Part I
International Regulations and Nonclinical Studies for Pharmaceuticals
The world market for drugs is large and growing. At the end of 2011, global sales of pharmaceuticals topped $950 billion. The United States (US), Canada, European Union 5 (EU51) and Japan account for almost 85% of pharmaceutical sales (IMS, 2012a) with the balance of the market spread across the rest of the world (ROW). With the consolidation of major corporations and the emergence of small worldwide pharmaceutical enterprises, the face of the pharmaceutical industry continues to evolve. Within this changing global landscape, individual countries and regions continue to have unique regulations and guidances that drug companies must follow for product approval in those regions. Although the larger markets are often the first that are targeted for regulatory submission and approval, this does not mean that an applicant should minimize the regulatory requirements of other areas, in particular those of the “Pharmerging” markets such as India, South America and China. These markets are expected to expand significantly over the next five years and potentially outpace the growth in the more traditional geographic regions. Approvals in those regions can be rigorous and time consuming. However, a basic premise of the

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industry continues to be that the first to market captures a major portion of the sales while the successive entries in a drug class fight to develop a market presence and maintain market share. Therefore, regardless of the geographic region and the associated challenges, drug development and nonclinical programmes must always integrate this “first to market” view as part of their regulatory strategy.

In this era of evolution, development and marketing has become fiercely competitive. The industry spends millions of dollars on developing new drugs although it is well known that the chance of any single candidate reaching the marketplace is extremely low. Overall, it has been estimated that for every 5000–10 000 candidate drugs, on average only one successfully reaches the consumer market (DiMasi, 2001; PhRMA, 2012), and the probability of that new drug entering the market is highly dependent on the therapeutic class (Adams and Brantner, 2006; Kaitin and DiMasi, 2011). Therefore, industry proceeds with some caution as it pursues development and branches into new classes of drugs or biologics. Companies will often invest a great deal of capital into rapid screening technology to better eliminate those compounds that show limited promise. With the advent of the various “omics” technologies and emphasis on the development of biomarkers of disease, the hope is that these technologies will allow for the targeting of specific disease endpoints and therefore a more selected market segment. Indeed, the development of pharmacogenomics has led to the possibility, as yet unrealized, of personalized medicine and the development of drugs and treatments for targeted subpopulations. Regardless of these advances, early stage drug candidates will still drop out of the development process for a variety of reasons, though most often these will be related to toxicity discovered during the preclinical phase or within the early clinical programme. Later stage development dropouts are most often due to lack of efficacy in the target population although economics plays an increasingly larger role in the choice to discontinue developing a drug or biologic candidate. This later scenario is common with small pharmaceutical enterprises that are dependent on venture firms and other sources of external funding to continue to fuel their development activities.

Efficacy, societal concern for safety and global leveraging of regulatory requirements are driving forces in the processes for drug development. In these processes, drug development strategies and the associated nonclinical safety assessment must consider certain “facts”. First, the cost of developing drugs and biologics is extremely high, with investments increasing sharply with each stage of development (DiMasi et al., 2003). Second, as stated earlier, most products will fail during development. While the true success rate for drug development is certainly greater than the often stated 1-in-5000 or more, it is clear that only 3–5% of those products that enter initial clinical evaluations become marketed drugs. With this in mind, many companies choose to undertake only those safety and screening studies “required” to start clinical studies. Larger companies often take a broader, more conservative investigative approach in order to ensure clinical safety and to address anticipated requirements across regions. The downside to this latter approach is that a large number of resources are devoted to a more comprehensive nonclinical programme when later stage clinical success of the candidate is not assured. Over time, several priorities in the nonclinical programmes have developed. First, “kill the losers” as early as possible and, second, minimize the time spent in developing a potentially unsuccessful drug. These principles have produced a spectrum of strategies in the
nonclinical safety assessment of drugs, best illustrated by looking at the two extremes.

**Strategy A: Do Only What You Must.** Financial limitations, particularly in small companies, drive the nonclinical and clinical planning. At later stages of development the candidate therapeutic will be licensed to, or a partnership developed with, a larger company. Therefore, the focus is to undertake only the minimum technical and regulatory steps necessary to get a molecule to that critical partnering point in development.

