Nature of body contact (see 4.2)		Contact duration (see 4.3)	A – Limited (<24 h); B – prolonged (24 h to 30 days); C – permanent (>30 days)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subacute and subchronic toxicity	Genotoxicity	Implan- tation	Hemo- compatibility
Surface device	Skin	A	X	x	x						
		B	x	x	x						
		C	x	x	x						
	Mucosal membrane	A	x	x	x						
		B	x	x	x						
		C	x	x	x		x				
External communi- cating device	Breached or compromised surface	A	x	x	x						
		B	x	x	x						
		C	x	x	x		x				
	Blood path, indirect	A	x	x	x	x					x
		B	x	x	x	x					x
		C	x	x	x	x			x		x
	Tissue/bone/ dentin	A	x	x	x						
		B	x	x	x	x	x		x		x
		C	x	x	x	x	x		x		x
	Circulating blood	A	x	x	x	x					x
		B	x	x	x	x	x		x		x
		C	x	x	x	x	x		x		x

(continued)

TABLE 34 (continued)

Medical device categorization by		Biological effect									
Nature of body contact (see 4.2)											
Category	Contact	Cytotoxicity (>30 days)	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subacute and subchronic toxicity	Genotoxicity	Implan- tation	Hemo- compatibility		
Implant device	Tissue/bone	A	x	x							
		B	x	x	x	x	x			x	
		C	x	x	x	x	x			x	
	Blood	A	x	x	x	x				x	
		B	x	x	x	x	x			x	
		C	x	x	x	x	x			x	

Note: this table is a framework for the development of an assessment program and is not a checklist (see Clause 6)

Table 35 Supplementary evaluation tests for consideration

Medical device categorization by		Biological effect				
Nature of body contact (see 4.2)		Contact duration (see 4.3) A – Limited (<24 h); B – prolonged (24 h to 30 days) C – permanent (>30 days)	Chronic toxicity	Carcino-genicity	Reproductive/ developmental	Biode- gradation
Category	Contact					
Surface device	Skin	A				
		B				
		C				
	Mucosal membrane	A				
		B				
		C				
	Breached or compromised surface	A				
		B				
		C				
External communi- cating device	Blood path, indirect	A				
		B				
		C	x	x		
	Tissue/bone/ dentin	A				
		B				
		C	x	x		
	Circulating blood	A				
		B				
		C	x	x		
Implant device	Tissue/bone	A				
		B				
		C	x	x		
	Blood	A				
		B				
		C	x	x		

Note: this table is a framework for the development of an assessment program and is not a checklist (see Clause 6)

Topical Devices

These devices are most commonly drug delivery systems (such as transdermal patches) and thus a part of a combination product, or a wound dressing. Table 38 summarizes the test requirements.

Table 36 FDA device categories and suggested testing

Biological tests											
Short term											
Device categories	Irritation tests	Sensi- tization assay	Cytotoxicity	Acute systemic toxicity	Hemocom- patibility/ hemolysis	Pyrogenicity (material- mediated)	Implantation tests	Mutagenicity (carcinogenicity)	Long term		
									Subchronic toxicity	Chronic toxicity	Carcino- genesis bioassay
Body contact											
duration											
A-transient (<24 h)											
B-short-term (24 h – 29 days)											
C-long-term (>30 days)											
Intact	A	*	*	*							
surfaces	B	*	*	*							
	C	*	*	*	*						
External devices											
Breached or surface compromised	A	*	*	*	*						
	B	*	*	*	*				*		
	C	*	*	*	*		*	*	*		
Intact natural channels	A	*	*	*	*		*				
	B	*	*	*	*		*	*	*		
	C	*	*	*	*		*	*	*	*	

Table 37 Test matrix for implanted devices

Task/ISO testing requirement (if developed as medical device component)	Test for compliance
10993-1/Pharmacopeia pyrogenicity	Rabbit pyrogenicity
10993-3: Carcinogenicity	Qualify by literature (lit review/risk assessment), or 2-year implant study
10993-3: Genotoxicity	Ames test, chromosomal aberration study and in vivo mouse micronucleus study
10993-3: Reproductive toxicity	Qualify by literature, or conduct designated studies
10993-4: Hemocompatibility	Hemolysis – direct contact
10993-4: Hemocompatibility	Coagulation in vitro
10993-4: Hemocompatibility	Thrombogenicity
10993-5: Cytotoxicity	Cytotoxicity – ISO elution
10993-6: Local tissue tolerance/implantation	Intracutaneous reactivity
10993-10: Irritation/intracutaneous	Intracutaneous reactivity
10993-10: Sensitization	Guinea pig maximization study or local lymph node assay (LLNA) ^a
10993-11: Acute systemic toxicity	USP/ISO systemic injection test
10993-11: Subchronic toxicity	Implant (injection) study in rats 3–9 month
10993-13: Identification of degradation products from polymeric medical devices	Immersion/extraction and analysis of leached materials
10993-15: Identification of degradation products from metals and alloys	Immersion/extraction and analysis of leached materials
10993-16: Toxicokinetic study design for degradation products and leachables	Typically performed as a portion of subchronic implant study
10993-18: Chemical characterization of materials	Varies
10993-19: Physicochemical, morphological, and topographical characterization of materials	Varies
10993-20: Principles and methods for immunotoxicology testing of medical devices	Varies- generally tier one endpoints evaluated as part of subchronic study

