Pharmaceutical Toxicology in Practice

A Guide to Non-Clinical Development

Edited by
Alberto Lodola
Jeanne Stadler

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INTRODUCTION

Alberto Lodola and Jeanne Stadler

Toxicology is defined variously as: *"a science that deals with poisons and their effect"* and *"the scientific study of the characteristics and effects of poisons"* [1, 2]. Rather dramatically, the emphasis is on "poisons"; a more inclusive definition of toxicology is, in our view, *"the study of symptoms, mechanisms, treatments, and detection of poisoning, especially the poisoning of people."* Within this context, toxicology has a long, checkered history, which is described in an interactive online poster, which has been produced by Gilbert and Hayes [3]. This poster describes the principal milestones in the evolution of toxicology and effectively illustrates the point that, for many years, toxicology was indeed principally concerned with the use of and protection from, exposure to poisons. It was not until the sixteenth century that Paracelsus highlighted the link between poisons and "remedies" [3]. With the passage of time, this "preindustrial" view of toxicology gave way to the modern "postindustrial" era of toxicology. As a result, the toxicological sciences have matured and expanded to include a range of specific subdisciplines of toxicology as follows:

- *Clinical toxicology,* the diagnosis and treatment of poisonings,
- *Forensic toxicology,* the use of analytical chemistry, pharmacology, and clinical chemistry to aid medicolegal investigation of death, poisoning, and drug use,
- *Industrial or occupational toxicology,* which deals with potential harmful effects of materials, products, and wastes on health and working environments,

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- *Environmental toxicology,* the study of the potential effects upon organisms of the release of materials derived from human activities into the natural environment and
- *Pharmaceutical toxicology,* the study of the potential effects on organisms of novel or established pharmaceuticals.

This book focuses on pharmaceutical toxicology and, in particular, nonclinical toxicology. Traditionally, nonclinical toxicology has had a bad image within pharmaceutical companies. This is often due to a poor understanding of the role of nonclinical toxicology in drug development. The regulatory guidelines that govern the design and conduct of toxicity studies still require, in most cases, that adverse events are produced in studies, or at a minimum, that very high doses (relative to clinical doses) be tested. As a result, toxicologists were/are seen as "drug killers," or colleagues who conduct animal studies at unrealistically high doses of the test compound. In recent years, reforms within pharmaceutical companies, driven by changing scientific, regulatory, and economic environments, have meant that there is a greater interaction between different areas of a drug development organization. Consequently, there is increased understanding of the role of toxicology studies within drug development. Not only is toxicology, and the toxicological scientist, an integral part of the identification of drug candidates, structural optimization, and lead candidate selection, but it is a cornerstone of managing attrition. Yes, toxicology can "kill" a compound, but ideally, they will be compounds with unacceptable and/or unmanageable toxicities, and this attrition will occur as early in the development cycle as possible. This is good for the patient and is good economics. Nevertheless, on occasion, despite the best efforts of all those involved, a drug has to be withdrawn from use. Consider the case of Vioxx (rofecoxib), a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID). This class of drugs was developed as a safer alternative to mixed COX-1/COX-2 NSAIDs such as aspirin, ibuprofen, and naproxen. It is now believed that all NSAIDs, when taken chronically, produce an increased risk of gastrointestinal bleeding and liver and kidney toxicity. In addition to problems typically associated with NSAIDs, several studies questioned the cardiovascular safety of Vioxx. In 2000, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, which compared Vioxx and naproxen, found that the risk of cardiovascular problems, including heart attack, chest pain, stroke, blood clots, and sudden death, was more than two times higher in the Vioxx group than in the control group and five times the risk of heart attack when compared to patients taking naproxen. Subsequently, the U.S. Food and Drug Administration (FDA), based on the analysis of the medical records of 1.4 million patients, suggested that Vioxx may have contributed to an additional 27,785 heart attacks or sudden cardiac deaths from 1999 to 2003. Because of these findings and data from additional studies, Vioxx was (voluntarily) withdrawn from the market by the manufacturer in 2004 [4]. It is worth noting that this withdrawal occurred despite the fact that many patients derived great benefit from this drug. Hopefully, in the future emerging technologies will help to target the use of drugs such as Vioxx to individual patients who have a maximal benefit/risk profile and in this way avoid the loss of valuable drugs to patients.