**Strategy Z: Minimize the Risk of Subsequent Failure.** Development proceeds through a series of well-defined and carefully considered milestone decision points. Studies and technical tasks are not often limited to the minimum needed for early development but are often augmented by additional study components. Many of the additional components are short-term toxicity screens or studies which are inexpensive and could be repeated later in the development process. Exactly what these “extra” components include will vary from company to company, and frequently reflect past experiences.

Clearly, most nonclinical programmes fall somewhere in between. Regardless of the strategy chosen, the studies performed to meet regulatory nonclinical safety assessment requirements can be thought of as belonging to three major categories:

- Those necessary to support the successful filing of an Investigational New Drug (IND) application, a Clinical Trial Authorization or equivalent, and to ensure subject safety in the subsequent first in human clinical studies.
- Those required to support the continued long-term clinical development of a drug, up to and including Phase 3 studies. These often include the longer subchronic and speciality studies.
- Those studies required to support a marketing approval application. These nonclinical studies typically include carcinogenicity studies and reproductive toxicity studies. In some cases, the timing of these studies could extend into the post-approval phase of the product lifecycle.

Exactly which study fits into what category is somewhat fluid, and this is heavily influenced by the therapeutic indication, the mechanism of action and the targeted treatment population.

In this book, we examine the international regulations for nonclinical drug development and how the safety of human pharmaceutical products is evaluated around the globe. Clearly, the guidance and regulations established by the US Food and Drug Administration (FDA) over the decades have played a critical role and have provided a baseline or framework for many of the regulations established worldwide. More recently the International Conference on Harmonization (ICH) has emerged as an essential process to consolidate guidance and regulations across the US, Europe and Japan. Although most countries have adopted the concepts of ICH, and many others are expected do so, there still remain country-specific requirements that are necessary for approval. The authors included within this book represent dozens of years of experience in the area of national and international nonclinical drug development. Therefore, we hope to provide a practical, if not comprehensive, assessment of the regulations required for nonclinical toxicology studies around the globe.
1.1 The Global Pharmaceutical Market

The pharmaceutical industry and all of its components operate as part of a global market. This globalization can be seen in all areas, including research, nonclinical and clinical evaluation and production of finished commercial products. Well-known examples of this exist in the sectors of chemical intermediates, active pharmaceutical ingredients (APIs) and in the manufacture of generic drugs. Over the last few decades, these industry segments have made major geographic shifts, with the chemical manufacturing of intermediates and APIs relocating almost entirely from the “West” to India and Asia. Whereas 20 or 30 years ago, Research and Development (R&D) and manufacturing of pharmaceutical products originated in the intended market region, it is now not uncommon to find bulk and finish production occurring in one part of the world for marketing and distribution in an entirely different geographical region.

Over the last 20 years, as the pharmaceutical market has seen robust growth and globalization, the overall cost of health care has been increasing at an alarming rating. Despite widespread public perception, the cost of pharmaceuticals, at least in the US, has not been the driving force behind this spending increase. According to the latest data from Centers for Medicare and Medicaid services (CMS, 2012), pharmaceutical expenditure in the US accounted for only 10% of total healthcare spending in 2010, versus 8.8% in 2000. Regardless of expenditure source, the end result has been heightened media and legislative scrutiny with, in some countries, the healthcare debates taking on a political “life-of-its-own” and the research-based pharmaceutical industry coming under fire as an easy target. It is expected and hoped that healthcare costs will begin to stabilize over time. The effect of currently proposed or future legislative reforms on the pharmaceutical industry is unknown but there is expectation that whatever “fixes” are put in place will result in some negative impact on the industry. With the high cost of pharmaceutical development and outside pressure on the industry, companies will continue to make efforts to control and improve development methods and optimize their expenditures. As part of this trend, there has been an increase in partnering, in-licensing of drug candidates, mergers and acquisitions, and the creation of fully integrated pharmaceutical networks or FIPnets (Kaitin and DiMasi, 2011). The industry has seen larger companies acquiring smaller competitors for R&D expertise, intellectual property, pipelines or marketed portfolio such as Sanofi’s acquisition of Genzyme or Takeda’s acquisition of Nycomed. There have been several major consolidations, including Pfizer’s acquisition of Wyeth and Merck’s merger with Schering Plough. As companies continue to examine cost-cutting initiatives, options of mergers and acquisitions and a variety of other “value adding” measures, the overall trend in the pharmaceutical industry appears to be that of consolidation and shrinkage.