All studies described above must be performed GLP. In Europe, the local lymph node assay (LLNA) is preferred

^aIn Japan, only the guinea pig maximization test (GPMT) is acceptable

Blood Path Direct

This special class of devices includes such things as stents (bare metal or drug-coated) catheters and in situ primary artery repair systems and require the studies summarized in Table 39. However, if there are component materials present, which add the possibility of releasing dangerous degradation products or impurities into the blood stream, testing to address these possibilities is also required.

Table 38 Medical devices (topical)

Task/ISO testing requirement (if developed as medical device component)		
	Test for compliance	Species
Regulatory status as a device component		
10993-5: Cytotoxicity	Cytotoxicity – ISO elution	In vitro
10993-6: Local tissue tolerance/ implantation	Intracutaneous reactivity	B
10993-10: Irritation/ intracutaneous	Intracutaneous reactivity	B
10993-10: Sensitization ^a	Guinea pig maximization study	G

All studies described must be performed GLP

^aIn Japan, only the GPMT is acceptable. In Europe, the LLNA is preferred

Table 39 Medical devices (blood path direct)

Task/ISO testing requirement (if developed as medical device component)		
	Test for compliance	Species
10993-1: Pyrogenicity	Rabbit pyrogenicity	
10993-3: Carcinogenicity	Qualify by literature (lit review/risk assessment) or perform study	
10993-3: Genotoxicity	Ames test, chromosomal aberration study and in vivo mouse micronucleus study	
10993-3: Reproductive toxicology literature	A single document will be prepared and provided for tasks 2 and 4	
10993-4: Hemocompatibility	Hemolysis – direct contact	
10993-4: Hemocompatibility	Coagulation in vitro	
10993-4: Hemocompatibility	Thrombogenicity	
10993-5: Cytotoxicity	Cytotoxicity – ISO elution	
10993-6: Local tissue tolerance/ implantation	Intracutaneous reactivity	
10993-10: Irritation/intracutaneous	Intracutaneous reactivity	
10993-10: Sensitization	Guinea pig maximization study	
10993-11 Acute systemic toxicity	USP/ISO systemic injection test	
10993-11 Subchronic toxicity	4-week (to 9 month) implant study in appropriate species	

All studies described must be performed GLP

Japan

The guidelines for biological studies required for applications for approval to manufacture or import medical devices (Notification No. 99, “YAKURI”) was put into force in 1995 and was replaced with the “Basic concept of biological safety studies of medical devices” in Feb. 2003 (Notification No. 0213001, “YAKUSHIN,” as part of the PLA – Pharmaceutical Assistance Law).

- In addition, a research project on evaluation method of efficacy and safety of medical devices was notified (Notification No. 36, “IRYOKIKI-SHINSA,” Feb. 2003). Notification No. 0213001 describes what testing is required for medical devices, and Notification No. 36 describes concrete methods. Table 4 presents the test selection grid under this requirement.
- The basic concept indicates that studies should be conducted in accordance with ISO 10993 in principle, i.e., based on the framework and principle of ISO 10993-1 “Evaluation and studies,” necessary evaluation parameters are selected according to the sites and duration of contact with the medical devices and then evaluation method for each parameter is selected based on the guidance for each study method as described in ISO 10993-2 and subsequent numbers. This test selection matrix is presented in Table 40.

Other Regulatory Guidances

Table 41 presents a summary of global device regulatory authorities and their Internet access sites.

Biological Tests

Also required to properly utilize the test selection tables provided to this point is knowledge of the objectives of the specified biological tests. These can be considered as follows. Where there are specific differences between ISO and Japanese requirements, these are pointed out.

Sensitization Assay: Estimates the potential for sensitization of a test material and/or the extracts of a material using it in an animal and/or human. ISO procedure is outlined in Table 42.

Irritation Tests: Estimates the irritation potential of test materials and their extracts, using appropriate site or implant tissue, such as skin and mucous membrane in an animal model and/or human. ISO procedures are outlined in Table 43; and for eye irritation in Table 44.

