

THE IMPORTANCE OF CARDIAC SAFETY ASSESSMENTS

1.1 INTRODUCTION

The importance of assessing the cardiac safety of noncardiac drugs, i.e., those that are not intended to treat cardiac conditions, has become very clear in recent years. A drug's propensity to influence the operation of the heart's electrical system in a certain deleterious manner is one of the most common causes of discontinuing a new drug's development program, failure to obtain marketing approval from a regulatory agency for a new drug, and removal of the drug from the market after approval (see Morganroth and Gussak, 2005). Some drugs lead to delayed cardiac repolarization, an occurrence that is explained in detail in due course and that plays a putative role in precipitating potentially lethal cardiac arrhythmias. Another occurrence of concern, and one that has prompted high-profile postmarketing regulatory actions in recent years, is discussion of potential links between a drug and other cardiac events such as fatal and nonfatal heart attacks. Assessments of cardiac safety have therefore become extremely important in contemporary drug development and pharmaceutical therapy.

This chapter provides an overarching introduction to the book's content. The process of new drug development is reviewed, along with the process of postmarketing surveillance. The term drug development is frequently used to describe the research and development that is done before an application requesting marketing permission is filed with a regulatory agency. Postmarketing surveillance refers to the monitoring of the drug's safety and therapeutic effectiveness once it has received marketing approval from a regulatory agency and is being prescribed by physicians and used by their patients. An additional term is also useful in the context of this book: the term lifecycle drug development embraces both premarketing and postmarketing activities. A drug's development in the sense of improving its safety and/or effectiveness profiles does not stop at the point of marketing approval. Data collected during the drug's use in large patient populations can lead to meaningful improvements in the drug. The term lifecycle drug development therefore emphasizes that it is vital to remain vigilant about the drug's effects from the very beginning of the drug discovery phase throughout the entire time that the drug is on the market and hence available for prescription to patients: this term captures the spirit of this book very well.

So too does the term integrated cardiac safety. A central tenet of this book is that it is beneficial to discuss the assessment methodologies used to collect information on cardiac safety at four stages of lifecycle drug development—drug discovery and design, nonclinical development, preapproval clinical development, and postmarketing surveillance—in one book, and to integrate this information to the greatest degree possible. The assessment methodologies used at these stages are quite different from each other, and an introduction to each methodology is therefore appropriate before discussing the information each provides. The term integrated cardiac safety also reflects another of the book's intentions, i.e., to bring together three areas within the overall spectrum of cardiac safety that are typically discussed separately. In this book these areas are termed proarrhythmic, generalized, and behavioral cardiac safety. Each of these areas is introduced in this chapter.

1.2 LIFECYCLE DRUG DEVELOPMENT

As Turner (2007) noted, the process of bringing a new drug to marketing approval is a lengthy, expensive, and complex endeavor. While precise quantification of “lengthy” and “expensive” is difficult, it is sufficient to note that respective values of 10–15 years and US\$1.3 billion are realistic and informative approximations in 2008. As noted in Section 1.1, a drug's life history can be meaningfully categorized into four stages. Safety assessments during these four stages can be meaningfully integrated since the safety of a drug is addressed at all four stages in its lifecycle. While these stages of investigation generally occur in the order in which they are listed, it is important to note that additional research falling within the remit of previous phases can be generated by the occurrence of safety concerns in a later phase. This scenario is particularly relevant when safety concerns are identified in postmarketing surveillance.

1.2.1 Drug Discovery and Design

Drug discovery and design can be thought of as the work done from the time of the identification of a therapeutic need to the time the lead drug candidate, the drug molecule deemed most likely to safely effect the desired therapeutic benefit, has been identified and optimized. *In silico* modeling has become an important aspect of this research. A drug candidate may be a small molecule or a biological macromolecule such as a protein or nucleic acid. Drug discovery activities vary between small molecules and macromolecules, but once a drug candidate has been identified and moves into the drug development phase, the regulatory governance of nonclinical and clinical trials and the marketing approval process are very similar in both cases. Discussions in this text focus on the discovery of small-molecule drugs.