Traditionally, nonclinical–toxicological assessment has been based largely on data derived from animal studies; this has all the well-known advantages and inconveniences associated with the use of animals. There is increasing pressure to reduce, if not eliminate, the use of animals for scientific experiments and to reduce the cost and time taken to develop new drugs. Ideally, therefore, animal toxicity studies should be replaced by a series of robust, highly predictive, low-cost, and simple to conduct *in vitro* and *in silico* (computational) studies. Much progress has been made in recent years toward this goal; however, we are still a long way from achieving this ideal. A range of *in vitro* studies, some of which are accepted by regulatory authorities, are now available to toxicologists; for example, the use of the 3T3 cell assay to test for phototoxicity potential [5]. In recent years, there have been great advances in decoding genes and DNA sequences from a number of organisms, a task that has been facilitated by the development of techniques such as microarrays [6, 7] and array-based comparative genomic hybridization [8, 9]. At present, one million sites in any individual's genomic DNA can be simultaneously interrogated, which facilitates study of the link between disease and genetic variation. As a result, genomic data for humans is increasingly available and important in drug development. Increased understanding of the human genome provides insight into the underlying mechanism/s of disease, which in turn supports the development of new approaches to treating and/or preventing diseases [10–12]. To illustrate this link, it is necessary for us to briefly discuss the role of genes in human disease and the effects of xenobiotics on genes. Human diseases are monogenic, chromosomal, or multifactorial in origin: *monogenic diseases* are caused by changes to a single gene [13,14], *chromosomal diseases* are produced by changes in chromosomes [15], and *multifactorial diseases* are the most common and are caused by variation in many genes, and may be influenced by the environment. Genes are either *constitutive* or *inducible*. Constitutive genes are expressed continuously and control the ability of DNA to replicate, express, and repair itself, plus they control protein synthesis and are central to regulating metabolism. In contrast, inducible genes are only expressed intermittently [16]. During the process of gene expression, DNA is transcribed to mRNA, which in turn is translated to protein. Central to the regulation of gene expression is chromatin, a histone-DNA complex. For any given gene, the histone-DNA complex is the inactive state of the gene. One mechanism by which genes are silenced is linked to the presence of positively charged amino acids in histones, which produce zones in the histone–DNA complex that are susceptible to DNA methylation which then regulates gene expression [17, 18]. Small noncoding RNAs, for example, RNAi, may also be involved in the gene regulatory processes. This complex process requires the coordination of modifications to histones, transcription factor binding, and chromatin remodeling and results in the unwinding of the DNA in the transcription zone. As a result, the DNA is accessible to activating and repressor transcription factors (TFs), which bind to a specific DNA-binding domain and an effector domain. On binding an activating TF, the effector domain then recruits RNA polymerase II, allowing transcription of the corresponding gene/s to occur [19–21]. TFs can also activate genes by binding to the enhancer regions, which are located upstream, downstream, or in the introns of a gene. Small noncoding RNAs are also involved in controlling gene expression. Because the regulation of genes involves the interaction of a number of different regulatory cascades, by interfering with these cascades xenobiotics