Cytotoxicity: With the use of cell culture techniques, this test determines the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by test materials and/or extracts from the materials. ISO procedures are outlined in Table 45.

Acute Systemic Toxicity: Estimates the harmful effects of either single or multiple exposures to test materials and/or extracts, in an animal model, during a period of less than 24 h. ISO procedure is presented in Table 46.

Hematocompatibility: Evaluates any effects of blood contacting materials on hemolysis, thrombosis, plasma-proteins, enzymes, and the formed elements using an animal model. Traditionally, hemolysis, which determines the degree

Table 40 Japanese MHW test selection guidelines

Device categories		Initial evaluation				Supplemental evaluation								
	Body contact	Contact duration	Cytotoxicity	Sensitization	Irritation or intracutaneous	Systemic (acute)	Subchronic toxicity	Genotoxicity	Pyrogen	Implantation	Hemocompatibility	Chronic toxicity	Carcinogenicity	
Surface devices	Skin	A	X	X	X									
		B	X	X	X									
		C	X	X	X									
	Mucosal membrane	A	X	X	X									
		B	X	X	X									
		C	X	X	X		X	X						
	Breached/compromised surface	A	X	X	X									
		B	X	X	X									
		C	X	X	X		X	X						
External communicating devices	Blood path indirect	A	X	X	X	X			X		X			
		B	X	X	X	X			X		X			
		C	X	X	X	X	X		X		X	X		
	Tissue/bone dentin communicating	A	X	X	X						X			
		B	X	X	X						X			
		C	X	X	X						X			X
	Circulating blood	A	X	X	X	X	X		X		X			
		B	X	X	X	X	X		X		X			
		C	X	X	X	X	X	X		X		X	X	
Implant devices	Bone/tissue	A	X	X	X	X								
		B	X	X	X					X				
		C	X	X	X						X		X	
	Blood	A	X	X	X	X	X			X		X		
		B	X	X	X	X	X		X		X	X		
		C	X	X	X	X	X	X		X		X	X	X
		A	X	X	X	X	X							
		B	X	X	X	X	X							
		C	X	X	X	X	X	X						

A represents temporary contact (<24 h); B represents short- and medium-term contact (24 h – 29 days); C represents long-term contact (>30 days)

Table 41 Non-US medical device regulators

Organization or publication	Web address	Sample main topics
CE marketing	www.sos.se/sose/nt/medtekn/cemark.htm	This is a Swedish government site which provides specific information regarding CE marketing, which is necessary to market medical devices in the European Community member nations
European Union (EU)	http://europa.eu.int/	This is a multilingual gateway to information about all activities of the EU
Health Canada	www.hc-sc.gc.ca	Provides useful information about the regulation of all medical products in Canada, and other Canadian government health programs
Medical Device Agency	www.medical-devices.gov.uk	Provides useful information about the regulation of medical devices in the United Kingdom
National Institute of Health Sciences – Japan	www.nihs.go.jp	Provides useful information about the regulation of medical devices and pharmaceutical products in Japan
Therapeutic Goods Administration	www.health.gov.au/tga	Provides useful information about the regulation of medical devices and pharmaceutical products in Australia

The table presents a summary of global device regulatory authorities and their Internet access sites

Table 42 Sensitization test procedures required by ISO 10993-10

ISO 10993-10

Sample preparation: extraction in polar and/or nonpolar solvents

Extraction ratio: extraction ratio is dependent on the thickness of device or representative portion

Extract used for testing. If extraction is not possible, the adjuvant and patch test can be utilized

Table 43 Intracutaneous reactivity test procedures required by ISO 10993-10 guidelines

ISO 10993-10

Number of test animals: three rabbits for 1–2 extracts

Number of test/control injections per extract: five test and five control injections

Evaluation of responses: quantitative comparison of responses of test and control responses

Table 44 Eye irritation testing procedures outlined in ISO 1093-10

ISO 10993-10

Time of exposure: 1 s

Grading scale: classification system for grading ocular lesions

Table 45 Cytotoxicity test procedures specified by ISO 10993-5 and USP

ISO 10993-10

Number of cells per dish: 0.5–1 million cells

Extraction ratio: 60 cm² per 20 ml if thickness 80.5 mm; 120 cm² per 20 ml if thickness 70.5 mm or 4 g per 20 ml

Exposure period: typically 24–72 h (2 h for filter diffusion test)

Toxicity determination: visual grading and/or quantitative assessments

Positive controls: materials providing a reproducible cytotoxic response (e.g. organo-tin-impregnated polyvinyl chloride)

of red blood cell lysis and the separation of hemoglobin caused by test materials and/or extracts from the materials in vitro, has been “the” representative test employed. A broader range of primary tests (adding evaluations of thrombosis, coagulation, platelets, and immunology aspects) is currently recommended. ISO procedure for hemolysis is outlined in Table 47.