The term drug design is used throughout this book since contemporary research in small-molecule drug discovery incorporates *in silico* methodologies that employ

predictive structure-function modeling in attempts to engineer a drug molecule that will successfully (therapeutically) interact with its target biological structure within the body while not interacting with nontarget biological structures.

1.2.2 Nonclinical Development

Once optimized, the drug candidate moves forward to a nonclinical development program, at which time the term investigational drug is commonly used. The term nonclinical development includes the nonhuman animal research that is currently necessary before permission will be given by regulatory agencies to test a new drug in humans, and also the additional nonhuman research that is done in parallel with preapproval clinical trials. Nonclinical research involves both *in vitro* and *in vivo* testing, and gathers critical information concerning drug dose, frequency, and route of administration as it relates to beneficial pharmaceutical therapy. Investigation of toxicity is also very important in nonclinical development. Some of the more lengthy, more complex, and more expensive nonhuman animal testing is typically not started until initial human testing reveals that the drug has a good safety profile in humans, and therefore has a reasonable chance of being approved for marketing if it also proves to be safe and effective in later clinical trials.

While human pharmacological therapy is the ultimate goal, understanding a drug's nonclinical biological activity is critical to subsequent rationally designed, ethical human trials. The term efficacy is used in preapproval clinical trials to refer to the desired therapeutic (biological) effect of the candidate drug, as discussed in the next section.

1.2.3 Preapproval Clinical Development

The pharmaceutical clinical trials conducted in a preapproval clinical development program examine the safety and efficacy of the drug in human participants. The term participant is used in this book to refer to anyone taking part in a clinical trial, while the term patient is reserved for individuals receiving pharmacological therapy from their personal physicians. Some participants may take part in a clinical trial at the recommendation of their physicians. These individuals are patients in the sense that they were under individual medical care from their physician at the time they commenced their participation in the trial, and they may well return to the same physician for further medical care upon their completion of participation in the trial. However, while they take part in a clinical trial, the term participant is appropriate.

The term efficacy refers to how well a drug achieves its intended therapeutic action during clinical trials. An investigational antihypertensive drug that does indeed lower blood pressure demonstrates efficacy, and the greater the drop in blood pressure, the greater the efficacy of the drug. It should be noted here that the term effectiveness also refers to how well a drug works, but it can be meaningfully

distinguished from the term efficacy. Efficacy is evaluated during tightly controlled clinical trials that include a total of perhaps 3,000 to 5,000 participants. While this total may seem a large number, a marketed drug may be prescribed to hundreds of thousands of patients. These patients will comprise a much more diverse set of individuals than the set of people who took part in the clinical trials, and they will likely take the drug in a less controlled (more realistic) manner. The term effectiveness relates to how well the drug works in the patient population taking the drug.

This book does not address the assessment of efficacy in detail since it focuses on drug safety. However, as introduced in Section 1.6, meaningful assessment of drug safety is operationalized in terms of assessing a drug's benefit-risk balance, and a drug's efficacy/effectiveness must therefore be considered alongside its safety when making the benefit-risk assessments that are of fundamental importance in lifecycle drug development. Discussions of efficacy assessments can be found in many books, including Durham and Turner (2008), Kay (2007), Piantadosi (2005), Senn (2007), and Turner (2007).

A drug's safety profile captures side effects that are caused by the drug: the terms adverse events and adverse drug reactions are typically used in preclinical trials and postmarketing surveillance, respectively. Since no drug can be guaranteed immune from side effects, a drug's safety profile is assessed in every phase of its development. The term toxicity profile is sometimes used in this context since, as just noted, every drug is likely have some unwanted side effects. Initial safety evaluations are conducted in healthy adult participants in first time in human (FTIH) studies. If all goes well in these trials, the investigative drug is administered to relatively small numbers of participants with the medical disease or condition of interest. If all goes well in these trials, subsequent trials are conducted in which the investigative drug is administered to a much larger number of participants with the disease or condition of interest. These larger trials are undertaken towards the end of a preapproval drug development program with the goal of providing an answer to a specific research question concerning the efficacy of the drug. The safety and efficacy data collected in these trials facilitate a regulatory agency's deliberations concerning the possible approval of the drug for marketing.