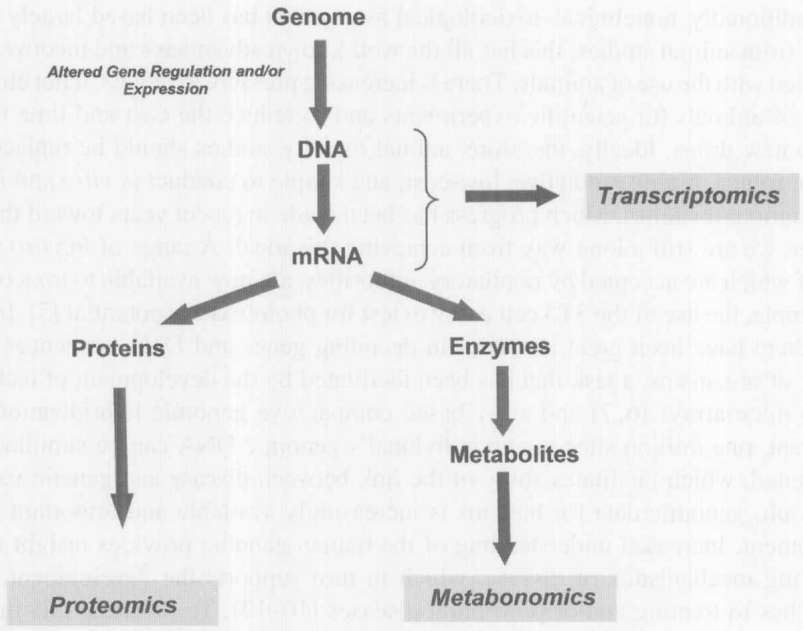

Figure 1.1. The "omics" technologies
The genome is comprised of all the genes, regulatory sequences and noncoding regions of an organism's DNA. The regulation of gene expression involves the interaction of a number of different regulatory cascades. By interfering with these cascades xenobiotics may alter gene expression, protein/enzyme production and in consequence cellular metabolism. These effects can be monitored by analysis of tissue DNA/RNA profile (Transcriptomics), protein/enzyme profiles (Proteomics) and metabolite production (Metaboniomics).

can alter gene expression and protein/enzyme production and, consequently, cellular metabolism. These effects can be monitored by analyzing tissue DNA/RNA profiles (transcriptomics), protein/enzyme production (proteomics), and metabolite production (metaboniomics) (see Fig. 1.1). Analysis of the "-omic" changes in different tissues, resulting from treating animals with a test compound may provide an early, specific indicator of toxicity [22, 23] and help to identify biomarkers of toxicity [24, 25]. This approach has great promise for developing new, specific, sensitive techniques to better characterize, and understand, the nonclinical toxicity of drug development candidates and their risk–benefit ratio. Nevertheless, despite the great strides that have been made in developing and applying these new technologies, the backbone of nonclinical safety assessment remains animal toxicity studies for the time being.

OBJECTIVES OF THIS BOOK

There is a wide range of excellent textbooks available, which review in detail individual and specialist aspects of pharmaceutical toxicology. Our focus is a more broad-based

and general description of the subject. We describe, with references to key source materials, the background to, and conduct of, the principal nonclinical studies that are central to nonclinical drug development. Although the discussion is primarily based on a description of the development of the low-molecular-weight organic molecules, which have been traditionally developed as pharmaceuticals, the general process we describe is also applicable to newer drug technologies (proteins, nucleic acids, nanoparticles, and the like) linked to recent advances in biotechnology. As we emphasize in individual chapters, regardless of the source and type of test compound or route of administration, the basic toxicological questions to be asked are the same. What changes is the range of studies deployed to answer these questions. What are the relevant questions? They are questions that help:

- the drug development scientist to understand the toxicological profile of the test compound,
- the drug discovery scientist to refine the chemical motif of the test compound to optimize efficacy and reduce side effects and
- the drug development team to advance the test compound to the clinic and then to the marketplace and the patient.

In many instances, the understanding of a complex process, such as drug development, is helped by reviewing real-life cases. This presents a problem, as drug development is done case by case, but, as we show, a baseline approach is provided by regulatory guidelines. We encourage the reader to review the advice we give in this book in the light of the type of compound that they are developing and the drug development strategies deployed for drugs that are currently on the market. While our reference point is the role and conduct of nonclinical studies in the support of drug development, for the most part the subject matter we cover applies more broadly to the toxicological evaluation of chemicals. To illustrate this, we can consider the role of toxicology in the REACH (Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals) process, which was implemented in the European Union (EU) in 2007. The REACH legislation was enacted as a way of managing the risks that chemicals may pose to health and the environment. This legislation applies to chemicals used in industrial processes, cleaning products, paints, clothes, furniture, and electrical appliances. In short, the use of all chemicals in the EU is covered by REACH [26]. In order to meet their legal obligations under REACH, manufacturers and importers of chemicals *must* identify and manage risks linked to the substances they manufacture and market. To do this, they submit a Registration Dossier to the European Chemicals Agency [27]. One element of this dossier is a Chemical Safety Report (CSR), which describes the chemical safety assessment for the chemical under consideration. In the CSR, registrants must present and discuss a range of data [28]:

- substance identity
- *physicochemical properties*

- *exposure/uses*/occurrence and applications
- *mammalian toxicity*
- *toxicokinetics*
- *chemical categories*
- ecotoxicity
- environmental fate, including chemical and biotic degradation

As this list shows, some data (items highlighted in italics) are similar to the nonclinical data required in drug development. Indeed, if it is available, nonclinical toxicity data can be used. Thus, Chapters 4–10 in this book, which deal with study conduct, types of study, and reporting, also apply to generating toxicity data for the CSR. However, remember that the underlying philosophy differs and thus will alter the risk assessment process relative to pharmaceuticals. In Chapter 11, we discuss the risk management of potential drug toxicities in humans. Again, the general principles that we discuss apply to the REACH risk management process, with the added complication that REACH also requires the preparation of an environmental risk management plan, which falls outside the scope of this book. Our attention is mostly on the "scientific" aspects of nonclinical toxicology. However, Chapters 3 and 4, and, to some extent, Chapter 10, deal with administrative/organizational aspects of nonclinical studies. These activities are sometimes overlooked, or relegated to a secondary importance; this is a mistake. Time spent optimizing these aspects of nonclinical activities can produce significant savings in terms of time and resources and reduces the possibility of errors in study conduct, data interpretation, data reporting, and risk management.

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THE REGULATORY ENVIRONMENT

Claudio Bernardi and Marco Brughera

INTRODUCTION

More than 400 years ago, Paracelsus (1493–1541), one of the "fathers" of the biomedical sciences, toxicology in particular, pointed out that "*all substances are poisons, and it is the right dose that differentiates a poison from a remedy*." This assumption generally applies to natural compounds such as animal venoms and poisonous plants and to chemically or biologically derived pharmaceuticals. Subsequently, in the eighteenth and nineteenthcenturies, the "art of toxicology" was further developed by a number of scientists (M.J. Bonaventura Orfila, Claude Bernard, Louis Lewin), who are now considered the founders of modern toxicology, resulting in 1893 in the publication by Rudolf Kobert (1854–1918) of one of the first textbooks on modern toxicology [1]. However, during this time scientists investigating the mechanisms of toxicity and attempting to define rational criteria for the detection of the toxic effects of xenobiotics, used different investigative approaches, which sometimes produced conflicting and misleading results. In more recent times, when this largely academic interest in toxicology was coupled with the more pragmatic interests of the nascent pharmaceutical industry, toxicology was "standardized" and given a legal dimension. This resulted in the appearance of regulatory authorities, which have oversight of the regulatory framework for drug development and the granting of marketing approval. In short, "regulatory toxicology" was born. As a result, regulatory authorities started to define the range of experimental data

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that pharmaceutical companies needed to support the conduct of clinical trials in humans with drugs in development and to obtain the authorization / permit to market new drugs.