In 2011, worldwide sales of drugs were $956 billion, an increase of 5.1% over 2010, with branded drugs accounting for nearly two-thirds of pharmaceutical spending. This branded share is projected to decline, however, to as low as 50% by 2016 as many of the large market products continue to come off-patent (IMS, 2012a; 2012b). The US still accounts for the largest share of the global pharmaceutical market with about $320 billion in annual sales, a slight gain of approximately 3.6% over 2010 (IMS, 2012c). For the same time period, sales in Europe remained relatively flat while Japan saw modest growth of 5.6%. The Pharmaerging markets, which include China, Brazil, India and Russia,
outpaced the more developed markets with a 29% gain in pharmaceutical spending in 2011. This growth was largely attributable to increased spending on generic drugs; however, these emerging markets are expected to continue to expand rapidly and could account for as much as 30% of global spending by 2016 (IMS, 2011; 2012a).

The global top 10 branded pharmaceuticals for 2011, which accounted for approximately 8.5% of the total worldwide sales, are presented in Table 1.1.

This list will see dramatic changes over the next few years due to patent expirations and the potential for new competition from biosimilars. Overall, the therapeutic areas that have seen the greatest development have been those encompassing large populations and chronic diseases, resulting in the model of the billion dollar “blockbuster” drug.

The concentration of total sales for a limited number of pharmaceuticals is thought to have distorted, at least for a time, the therapeutic research direction of new drug development. Now, with many of the blockbusters losing patent protection, development is moving away from that paradigm to one of focused therapeutics and specific patient populations. While precise international costs are not available, US pharmaceutical R&D spending is currently estimated to be at least $50–65 billion, based on an estimated 3500 pharmaceutical companies in the US (PhRMA, 2011; 2012). It is expected that there are similar numbers of companies and levels of R&D spending in Europe, and significant value coming from other parts of the world such as China, Australia, India, and Israel. While most of the public focuses on the largest companies, such as those in Table 1.2, the vast majority of companies are mid-sized, small and startups. Significantly, the innovations leading to new molecular entities (NME) and biologics appear to be arising primarily from these smaller organizations, with the larger companies licensing these new therapies or purchasing the technology outright.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Medicine</th>
<th>Company</th>
<th>Primary medical use</th>
<th>2011 sales (USD, billion)</th>
<th>Percent growth vs. 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lipitor</td>
<td>Pfizer</td>
<td>Cholesterol</td>
<td>12.5</td>
<td>−3.3</td>
</tr>
<tr>
<td>2</td>
<td>Plavix/Iscover</td>
<td>Bristol-Myers Squibb, Sanofi</td>
<td>Thrombotic events</td>
<td>9.3</td>
<td>3.7</td>
</tr>
<tr>
<td>3</td>
<td>Advair/Seretide</td>
<td>GlaxoSmithKline</td>
<td>Asthma</td>
<td>8.7</td>
<td>0.04</td>
</tr>
<tr>
<td>4</td>
<td>Crestor</td>
<td>AstraZeneca</td>
<td>Cholesterol</td>
<td>8.0</td>
<td>14.4</td>
</tr>
<tr>
<td>5</td>
<td>Nexium</td>
<td>AstraZeneca</td>
<td>Gastrointestinal disorders</td>
<td>7.9</td>
<td>−6.2</td>
</tr>
<tr>
<td>6</td>
<td>Seroquel</td>
<td>AstraZeneca, Astellas Pharmaceuticals</td>
<td>Schizophrenia</td>
<td>7.6</td>
<td>9.5</td>
</tr>
<tr>
<td>7</td>
<td>Humira</td>
<td>Abbott</td>
<td>Rheumatoid arthritis</td>
<td>7.3</td>
<td>17.8</td>
</tr>
<tr>
<td>8</td>
<td>Enbrel</td>
<td>Amgen, Pfizer</td>
<td>Rheumatoid arthritis</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>9</td>
<td>Remicade</td>
<td>Johnson &amp; Johnson, Merck, Tanabe</td>
<td>Rheumatoid arthritis</td>
<td>6.8</td>
<td>8.4</td>
</tr>
<tr>
<td>10</td>
<td>Abilify</td>
<td>Otsuka</td>
<td>Schizophrenia</td>
<td>6.3</td>
<td>14.3</td>
</tr>
</tbody>
</table>