Preapproval clinical trials are often categorized into various phases, with any given trial being identified as belonging to one of them. These categories include Phase I, Phase II, and Phase III trials. A traditional description of preapproval phases is as follows:

- Phase I trials. Pharmacologically oriented studies that typically look for the best dose to employ. Comparison to other treatments is not typically built into the study design.
- Phase II trials. Trials that look for evidence of activity, efficacy, and safety at a fixed dose. Comparison to other treatments is not typically built into the study design.
- Phase III trials. Trials in which comparison with another treatment (e.g., placebo, an active control) is a fundamental component of the design. These

trials are undertaken if Phase I and Phase II studies have provided preliminary evidence that the new treatment is safe and effective.

A more informative alternative system has been suggested by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The ICH is an amalgamation of expertise from various regulatory agencies and pharmaceutical-related organizations across the world. It publishes guidance documents on many aspects of clinical research. The ICH Guidance E8 provides an approach to classifying clinical studies according to their objective, as shown in Table 1.1. This book presents subsequent discussions of clinical trials using this descriptive terminology.

Table 1.1 The ICH Classification of Clinical Trials

Objective of Study	Study Examples
<p><i>Human Pharmacology</i> Assess tolerance. Describe or define pharmacokinetics (PK) and pharmacodynamics (PD). Explore drug metabolism and drug interactions. Estimate [biological] activity.</p>	<p>Dose-tolerance studies. Single and multiple dose PK and/or PD studies. Drug interaction studies.</p>
<p><i>Therapeutic Exploratory</i> Explore use for the targeted indication. Estimate dosage for subsequent studies. Provide basis for confirmatory study design, endpoints, methodologies.</p>	<p>Earliest trials of relatively short duration in well-defined narrow patient populations using surrogate of pharmacological endpoints or clinical measures. Dose-response exploration studies.</p>
<p><i>Therapeutic Confirmatory</i> Demonstrate/confirm efficacy. Establish safety profile. Provide an adequate basis for assessing benefit/risk relationship to support licensing [marketing approval]. Establish dose-response relationship.</p>	<p>Adequate and well-controlled studies to establish efficacy. Randomized parallel dose-response studies. Clinical safety studies. Studies of mortality/morbidity outcomes. Large simple trials. Comparative studies.</p>
<p><i>Therapeutic Use</i> Refine understanding of benefit/risk relationship in general or special populations and/or environments. Identify less common adverse reactions. Refine dosing recommendation.</p>	<p>Comparative effectiveness studies. Studies of mortality/morbidity outcomes. Studies of additional endpoints. Large simple trials. Pharmacoeconomic studies.</p>

Source: ICH E8: *General Considerations for Clinical Trials*

1.2.4 Postmarketing Surveillance

After a drug is approved for marketing, additional data concerning its safety and effectiveness are collected. As noted in the previous section, it is likely that the number of patients taking a marketed drug will be much larger than the total number of participants who took part in preapproval therapeutic confirmatory trials. This occurrence has a major implication for drug safety assessment: rare and potentially very serious side effects that were not seen during preapproval trials (it is probabilistically very unlikely that they would have been) may be seen at this point. These adverse drug reactions need to be identified and investigated.

Postmarketing surveillance monitors reports of adverse drug reactions and thus compiles extended safety databases (terms such as pharmacovigilance and pharmacoepidemiology studies are used in this context in other books, as discussed in Section 10.2). Postmarketing surveillance therefore plays a critical and integral role in lifecycle drug development: its goal is to ensure that all members of a target disease population receive the greatest possible protection from adverse drug reactions.

1.3 THE INTERNATIONAL COMMITTEE ON HARMONISATION

Regulatory agencies in many countries across the world oversee the development, marketing, and postmarketing use of drugs (and other medical interventions, including surgery and medical devices, not discussed in this book). The current regulatory environment is largely a result of the work of the ICH, an amalgamation of expertise from various agencies and organizations across the world.

