Nonclinical Safety Assessment
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Preface

This book, *Nonclinical Safety Assessment: A Guide to International Pharmaceutical Regulations*, was conceived as an update to the Alder and Zbinden text on international nonclinical testing regulations. This out-of-print text was published in 1988 prior to ICH but, at the time, represented a reasonably complete description of the testing requirements for pharmaceuticals. Since that time, the pharmaceutical industry has seen the implementation of ICH, development of new guidance and guidelines from FDA and the EU (CHMP), a new regulatory process in China and other regions, implementation of FDAMA, and so on. It is hoped that this book provides a practical description of nonclinical drug development regulations in the major market regions although we do recognize that this is not a static but a dynamic process that continues to evolve almost on a daily or weekly basis. Although we attempted to capture the state-of-the-art in regulatory toxicology development, we also recognize that certain aspects will change even during the publishing process. Not all regions are covered in this edition of the book. However, with the evolution of ICH, it is likely that all pharmaceutical regions will adopt the ICH concept with minimal alternatives in the testing strategy.

Regardless, the objective of this text is to provide a guide for those involved in nonclinical drug development. As you will see from the layout of the book, the initial section discusses the legislative and regulations for different regions. This is followed by specific chapters on the conduct, interpretation and regulatory considerations of nonclinical studies. The final section of the book describes biotechnology-derived products, vaccines, and so on and the nonclinical challenges and solutions for the clinical development of these sometimes difficult therapeutics.

This text is intended for those actively involved in the clinical development of a pharmaceutical product, whether as a toxicologist, pharmacologist, clinician, project manager, and other functional responsibilities. The approaches and methodologies described throughout this book provide a useful and scientifically valid means to drug approval.

We hope you find this a very useful resource.

The Editors
December 2012
Part I

International Regulations and Nonclinical Studies for Pharmaceuticals
Introduction

The Drug Development Process and the Pharmaceutical Market

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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 (EU5) 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
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 Pharmederging 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 1.1 Top 10 global pharmaceuticals by sales, 2011.**

<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 pseudobulbar 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 1.3  Top global therapeutic classes by sales, 2011.

<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).