(IMS, 2012d).
Over the last several years, focused development in targeted therapeutic areas has been the mainstay of many companies. The therapeutic areas that have received the greatest interest over the past decade are shown in Table 1.3. As suggested by this information, the trend has been to pursue therapies for the treatment of chronic diseases, particularly those that affect the ageing population. At the same time, several older or discarded drugs have been repurposed for new uses, such as thalidomide for multiple myeloma, doxepine hydrochloride for insomnia, or the combination of dextromethorphan and quinidine for psuedobulabar affect, and some very old drugs, such as digoxin, continue to be in use. In

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pharmaceutical company</th>
<th>2011 sales (USD, million)</th>
<th>Percent change vs. 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pfizer</td>
<td>56,427</td>
<td>-0.7</td>
</tr>
<tr>
<td>2</td>
<td>Novartis</td>
<td>51,632</td>
<td>10.1</td>
</tr>
<tr>
<td>3</td>
<td>Merck &amp; Co</td>
<td>40,119</td>
<td>6.9</td>
</tr>
<tr>
<td>4</td>
<td>Sanofi</td>
<td>39,478</td>
<td>2.4</td>
</tr>
<tr>
<td>5</td>
<td>AstraZeneca</td>
<td>36,974</td>
<td>2.9</td>
</tr>
<tr>
<td>6</td>
<td>Roche</td>
<td>34,869</td>
<td>5.7</td>
</tr>
<tr>
<td>7</td>
<td>GlaxoSmithKline</td>
<td>34,491</td>
<td>1.3</td>
</tr>
<tr>
<td>8</td>
<td>Johnson &amp; Johnson</td>
<td>27,664</td>
<td>0.0</td>
</tr>
<tr>
<td>9</td>
<td>Abbott</td>
<td>25,871</td>
<td>6.6</td>
</tr>
<tr>
<td>10</td>
<td>Teva</td>
<td>23,872</td>
<td>-2.5</td>
</tr>
<tr>
<td>11</td>
<td>Lilly</td>
<td>23,716</td>
<td>7.3</td>
</tr>
<tr>
<td>12</td>
<td>Takeda</td>
<td>17,767</td>
<td>6.1</td>
</tr>
<tr>
<td>13</td>
<td>Bristol-Myers Squibb</td>
<td>16,446</td>
<td>9.7</td>
</tr>
<tr>
<td>14</td>
<td>Bayer</td>
<td>16,390</td>
<td>4.3</td>
</tr>
<tr>
<td>15</td>
<td>Amgen</td>
<td>16,323</td>
<td>4.6</td>
</tr>
</tbody>
</table>

(IMS, 2012e; IMS, 2012f).

<table>
<thead>
<tr>
<th>Rank</th>
<th>Therapeutic class</th>
<th>2011 sales (USD, billion)</th>
<th>Percent growth vs. 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oncologics</td>
<td>62.2</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>Respiratory agents</td>
<td>39.4</td>
<td>7.3</td>
</tr>
<tr>
<td>3</td>
<td>Antidiabetics</td>
<td>39.2</td>
<td>11.4</td>
</tr>
<tr>
<td>4</td>
<td>Lipid regulators</td>
<td>38.7</td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>Antipsychotics</td>
<td>28.4</td>
<td>9.4</td>
</tr>
<tr>
<td>6</td>
<td>Angiotensin II Antagonists</td>
<td>27.4</td>
<td>-0.7</td>
</tr>
<tr>
<td>5</td>
<td>Anti-ulcerants</td>
<td>26.9</td>
<td>-6.4</td>
</tr>
<tr>
<td>8</td>
<td>Autoimmune Agents</td>
<td>24.4</td>
<td>14.1</td>
</tr>
<tr>
<td>9</td>
<td>Antidepressants</td>
<td>20.4</td>
<td>-1.5</td>
</tr>
<tr>
<td>10</td>
<td>HIV Antivirals</td>
<td>17.4</td>
<td>9.5</td>
</tr>
<tr>
<td>11</td>
<td>Platelet Aggregation Inhibitors</td>
<td>16.4</td>
<td>4.1</td>
</tr>
<tr>
<td>12</td>
<td>Anti-Epileptics</td>
<td>14.1</td>
<td>10.1</td>
</tr>
<tr>
<td>13</td>
<td>Vitamins &amp; Minerals</td>
<td>13.9</td>
<td>6.1</td>
</tr>
<tr>
<td>14</td>
<td>Vaccines</td>
<td>13.4</td>
<td>13.0</td>
</tr>
<tr>
<td>15</td>
<td>Narcotic Analgesics</td>
<td>12.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

(IMS, 2012a).
the last 10–15 years, new drug classes have emerged that have grown significantly in terms of expenditures and have shown major therapeutic advances by either reducing disease burden (statins) or unacceptable side effects (atypical antipsychotics) (Dickson and Gagnon, 2004).