Pyrogenicity (Material Mediated): Evaluates the material mediated pyrogenicity of test materials and/or extracts. ISO and USP procedures are outlined in Table 48. Note that the LAL assay is accepted universally for endotoxin-associated pyrogenicity.

Implantation Tests: Evaluates the local toxic effects on living tissue, at both the gross level and microscopic level, to a sample material that is surgically implanted into appropriate animal implant site or tissue, e.g. muscle, bone; for 7–90 days. ISO procedure is outlined in Table 49.

Mutagenicity (Genotoxicity): The application of mammalian or nonmammalian cell culture techniques for the determination of gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by test materials and/or extracts from materials. Selected tests representing gene mutation tests (Ames or mouse lymphoma), chromosomal aberration tests (CHO) and DNA effects tests (mouse micronucleus and sister chromatid exchange) should generally be employed. ISO procedure is outlined in Table 50.

Subchronic Toxicity: The determination of harmful effects from multiple exposures to test materials and/or extracts during a period of one day to less than 10% of the total life of the test animal (e.g. up to 90 days in rats).

Table 46 Outline of ASTM and ISO/USP procedures for acute systemic toxicity

ASTM	
Response	Description
Normal, no symptoms	Mouse exhibits no adverse physical symptoms after injection
Slight	Mouse exhibits slight but noticeable symptoms of hypokinesia, dyspnea, or abdominal irritation after injection
Moderate	Mouse exhibits definite evidence of abdominal irritation, dyspnea, hypokinesia, ptosis, or diarrhea after injection. (Weight usually drops to between 15 and 17 g)
Marked	Mouse exhibits prostration, cyanosis, tremors, or severe symptoms of abdominal irritation, diarrhea, ptosis, or dyspnea after injection. (Extreme weight loss; weight usually less than 15 g)
Dead, expired	Mouse dies after injection
Interpretation	
The test is considered negative if none of the animals injected with the test article extracts shows a significantly greater biological reaction than the animals treated with the control article	
If two or more mice show either marked signs of toxicity or die, the test article will not meet the requirements of the test	
If any animals treated with a test article shows slight signs of toxicity, and not more than one animal shows marked signs of toxicity or dies, a repeat test using freshly prepared extract should be conducted using groups of ten mice each. A substantial decrease in body weight for all animals in the group, even without other symptoms of toxicity, requires a retest using groups of ten mice each. In the repeat test, the requirements are met if none of the animals injected with the test article shows a substantially greater reaction than that observed in the animals treated with the control article	

Table 47 Hemolysis can be assessed by any of several validated methods to assay hemoglobin in plasma

ISO 10993-4
Hemolysis can be assessed by any of several validated methods to assay hemoglobin in plasma

Table 48 Pyrogen test procedures required by ISO 10993-11 (in which cases it stands in place of this test) guidelines

ISO 10993-11

Number of animals: three rabbits required; comparison of febrile response in test animals to baseline temperature for the evaluation of pyrogenicity potential

Test duration: test measurement intervals: every 30 min for 3 h

Evaluation: cutoff for positive febrile response: 0.5°C

Table 49 ISO 10993-3 guideline used historically for assessing the effects of device or material implantation

ISO 10993-3

Time point(s) of assessment: sufficient to achieve steady state; (e.g. 2, 4, 6, and 12 weeks)

Number of animals: at least three per time period of assessment

Number of samples of evaluation: at least eight per time period for test and control

Evaluation criteria: comparative evaluation of responses to test and control materials

Table 50 Genotoxicity testing procedures required by ISO 10993-3

ISO 10993-10

Extraction vehicles: a physiological medium is used and, where appropriate, a solvent (e.g. dimethylsulfoxide)

Extraction: extract test material and test the extract or dissolve material in solvent and conduct test. The conditions of extraction should maximize the amount of extractable substances, as well as subject the test device or material to the extreme conditions it may be exposed to, without causing significant degradation. Extraction ratio is dependent on the thickness of test material

Chronic Toxicity: The determination of harmful effects from multiple exposures to test materials and/or extracts during a period of 10% to the total life of the test animal (e.g. over 90 days in rats). For an implanted device, the expectation is that the study will extend to 9–12 months or the duration or patient implantation (whichever is shortest). It is common to incorporate interim termination groups at 30 and 90 days into a chronic implantation study to accommodate the subchronic determinations.