The evaluation of experimental data for novel drugs, by an independent regulatory authority, was implemented at different times in different regions. One of the first regulatory authorities to be established was the US Food and Drug Administration (FDA), and was a result of the the Elixir Sulfanilamide disaster [2]. In 1932, it was shown that a chemical derivative of the red dye, Prontosil, had antibacterial properties and when treated with this modified dye, patients who were severely ill from a streptococcal infection made a complete recovery. Subsequently, other researchers developed modified Prontosil compounds, which eventually lead to the discovery of the so called "sulfonamide drugs." Sulfanilamide, used safely in tablet and powder form since 1936, was the first member of the sulfonamide family of drugs that are used today. In 1937, a liquid form of the drug (Elixir Sulfanilamide), using diethylene glycol to dissolve the sulfanilamide, was commercialized in the United States. In the absence of any legal requirement to do so, no additional nonclinical testing of this novel formulation was conducted, and in spite of the known toxic properties of diethylene glycol, Elixir Sulfanilamide was used to treat patients. From September to October 1937, more than 100 people died as a direct consequence of treatment with Elixir Sulfanilamide. This tragedy could have been avoided if a few, relatively simple, toxicity studies had been conducted with the reformulated drug. Japanese regulatory authorities were formed in the 1950s and in many European countries in the 1960s, following the thalidomide tragedy [3]. Thalidomide first entered the German market in 1957 as an over-the-counter remedy; the product was regarded as "completely safe" "even during pregnancy." From 1957 to 1961, thalidomide was marketed in about 50 countries and was used to treat pregnant women against morning sickness and stress, and to help them sleep. Thalidomide does not have any acute toxicity; a fatal overdose is virtually impossible, and peripheral neuropathy is probably its dose-limiting factor. However, although some studies have shown a dose dependence of peripheral neuropathy, typically after a dose of 40–50 g, in other studies neuropathy only occurred at a dose of just 3–6 g. In 1956, the wife of an employee of the drug's manufacturer (Chemie Grunenthal) assumed samples of the drug, and she gave birth to a baby born with malformations. Soon thereafter, there were additional reports of malformed children born to mothers treated with thalidomide, and a common pattern of limb deformities (principally phocomelia) emerged. In all, from 1956 to 1962, about 10,000 children were born with severe malformations to mothers who had been treated with thalidomide. Dr. W.G. McBride, at Crown Street Women's Hospital, Sydney, Australia, first raised suspicions of the link between thalidomide use in pregnant women and malformations. The drug was withdrawn from the market in 1961. Consequently, there was a rapid increase in the laws, regulations, and guidelines for reporting and evaluating the safety, quality, and efficacy data of new drugs. Against this background of national and/or regional regulatory authorities having responsibility for developing the requirements for drug registration, differences in regulatory requirements emerged; this came at a time when the pharmaceutical industry was becoming internationally orientated and was developing global marketing strategies. Indeed, the requirements for quality, safety, and efficacy data were so divergent between (national) regulatory authorities that the pharmaceutical industry sometimes had to repeat time-consuming

and expensive studies to market the same drug in different countries. Given government concerns over rising health care costs, the pharmaceutical industry's concern over the escalating cost of research and development and the public's expectation of rapid access to safe, efficacious new medicines, it became apparent that there was a need to rationalize and harmonize these regulations.

THE INTERNATIONAL CONFERENCE ON HARMONIZATION

To address issues of national divergence in regulatory requirements for pharmaceutical development, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990. In brief, the purpose of ICH [4] is to:

- provide a forum for regulatory authorities and the pharmaceutical industry to discuss the requirements for drug development,
- update harmonized technical requirements in the light of advances in science and technology,
- ensure that there is a harmonized approach to the development of new guidelines/requirements,
- facilitate the adoption of new or improved research and development approaches, and
- facilitate the dissemination of harmonized guidelines and encourage common standards.

The ICH process was launched by representatives of regulatory agencies and industry associations of Europe, Japan, and the United States. The ICH Steering Committee (SC) was established to oversee the process in which expert working groups (EWGs) would engage the scientific and technical aspects of each harmonization topic. The first SC meeting decided that safety, quality, and efficacy would have been the focus for the initial harmonization activity.

Key Players in the ICH Process

Key players in the ICH process are the six parties drawn from regulatory bodies and pharmaceutical companies in Europe, Japan, and the United States:

- European Commission (EC),
- European Federation of Pharmaceutical Industries and Associations (EFPIA),
- Japanese Ministry of Health, Labour and Welfare (MHLW),
- Japan Pharmaceutical Manufacturers Association (JPMA),
- United States Food and Drug Administration (FDA) and
- Pharmaceutical Research and Manufacturers of America (PhRMA).