A major factor to consider in the development of new therapeutic entities is cost, which can present significant hurdles to the smaller, innovative companies. DiMasi et al. (2003) examined the development costs of 68 pharmaceuticals based on a survey from 10 drug companies. The estimated average development cost per new drug was $802 million (in 2000 dollars). Dickson and Gagnon (2004) further demonstrated that the cost of development to approval has increased over time from 1979 to 2003 and, more recently, that cost has been revised upwards to $1 billion or more (Adams and Brantner, 2010). Furthermore, the average time to approval has increased. While the time from discovery to approval in the 1960s was estimated to be about eight years, in the current decade that timeline has increased to 12–14 years (Dickson and Gagnon, 2004; PhRMA, 2012). Although the costs and timing to approval represent primarily “big pharma”, the drug development process in smaller enterprises is estimated to be about the same. Active drug development in the small companies is critical for their survival but many of the small companies have limited (one or two) NMEs in their pipeline. Hence, all of their energy and resources are developed to the success of that single entity, at least through early clinical studies. At that point, in order to have the financial resources necessary to continue their programmes, the smaller companies must often look for partnering opportunities.

In the US, the National Institutes of Health (NIH) helps to support the development of pharmaceuticals with funding to academic institutions or nonprofit groups and, more recently, through small business innovation and research (SBIR) grants. Although not completely certain, the costs from discovery through early development of these drugs are anticipated to be the same as those developed in larger industrial laboratories. However, the number of approved drugs that originate through this means is small. For example, it was found that of the 47 approved drugs that reached $500 million in US sales in 1999, only four originated either directly or indirectly through governmental support (DiMasi et al., 2003).

1.2 Looking to the Future

Crommelin et al. (2010) provide interesting scenarios and predictions of the pharmaceutical industry during the next decade. Some of the predictions are somewhat disturbing but certainly could reflect the changing environment in the industry. The authors suggest that large target population breakthroughs (blockbuster drugs) will not be delivered into the market. They see drugs for smaller populations, such as orphan diseases, and believe that society will need to spend considerable resources in order to fill the pharmacological “toolbox”. Furthermore, the authors believe that advances in delivery technology will blur the distinctions between drugs and devices. Indeed, it is expected that such an increase in combination drug/device products will be seen in the next decade. They further indicate that the major pharmaceutical companies will continue to dominate but only to the extent that they have the resources and expertise for development, and with this shift, Chinese and Indian pharmaceutical companies will slowly enter the group of
leading innovative firms. That scenario has already been seen with the accession of Teva Pharmaceuticals, which entered into the international generics market in the 1990s but is now one of the top 10 pharmaceutical companies in the world.

Another complicating factor in considering the pharmaceutical market sector is the sheer diversity of products involved. In the next decade, the number of biotechnology-derived products will continue to expand, particularly in the fields of oncology and immunologic therapies. Small molecules will continue to dominate for some time as NMEs, second, third or fourth generation molecules, line extensions and generics, although biotechnology products will constitute a growing percentage of INDs and, just as important, a larger proportion of total pharmaceutical sales. The challenges of early stage development and assessing the safety of these biologic and biotechnology-derived substances are very different. Although there continues to be an increasing trend towards final drug (biologic) approval, there have also been increases in approval time. The reasons are diverse, some ascribing it to implementation of risk evaluation and mitigation strategies (REMS) but others believe it is only the reasonable rationale to ensure the appropriate time to adequately review increasingly complex products for difficult-to-target conditions (Hughes, 2010).

In summary, the pharmaceutical market will continue see growth although the double digit increases of the 1990s and 2000s are not expected. The era of the “blockbuster” drug is over with the pharmaceutical companies now challenged to go forward with more focused development and to work towards the concept of “personalized” medicine. Continued worldwide regulatory pressures for safe and effective drugs will force drug companies to consider how resources are devoted to the “pipeline” of new molecular entities and biologics. Indeed, there is an expectation by some that eventually the increase in biotechnology-derived therapies will outpace the small molecule in the coming decades.