Carcinogenesis Bioassay: The determination of the tumorigenic potential of test materials and/or extracts from either single or multiple exposures, over a period of the total life (e.g. 2 years for rat, 18 months for mouse, or 7 years for dog). Evaluation of the response to subcutaneous implantation in rodents requires consideration of the Oppenheimer effect, specific to this species.

Pharmacokinetics: To determine the metabolic processes of absorption, distribution, biotransformation, and elimination of toxic leachables and degradation products of test materials and/or extracts.

Reproductive and Developmental Toxicity: The evaluation of the potential effects of test materials and/or extracts on fertility, reproductive function, and prenatal and early postnatal development.

The tests for leachables, such as contaminants, additives, monomers, and degradation products, must be conducted by choosing appropriate solvent systems that yields a maximal extraction of leachable materials to conduct biocompatibility testing. The effects of sterilization on device materials and potential leachables, as well as toxic by-products, as a consequence of sterilization should be considered. Therefore, testing should be performed on the final sterilized product or representative samples of the final sterilized product.

Coordination of Phasing (Timing) of Nonclinical Testing with Medical Devices.

Device development (and the phasing of nonclinical safety evaluation performed with it) is very different from the corresponding processes for drugs.

First, clinical trials may or may not be required for device approval. If clinical trials are required, it is because the proof of efficacy is needed for the device. If the 510(k) route to approval is being employed, then clinical evaluation (of the devices efficacy) will generally not be required if the similarity to the predicate is sufficient to provide confidence that no concern as to the device working in a clinical setting exists.

If, however, such a concern exists or the route to approval is via a PMA, then one or more clinical trials will be required. While an IDE must be submitted for review prior to any such trial, there is great asymmetry in the potential patient risks (and therefore on the scope of required pre-IDE nonclinical safety testing) in such trials based primarily on whether the device is to be implanted in the body or not.

The reason is simple – an implanted device (heart valve, orthopedic, pacemaker, or coronary vascular stent, for example) once in place cannot simply be turned off or taken off if there is a safety problem. Rather, a surgical procedure (with its inherent risks) is required. It is thus considered that the patient exposure part of a risk consideration must be prolonged to permanent. In such cases, subchronic animal studies of suitable length (and perhaps even carcinogenicity and reproductive toxicity studies) may be required prior to the initiation of a clinical study. Also, because of this duration of exposure component of the risk consideration for implanted devices, true phase I trials in normal volunteers are not justifiable. Rather, even the first clinical trials are done in patients.

Another implication of this paradigm is that for most devices where a clinical trial and IDE are required, all the nonclinical safety testing required for marketing approval is both required and performed as part of the IDE development program.

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FDA (1998) Guidance for the Medical Device Industry on PMA Shell Development and Modular Review, <http://www.fda.gov/ohrms/dockets/98fr/980896gd.pdf>

FDA Medical Device Guidances Table

FDA, Medical Device Reporting Guidance Documents, <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/topicindex/guidance.cfm?topic=224>

FDA, Device Advice, <http://www.fda.gov/cdrh/devadvice/>

FDA, Device Advice, Clinical Trials and IDE Guidance Documents, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfIDE/da_ide_topic.cfm

ISO

AAMI TIR19:1998 & TIR 19/A1:1999, Guidance for ANSI/AAMI/ISO 10993-7:1995, Biological evaluation of medical devices-Part 7: Ethylene oxide sterilization residuals

ANSI/AAMI/ISO 10993-1:1997, Biological evaluation of medical devices-Part 1: Evaluation and testing

ANSI/AAMI/ISO 10993-2:1993/(R)2001, Biological evaluation of medical devices-Part 2: Animal protection requirements

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ANSI/AAMI/ISO 10993-5:1999, Biological evaluation of medical devices-Part 5: Tests for cytotoxicity, *in vitro* methods

ANSI/AAMI/ISO 10993-6:1995/(R)2001, Biological evaluation of medical devices-Part 6: Tests for local effects after implantation

ANSI/AAMI/ISO 10993-7:1995/(R)2001, Biological evaluation of medical devices-Part 7: Ethylene oxide sterilization residuals

ANSI/AAMI/ISO 10993-8:2000, Biological evaluation of medical devices-Part 8: Selection and qualification of reference materials for biological tests

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ANSI/AAMI/ISO 10993-11:1993, Biological evaluation of medical devices-Part 11: Tests for systemic toxicity

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 PowerPoint Slides: Medical Devices: Clinical Trials, Peter Ruys
 PowerPoint Slides: Medicinal Products & Medical Devices: Clinical Trials, Sanja Illic (*mentions FDA regulations, ICH GCPs, Directives, CIOMS guidelines*)
 PowerPoint Slides: Classification of Medical Devices, Conformity Assessment, Routes to CE Marking and Technical Documentation, Paul Brooks
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Appendices