The ICH arose since the regulations for submitting documentation requesting marketing approval of a drug were historically quite different between countries. Data requirements around the world were dissimilar, meaning that studies often had to be repeated to satisfy national regulatory requirements if marketing permission was desired in multiple countries. This lack of uniformity meant that nonclinical and clinical studies had to be repeated, resulting in additional and unnecessary use of animal, human, and material resources. It also meant that bringing a drug to market in various countries took longer than necessary, delaying its availability to patients.

Harmonization of regulatory requirements was pioneered by the European Community (now the European Union, EU) in the 1980s as it moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonization was feasible. The harmonization process was then extended to include Japan and the United States. The ICH was formed from a government body and an industry association from each of these regions. These bodies and associations are:

- The European Commission, and the European Federation of Pharmaceutical Industries and Associations;

- The Japanese Ministry of Health, Labour and Welfare and the Japan Pharmaceutical Manufacturers Association;
- The United States Food and Drug Administration (specifically, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research) and the Pharmaceutical Research and Manufacturers of America.

1.3.1 Goals of the International Committee on Harmonisation

The ICH has several goals, including:

- To maintain a forum for a constructive dialog between regulatory authorities and the pharmaceutical industry on differences in technical requirements for marketing approval in the EU, the United States, and Japan in order to ensure a more timely introduction of new drugs and hence their availability to patients.
- To facilitate the adoption of new or improved technical research and development approaches that update or replace current practices. These new or improved practices should permit a more economical use of animal, human, and material resources without compromising safety.
- To monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data.
- To encourage the implementation and integration of common standards of documentation and submission of regulatory applications by disseminating harmonized guidelines.
- To contribute to the protection of public health from an international perspective.

1.3.2 Guidances Issued by the International Committee on Harmonisation

The ICH has produced many guidance documents for sponsors to use in various aspects of drug development research and documentation, including drug quality, safety, and efficacy. These guidances are arranged in four categories:

- Quality (designated by the letter Q)
- Nonclinical Safety (S)
- Clinical Efficacy and Clinical Safety (E)
- Joint Safety/Efficacy (Multidisciplinary, M)

Guidances that discuss evaluations of safety issues in both nonclinical and clinical research include those listed in Table 1.2. (The safety guidances that fall in the “E” category are sometimes listed separately from the safety guidances that fall in the “S” category. See the ICH web site, <http://www.ich.org>, for more detailed information on all their guidances.)

Table 1.2 ICH Guidelines Addressing Safety Issues

Guidance (Yr. Finalized)	Title
S1A (1996)	The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals
S1B (1998)	Testing for Carcinogenicity of Pharmaceuticals
S1C (1995)	Dose Selection for Carcinogenicity Studies of Pharmaceuticals
S1C(R) (1997)	Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes
S2A (1996)	Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals
S2B (1997)	Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals
S3A (1995)	Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies
S3B (1995)	Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies
S4A (1999)	Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)
S5A (1994)	Detection of Toxicity to Reproduction for Medicinal Products
S5B (1996)	Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility
S6 (1997)	Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals
S7A (2001)	Safety Pharmacology Studies for Human Pharmaceuticals
S7B (2005)	The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals
S8 (2006)	Immunotoxicity Studies for Human Pharmaceuticals
M3 (1997)	Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
E1A (1995)	The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-life-threatening Conditions
E2A (1995)	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2C (1997)	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E2C Addendum (1997)	Addendum to ICH E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E2D (Draft 2003)	Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting
E2E (2005)	Pharmacovigilance Planning
E14 (2005)	Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