1.3 Legal and Regulatory Considerations in Drug Development

In the US, the laws that are applicable to the approval of a drug product are the Federal Food and Drug Cosmetic Act (FFDCA) and its various amendments. For each amendment to the FFDCA that is passed, the FDA must develop regulations in order to implement the legislative revisions. Those regulations pass through an administrative rulemaking process that is documented in the Federal Register and the final regulations are then “codified” and published in the Code of Federal Regulations (CFR). For drug and medical devices, as well as foods, cosmetics and dietary supplements, the FDA regulations are contained in Title 21. Those regulations specific to human drugs can be found in Subchapter D (Parts 300–399) while regulations for Vaccines and Biologics are in Subchapter F (Parts 600–680) and Medical Devices are found in Subchapter H (Parts 800–898). For human drugs the definition of a new drug can be found in 21 CFR Subchapter D, Part 310.3(g):

“A new drug substance means any substance that when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug but does not include intermediates used in the synthesis of such substance.”
The regulations then proceed to define what constitutes an NME, a generic drug and drug combination products. For toxicologists, the most relevant sections of the FDA regulations are 21 CFR Subchapter D, Parts 312 and 314 and Subchapter F, Part 601. These sections describe the Investigational New Drug Application (IND), the New Drug Application (NDA) and Biological License Application (BLA), respectively. Those processes and applications will be described in later chapters in this book. The major focus for a toxicologist working in the pharmaceutical industry is on preparing the toxicology “packages” to support these applications and overseeing the nonclinical studies necessary to support clinical studies. In a nutshell, the law requires solid scientific evidence of safety and efficacy before a new drug or medical device will be permitted in clinical trials or placed into the market.

In the European Union, the process for regulatory drug approval or authorization is somewhat similar. For new biological or high-technology products, orphan drugs, products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions and viral diseases, the approval pathway is “centralized” through the European Medicine Agency (EMA). A marketing authorization application (MAA) is prepared according to standard format (CTD) and submitted to the Medicines Bureau of EMA. Those applications are then reviewed by the Committee for Medicinal Products for Human Use (CHMP) and registration authorizations decisions for the EU are made. Drugs are reviewed as either Part A or Part B drugs, with Part A drugs having the more formidable process review since these are biotechnology-derived products. Part B drugs, are the usual small molecule drug products as new molecular entities (NME), new formulations or for new indications. Other new active substances might be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation. There are several other pathways available for those drug products that fall outside the scope of the EU centralized process. These include the decentralized process for simultaneous authorization in sponsor-selected countries, the mutual recognition procedure, or the national process for product authorization within a single country.

The approval process in Japan is likewise similar to that of the EU and the United States. The Pharmaceuticals and Medical Devices Agency (PMDA) is an independent administrative organization charged with the review of new drug and medical device products. Within this organization, there are different branches, each having responsibility for the review of drugs or medical devices. The regulations of the PMDA do not include the “quasi-drug” category. Quasi-drugs are products ranging from deodorants, hair dyes, hair growers and depilatories, medicated cosmetics (notably whitening agents) and medicated toothpaste to sanitary napkins and over-the-counter health drinks. The quasi-drugs are reviewed within the Japanese authority but outside the regulatory structure for human pharmaceuticals and medical devices.

The legal and regulatory processes briefly described here represent those countries or regions that participate in the ICH process. Other countries and regions have their own processes that must be considered when gaining regulatory approval of a drug. These are discussed further in the appropriate chapters of this book.
1.4 The Drug Development Process – General Considerations

Prior to entry into the drug development process, a large amount of resources and brainpower goes into “discovery” – the research that leads to optimal selection of a substance that shows greater promise than others for ultimate approval and marketing. The discovery process has seen radical changes over the last 5–10 years as research continues to make strides in identifying biomarkers of disease (Amur et al., 2008; Krishna et al., 2008; Tesch et al., 2010). Biomarkers for breast cancers, leukaemia, prostate cancer and diabetes have led to the development and validation of in vitro models that are used to determine early efficacy of potential new drugs. In vivo animal models of diseases have also furthered the development of specific, targeted therapies. In addition to these animal- and cell-based models, a great effort has been devoted in recent years to in silico models and the development of bioinformatic databases which have further reduced the time and resources in the discovery process (Ekins et al., 2007; Muster et al., 2008; Pauli et al., 2008; Hutter, 2009). Using all of these resources, a lead compound and backups are selected for further development.