GCPs

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FDA, Introduction: Good Clinical Practice, <http://www.fda.gov/cdrh/devadvice/ide/index.shtml#gcp>
ICH, Guideline for Good Clinical Practice (E6), <http://www.ich.org/LOB/media/MEDIA482.pdf>
Ohno, Y. (2002) ICH Guidelines-Implementation of the 3Rs (Refinement, Reduction, and Replacement): Incorporating Best Scientific Practices into the Regulatory Process, *ILAR Journal*, Vol. 43, supplement, http://dels.nas.edu/ilar_n/ilarjournal/43_suppl/v43supOhno.pdf
PowerPoint Slides: GCP and Post Marketing Surveillance Requirements, Janet Vessotskie

Forms

FDA, Medical Device Reporting-Forms and Instructions, <http://www.fda.gov/cdrh/mdr/mdr-forms.html>
FDA, Device Evaluation Information-Forms, <http://www.fda.gov/cdrh/ode/ode-forms.html>

Acronyms

FDA, Glossary of Acronyms, <http://www.fda.gov/oc/oms/ofm/budget/2004/Tables/glossary.htm>, 2004.
FDA, FDA/CVM-Related Acronyms and Abbreviations, <http://www.fda.gov/cvm/acronym.htm>
FDA, Abbreviations and Acronyms, http://www.fda.gov/cdrh/ost/reports/fy95/abbreviations_acronyms.html
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Drug Information Resources-Ebling Library (provides many links to some of the websites in this list) http://www.hsl.wisc.edu/subject_guides_toolkits/subject_guides/drug_info/index.cfm
Regulatory Affairs Professionals Society, www.raps.org
<http://www.buysafedrugs.info/>
<http://www.phrma.org/>
FDA Drug Approvals List, <http://www.fda.gov/cder/da/da.htm>
Electronic Orange Book, <http://www.fda.gov/cder/ob/default.htm>

Drug Information Association, <http://www.diahome.org/en/http://www.pharma-lexicon.com/>
 National Institute on Drug Abuse, <http://www.nida.nih.gov/drugpages.html>
 CDER, Regulatory Information, <http://www.fda.gov/cder/regulatory/default.htm>
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 FDA, Device Evaluation Information-Forms, <http://www.fda.gov/cdrh/ode/ode-forms.html>
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Appendix A

Notable Regulatory Internet Addresses

Organization or publication	Web address (URL)	Sample main topics
ABPI Agency for Toxic Substances and Disease Registry	http://www.abpi.org.uk/ www.atsdr.cdc.gov	
Association of Clinical Biochemists	http://www.leeds.ac.uk/acb/	Items of general medical interest and an assay finder to help researcher find methods or labs to measure a wide variety of hormones, metals, enzymes, and drugs in body fluids
Australian Therapeutic Goods Administration	http://www.tga.gov.au/	Medical Devices; GMP Codes; Parliamentary Secretary's Working; Status Document; Party on Complementary medicines; Medical Releases; Publications; Site map; Related Sites
Canadian Health Protection Board	http://www.hc-sc.gc.ca	Medical Devices; Chemical Hazards; Food; Product Safety; Science Advisory Board; Diseases; Radiation Protection; Drugs; HPB Transition Policy, Planning and Coordination
Centre for Medicines Research	http://www.cmr.org/	
ChemInfo	www.indiana.edu/~cheminfo/ca_csti.html	SirCH: Chemical Safety Or Toxicology Information
Clinical Pharmacology Drug Monograph Service	http://www.clinicalpharmacology.com	

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Organization or publication	Web address (URL)	Sample main topics
Clinician's Computer-Assisted Guide to the Choice of Instruments for Quality of Life Assessment in Medicine	http://www.qlmed.org/medico.html	This contains hypertext with references to QoL measurements divided into (a) general diseases, (b) specific diseases and therapies, (c) health organizations, and (d) bibliography.
ClinWeb	http://www.ohsu.edu/research	Oregon Health Sciences University
CNN Interactive (Health)	http://www.cnn.com/HEALTH/	Up-to-date information on health issues, including drug safety concerns and withdrawals
Code of Federal Register	http://www.access.gpo.gov/nara/cfr/index.html	For proposed rules and regulations
Code of Federal Regulations	http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1	NARA Code Sections
Committee on Safety of Medicines (CSM)	http://www.open.gov.uk/en/healthandwellbeing/index.htm	
Cornell Legal Library	http://www.law.cornell.edu	Code of Federal Regulations; Supreme Court Decisions; U.S. Code; Circuit Courts of Appeal
Current Problems in Pharmacovigilance	http://www.mhra.gov.uk/index.htm	
Cutaneous Drug Reactions	www.umm.edu/altmed/articles/cutaneous-drug-000044.htm	
DIA Home Page	http://www.diahome.org	Home Page of the Drug Information Association
Doctor's Guide to the Internet	http://www.pslresearch.com	
Handbook for Good Clinical Research Practice	www3.nhlbi.nih.gov/research/resources/DAIDSclinrsch	
Druginfonet	http://www.druginfonet.com	
EMBASE	http://www.healthgate.com/healthGate/price/embase.html	
EPA	www.epa.gov	
Eudra Net: Network Services for the European Union Pharmaceutical Regulatory Sector	http://ec.europa.eu/idabc/en/document/2291	Includes information on the European Agency for the Evaluation of Medicinal Products.
		Europa European Agency for the Evaluation of Medicinal Products