1.4 REGULATORY AGENCIES

There are many regulatory agencies around the world that are responsible for the governance of new drug development in their respective countries. Accordingly, following the practice employed in Turner (2007), the general phrase regulatory agency is used wherever possible in this book. On certain occasions, however, specific agencies are discussed. Since both authors of this book live and work in the United States, and since each of us has had involvement in the Food and Drug Administration (FDA) and FDA-related activities, it is fair to say that more text is probably allocated to the FDA than to other regulatory agencies. Nevertheless, the postmarketing-related work of the European Medicines Agency (EMA: this agency was previously called the European Medicines Evaluation Agency, and this organization's widely known acronym was retained when its name was modified) is discussed in some detail: the EMA has recently been ahead of the FDA in some very salient areas of regulation. We hope that readers in other countries will recognize that our FDA-specific discussions almost always address issues of international regulatory concern. Additionally, the Further Reading section at the end of this chapter contains references that provide discussion of regulatory activity in the EU, several individual countries within the EU, and Japan.

1.4.1 The Food and Drug Administration

The regulatory agency responsible for the governance of new drug development in the United States is the FDA. The FDA is housed within the Public Health Service, part of the Department of Health and Human Services. Redefined in the 1997 FDA Modernization Act, the FDA's relatively broad mission includes providing reasonable assurances that foods and cosmetics (both of which are regulated products) are safe, and that drugs and devices (also regulated products) are safe and effective. Several program centers facilitate the FDA's operations, including:

- The Center for Drug Evaluation and Research (CDER)
- The Center for Biologics Evaluation and Research (CBER)
- The Center for Veterinary Medicine (CVM)
- The Center for Devices and Radiological Health (CDRH)
- The Center for Food Safety and Applied Nutrition (CFSAN)

The FDA becomes involved in new drug development when nonclinical research conducted by a sponsor starts to indicate that the investigative drug has potential benefits in humans (Ascione, 2001). Regulatory oversight does not apply to drug discovery and design, and some of the earlier aspects of nonclinical development are not conducted under regulatory oversight either. However, many later aspects of nonclinical development and all aspects of clinical development are conducted under regulatory governance. This governance also includes manufacturing processes.

There are many regulatory requirements for new drug development and approval. Before a sponsor submits a request for a drug to be registered for human use, a tremendous amount of highly specified laboratory testing, nonclinical work, and clinical trials need to be performed. In all cases, the procedures and results must be documented appropriately. From a regulatory perspective, if the research is not documented, for all intents and purposes it has not been done.

This applies to nonclinical development as well as clinical development. Nonclinical work is reported to the FDA in an Investigational New Drug Application (IND). This document is reviewed to see if clinical work should be allowed to start. Once the clinical development program is completed, all of the developmental work will be reported to the FDA in a New Drug Application (NDA) or a Biologicals License Application (BLA). If the review of these enormous documents goes well, the drug will be approved for marketing.

The new drug development and approval process includes several principal steps (Regulatory Affairs Professionals Society, 2005; see also 2007):

- Nonclinical testing.
- Submission of an IND.
- FDA review of the IND.
- Preparation and submission of an NDA or a BLA following clinical research.
- FDA review and approval of the NDA or BLA.

While the ICH publishes an extensive list of guidances, individual regulatory agencies also publish guidance documents. For example, the FDA publishes Guidances for Industry that can be located via the FDA's web site (<http://www.fda.gov>). Web sites for guidances published by the EMEA are provided in the next section.

1.4.2 The European Medicines Agency

The EMEA is headquartered in London. This agency coordinates the evaluation and supervision of medicinal products throughout the EU, thereby bringing together the scientific resources of the EU member states (27 at the time of writing in 2007).

The regulatory documentation submission process is not identical in different countries, and this is exemplified by differences between FDA and EMEA processes. In the European system a Clinical Trial Application (CTA) is submitted by the sponsor at the point when an IND would be submitted to the FDA. Since a CTA is protocol specific, one CTA must be filed for each clinical study protocol, which means that the number of individual CTAs increases during a clinical development program. Additionally, CTAs are based on summary information only.

When a sponsor's clinical development is completed the sponsor submits a Marketing Authorisation Application (MAA), the vehicle used for both small

molecule drugs and biologics. Two submission routes are available (in general) from which the sponsor may choose:

- The centralised procedure.
- The decentralised procedure.