The drug development process then follows a logical and somewhat general pathway to first-in-human trials although, depending on the product, some companies might choose to take a more customized approach for entry into early human exposure. For the general case approach to nonclinical safety assessment, there are a few fundamental assumptions about the drug under development. 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 depend on the route of administration, but the use of other routes (e.g., intravenous, topical), will influence what is done for nonclinical safety assessment. A second assumption relates to the frequency of drug administration and the dosage form. Most often, the drug is administered once daily (QD) although there continues to be the development of drugs for twice daily (BID) or three-times daily (TID) as well as weekly or monthly administration; this latter is more common for development of biologics and anticancer therapies. Extended release formulations present their own set of challenges in terms of optimum pharmacokinetics and the evaluation of off-target effects. Dosage forms commonly used include liquids, tablets, and capsules although other delivery means, such as inhalants, topical patches, depots and implants are not infrequent and will need to be considered in the nonclinical programme.

The nonclinical studies required to initiate clinical studies of pharmaceuticals in humans are variously labelled as first-in-human or “FIH enabling” or, in the United States, “IND enabling” studies. For many drug candidates, it may comprise the only regulatory nonclinical safety work that will ever be done, since progression into further development will be based primarily on the successful outcome of these early clinical studies.

The nonclinical studies needed for opening an IND or CTA are to be performed in compliance with Good Laboratory Practice regulations (GLP). Prior to initiating studies, certain preparatory steps must be performed in order to successfully achieve such compliance:

1. Sufficiently pure drug substances must be produced and characterized. It is extremely important that the purity of the drug substance used in the nonclinical studies be no greater than what is intended to be used in the clinical programme in order that the
impurities become “qualified” as the studies progress. Use of a higher purity in non-clinical studies will generally result in a regulatory agency “Clinical Hold” on the clinical trial programme until data are developed to demonstrate the safety of the drug substance relative to potential impurities. In addition, the stability of both the drug substance (API) and drug product (API with included excipients) under appropriate storage conditions and in the anticipated animal dosing formulation must be demonstrated.

2. The GLP-compliant analytical and bioanalytical methods must be developed and validated to verify the purity of the drug substance, concentrations of the drug in dosing solutions as well as detecting the drug substance and metabolite(s) in blood or other matrices. The development and validation of these methods is almost always a rate-limiting step in the nonclinical programme, so it is advisable to complete the method developments prior to initiating the pivotal toxicology studies. Furthermore, the bioanalytical methods must be developed for the selected test species (rodent and nonrodent) that is to be used in the nonclinical studies, and in the concentration range anticipated. Therefore, early analytical development could be critical to the timing and outcome of a competitive nonclinical programme.

With the preparatory work in place, the nonclinical studies can commence. The details of specific study designs are described elsewhere in this book; however, the study designs are generally compliant with those outlined in the OECD guidelines and other internationally recognized testing protocols (for example, the FDA Red Book).

The results of early pharmacology studies, as well as initial pharmacokinetic studies conducted to examine the efficacy and bioavailability of the drug, can often serve to establish dose levels for early dose rangefinding toxicity studies. Acute toxicity studies are not required for entry into the clinical trial although some variation of these studies is usually conducted to help with the setting of dose levels for repeat dose toxicity studies (ICH M3R2). In the absence of such data, a dose escalation study can be undertaken, and is generally advisable for initial studies to be conducted in both rodents and nonrodents.

The IND (CTA)-enabling studies consist of repeat-dose toxicity studies in both a rodent and a nonrodent species. These studies will need to be at minimum two weeks in duration followed by a recovery phase. In recent years, the study duration has trended towards four weeks followed by recovery in order to adequately fulfill regulatory requirements. The rat is the typical rodent species, with the dog often used as the nonrodent species. However, the nonhuman primate (NHP) is typical for biotechnology-derived products since this animal model is immunologically competent and similar to humans when compared to other nonrodent species (ICH S6R1). For topical drugs, the minipig is becoming the more acceptable nonrodent species, replacing the rabbit and dog. In all of these studies, blood samples will need to be collected for toxicokinetics.