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Organization or publication	Web address (URL)	Sample main topics
EMA	http://www.eudra.org/emea.html	
European Sites	http://www.eucomed.be/eucomed/links/links.htm	European Institutions; Related Sites
European Pharmacovigilance Research Group	http://europa.eu/pol/rd/	
Food and Drug Administration (FDA)	www.fda.gov	Foods; Human Drugs; Biologics; Animal Drugs; Cosmetics; Medical Devices/ Radiological Health
FDA – CBER Center for Biologics Evaluation and Research	http://www.fda.gov/cber	
CBER What's New	http://www.fda.gov/cber/whatsnew.htm	
FDA – CDER Center for Drug Evaluation and Research	http://www.fda.gov/cder	
FDA Adverse Events Database	http://www.fda.gov/cder/adr	
CDER What's New	http://www.fda.gov/cder/whatsnew.htm	
FDA – CDRH Search site	www.fda.gov/cdrh/index.html	Home page Search CDRH site Comment on CDRH site
Comment	www.fda.gov/cdrh/search.html	
	www.fda.gov/cdrh/comment4.html	
Device Advice	www.fda.gov/cdrh/devadvice/32.html	
PDF Reader	www.fda.gov/cdrh/acrobat.html	
FDA – CFSAN Center for Food Safety and Applied Nutrition	http://vm.cfsan.fda.gov	
FDA – Center for Toxicological Research	http://www.fda.gov/nctr/index.html	
FDA – CVM Center for Veterinary Medicine	http://www.fda.gov/cvm/default.html	
FDA – “Bad Bug Book”	Vm.cfsan.fda.gov/~mow/intro.html	
FDA – Bioresearch Monitoring	www.fda.gov/ora/compliance_ref/bimo/default.htm	
FDA – Breast Implants	http://www.fda.gov/cdrh/breastimplants/index.html	
FDA – Cosmetics	http://vm.cfsan.fda.gov/~lrd/cosmetm.html	
FDA – Dietary Supplements	http://vm.cfsan.fda.gov/~dms/supplmt.html	
FDA's Electronic Freedom of Information Act	http://www.fda.gov/foi/	

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Organization or publication	Web address (URL)	Sample main topics
FDA's Electronic Freedom of Information Act Dockets	www.fda.gov/ohrms/dockets/	
FDA – Newsroom	www.accessdata.gov/news	What's New; Import Program; Inspectional, Science and Compliance References; Federal/State Relations
FDA-guidance documents	http://www.fda.gov/cder/guidance	
FDA-guides to inspection	www.fda.gov/ora/inspect_ref/default.htm	Design Control Report and Guidance Text
Photosafety Testing 07-05-00	http://www.fda.gov/cder/guidance/3281dft.htm	
Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products 06:01:00	http://www.fda.gov/cder/guidance/2887fnl.htm	
FDA – MedWatch	http://www.fda.gov/medwatch/	USFDA drug adverse event reporting system
FDA – Tampons	http://www.fda.gov/oc/opacpm/topicindexes/tampons.html	
Food and Drug Law Institute	http://www.fdli.org	Special Interest; Publications; Multimedia; Order Products; Academic Programs; Directory of lawyers and Consultants; Contact Us
American Health Information Management Association (AHIMA)	http://www.ahima.org	About HIMA; Newsletter; HIMA Calendar; Industry Resources; Business Opportunities; FDA/EPA/OSHA; Reimbursement/Payment; Global Year 2000; Government Relations; Public Relations; Small Company; Diagnostics
Health on the Net Hyppos Project	http://www.hon.ch www.dbag.unifi.it/inwat/presentations/andaloro.pdf	Information in Italian and English about the Hyppos Project, which has led to the development of a QoL tool for the measurement of hypertensive patients in Italy. It contains a description of the project, the tool, publications about the development of the tool and its application, plus general references to QoL and hypertension

(continued)

Organization or publication	Web address (URL)	Sample main topics
International Classification of Disease (ICD)-10	www.who.int/whosis/icdic/	
International Conference on Harmonization (ICH) 3 Home Page	www.fda.gov/cber/ich/ichguid.htm	Official ICH Web site with documents (needs a password) ICH documents
International Federation of Pharmaceutical Manufacturers	www.ifpma.org	ICH documents and postings; International Pharmaceutical issues
International Regulatory Monitor (Monitor)	www.fdanews.com/store/product/detail?productID=26167	Editorial Portion of Newsletter
International Society of Pharmacoeconomics	http://www.pharmacoepi.org	
InterPharma	http://www.interpharma.co.uk	The latter are vast sites with links to other databases for pharmaceutical support sites— http://www.MedsiteNavigator.com
AMA	http://www.ama-assn.org/jama	This gives many other useful USA sites
Japanese Ministry of Health, Labour, and Welfare	http://www.mhlw.go.jp/english/index.html	Organization; Y2K Problem; Statistics; White Paper; Related Sites
Library of Congress	www.loc.gov/index.html	Searchable database of federal legislation, Congressional Record, and committee information
Market and Exploitation of Research	http://www.cordis.europa.eu/libraries/en/randdres.html	
Medical Device Link	http://www.devicelink.com	News; Consultants; Bookstore; Links; Discussion; Magazines (MDDI; MPMN; IVD Technology)
Medicines and Healthcare Products Regulatory Agency (MHRA)	www.mhra.gov.uk/index.htm	
Medical Matrix	http://www.medmatrix.org	
Medical Research Council	www.mcr.ac.uk/	
Medscape	http://www.medscape.com	
Multilingual glossary of medical terms	http://users.urgent.be/~rvdstich/eugloss/welcome.html	
National Archives and Public Records Administration	www.gpoaccess.gov/nara/index.html	Code of Federal Regulations; Federal Register; Laws; US Congress Information

(continued)

Organization or publication	Web address (URL)	Sample main topics
National Institutes of Health (USA)	http://www.nih.gov	
National Library Network	www.toxnet.nlm.nih.gov	TOXNET: Toxicology Data Network, a cluster of databases on toxicology, hazardous chemicals, and related areas
National Toxicology Program	http://ntp-server.niehs.nih.gov/	
New Quality System (QS) Regulation	www.fda.gov/ora/Inspect_ref/igs/qsitguide.htm	FDA Talk Paper Announcing the GMP Final Rule text
Organised Medical Network Information	http://www.omni.ac.uk	
Pharmaceutical and Medical Safety Bureau—Japan	http://www.mhlw.go.jp/english	
PharminfoNet	www.centerwatch.com/pharminfonet	Independent assessment of therapeutics and advances in new drug development
Pharmweb	http://www.pharmweb.net	Information resource for pharmaceutical and health-related information
PSL Quality of Life Assessment in Medicine	www.PSLgroup.com www.qolid.org	This contains hypertext with references to QoL measurements divided into (a) assessment tools, (b) reference organizations and groups, (c) diseases, symptoms, and specific populations, (d) the top ten journals that publish articles of interest to QoL assessment in medicine, (e) methodology, and (f) bibliographical research.
Regulatory Affairs Professionals Society (RAPS)	http://www.raps.org	Certificates; Resource Center; Publications; Chapters; Related Links; Contacting RAPS
Reuters Health Information Services	http://www.reutershealth.com	
SCRIP: World Pharmaceutical News	www.scripnews.com	
International Health Terminology Standards development organization	www.ihtsdo.org	

(continued)

Organization or publication	Web address (URL)	Sample main topics
College of American Pathology	www.cap.org/apps/cap.portal	
Swedish Medical Products Agency	http://www.lakemedelsverket.se/tpi/startpage____3.aspx	
U.S. Department of Agriculture (USDA)	http://www.usda.gov	
Food Safety	http://www.foodsafety.gov/	
USDA—FMS Farm Service Agency	http://www.fsa.usda.gov/fsa	
USDA—FSA Food and Nutrition Service	http://www.fns.usda.gov/fns/	
USDA—FSIS Food Safety and Inspection Service	http://www.usda.gov/fsis	
U.S. Department of Commerce	www.commerce.gov	Bureau of Export Administration; International Trade Association; Patent and Trademark; National Institute of Standards and Technology
U.S. Pharmacopoeia	www.usp.org	
University of Pittsburgh	www.pitt.edu	
World Health Organization	http://www.who.int/en	Governance; Health Topics; Information Sources; Reports; Director-General; About WHO; International Digest of Health; Legislation (http://www.who.int/pub/dig.html)
Pumed	http://pubmed.gov/	

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