In the US, it is possible to undertake a single-dose clinical study based on single-dose toxicity studies in rodents and nonrodents. However, these nonclinical studies will need to be “gold-plated”. That is, the studies will need to include all parameters typically included in well-designed repeat-dose toxicity studies. Other than the usual in-life measures, the studies will need to include clinical pathology, gross and microscopic pathology, ophthalmology and, for nonrodents, electrocardiogram evaluations. A single-dose nonclinical study to support a single-dose clinical study would be appropriate if the clinical
therapy itself is only a single administration, for example, some antivirals. Otherwise, it
would be most cost- and time-effective to undertake the repeat-dose studies to support the
single-dose clinical study.

Some pharmaceutical companies often prefer to conduct 90-day in addition to 4-week
studies as the IND-enabling toxicity studies, and this could be related to experience with
previous drug candidates as well as the intended duration of multiple-dose clinical
studies. Although this represents a conservative approach to drug development, doing a
90-day study further assures the safety of the drug candidates going forward into
early clinical trials. The downside is that there is a large expenditure associated with these
studies with no assurance that the clinical candidate will progress far enough in develop-
ment to justify the cost.

For the IND-enabling programme, genotoxicity studies also are needed. According to
ICH guidance (ICH S2 and ICH M3R2), an in vitro mutagenicity study and an in vitro
chromosomal aberration study are generally needed for the IND or CTA. If either of these
studies are “positive”, then the in vivo chromosomal aberration study will be needed along
with an evaluation of the weight of evidence approach for genotoxicity. If the in vivo study
is also positive, it is likely that the drug would be abandoned. Furthermore, the regulatory
authority could request that the sponsor undertake other genotoxicity studies, for exam-
ple, COMET assay, UDS, and so on (see Chapter 14). Similar to the repeat-dose studies
described above, some companies will undertake all three initial studies prior to submis-
sion of the IND. This decision is often based on prior experience with a similar drug or
could represent company policy. Exceptions to the requirement to conduct genotoxicity
studies are made for certain drug classes, such as oncologics, and also for certain biologics.

Finally, the core battery of safety pharmacology studies will be necessary (ICH S7).
The core battery consists of an evaluation of the central nervous system (CNS) and respira-
tory systems in the rat and an evaluation of the cardiovascular system (CVS) in the dog.
Over the last few years, a combined study of CVS and respiratory system in the dog or
nonhuman primates (NHP) has become more common as this tends to reduce the timeline
for development (Lindgren et al., 2008; Pugsley et al., 2008). Further, this study design
has been found to be acceptable to the regulatory authorities. Development and validation
of this combined study in other species, such as the minipig, also has been reported
(Authier et al., 2008; 2009; 2011).

The discussion above reflects the general approach of the IND-enabling programme for
small molecules. For biotechnology-derived substances, the development approach is
more complex and often is done on a “case-by-case” basis depending on the product and
the intended application. Most often for biotechnology-derived substances, single-dose
studies in the appropriate animal model, usually the NHP, and the rat are undertaken to
determine dose levels and species to be used in subsequent repeat-dose studies. For these
latter studies, the duration of dosing may only be four weeks although durations of up to
six months have been conducted. The dose regimen usually consists of administering the
drug 1–3 times/week. Evaluation of the blood levels of biotechnology-derived substances
as well as blood levels of neutralizing antibodies is necessary. The development of bio-
logic products is further described in Chapter 18.

The IND or CTA can usually be submitted with the toxicology studies described above.
In some cases, an early fertility and embryofetal study (Segment I) and an embryofetal
developmental toxicity study (Segment II) are conducted depending on the class of drugs
being examined as well as whether toxicity signals are identified in the repeat-dose studies. As described above, some companies may undertake these studies as a matter of established routine in their drug development process. This might seem more than required but could be a reflection of the culture of the company.

Overall, the drug development process described in this introduction represents a general “best” case. It is not uncommon that issues arise during the development process that cause delays for the conduct of additional studies. One must remember that, by design, a biologically-active compound is being intentionally administered to animals and it is expected that some unknown and potentially adverse responses will occur. It is how those responses are managed, how they experimentally translate to risks in humans, and the amount of resources available to the company to evaluate the responses and the risks that will ultimately determine whether this drug proceeds to further development.

References


Websites

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