The centralised procedure, which has been in place since 1995, leads to a single EU Scientific Opinion, which is then translated into a pan-EU decision by the European Commission. While this procedure is mandatory in some cases (e.g., for biotech drugs, and drugs intended for oncology, human immunodeficiency virus (HIV), diabetes, and neurodegenerative disease indications), it is also gaining popularity for all new chemical entities.

The decentralised procedure has been in place since 2006. The review of the MAA is conducted by a single agency, called the Reference Member State (RMS). However, other EU countries in which the sponsor wishes to market the drug receive a copy of the MAA and are involved in confirming the assessment made by the RMS. These additional agencies are called Concerned Member States (CMSs). The decentralised procedure has its roots in the earlier mutual recognition procedure that was put in place in 1995. The mutual recognition procedure operated in a similar way except that the CMSs did not receive the whole MAA until after the RMS had approved the product. In both the decentralised and the mutual recognition procedure, EMEA and the Committee for Medicinal Products for Human Use (CHMP) do not get involved unless the RMSs and CMSs cannot reach a consensus decision.

In the case of many new chemical entities ([NCEs], those for which the centralised procedure is not mandatory), choosing between the centralised and decentralised procedure involves many factors, and the decision is a strategic milestone involving medical practice, manufacturing plans, the nature of the product, market forces, and the size, resources, and strengths of the sponsor in the EU (see Harman, 2004, for more details).

Similarly to the FDA, CHMP and its Expert Working Parties provide scientific and regulatory guidelines that apply across the EU to complement ICH guidances. (Regulatory agencies in other countries and regions may develop guidelines as needed.) Thus, while considerable progress towards harmonization has been made, it is still important for those seeking global regulatory approvals to consider regional and national regulatory guidance. (For further information see <http://www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm> and http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html.)

1.5 THE ROLE OF BENEFIT-RISK ASSESSMENT

The engine that drives new drug development is typically an unmet medical need, which is ultimately an unmet biological need (some new drugs are developed to

address a medical need that is not being optimally addressed by existing drugs). That is, a drug is needed for the treatment or prevention of patients' biological states that are of clinical concern. Efficacy considerations in clinical trials and effectiveness considerations in postmarketing surveillance are therefore important. However, as highlighted by this book's content, so too are safety considerations. The ultimate goal of new drug development, then, is to produce a biologically active drug that is reasonably safe, well tolerated, and useful in the treatment or prevention of the disease or condition of concern. The word reasonably in the previous sentence may initially seem strange, but all drugs are likely to have side effects. The important goal, therefore, is to ensure a reasonable benefit-risk ratio, or benefit-risk balance.

1.5.1 THE EMPLOYMENT OF RATIOS IN LIFECYCLE DRUG DEVELOPMENT

The formation and calculation of mathematical ratios is a useful way to compare two quantities in many circumstances, including several in clinical research and drug development. Imagine that a sports team has won 15 games and lost 5 games in a season. How can the team's performance be captured in a relational manner? One way is to say that it won 10 more games than it lost. Another way is to calculate the ratio of games won to games lost. This is done simply and meaningfully by dividing the number of games won by the number of games lost. In this example, the number of games won is considered the numerator in this division, and the games lost is considered the denominator. Therefore, we have:

$$\frac{15 \text{ games}}{5 \text{ games}} = 3.00 \quad (1.1)$$

That is, the team won three times as many games as it lost.

Note here that the calculation could have been done the other way round, as shown in Equation 1.2. That is, we could have chosen the number of games lost as the numerator and the number of games won as the denominator:

$$\frac{5 \text{ games}}{15 \text{ games}} = 0.33 \quad (1.2)$$

The interpretation here would be that the team lost one-third as many games as it won. This statement, while also mathematically true, does not seem to flow as easily as the statement associated with Equation 1.1, i.e., the statement that the team won three times as many games as it lost. This example is provided here simply to illustrate that the choice of numerator and denominator is important for meaningful dissemination of information, a subject that is discussed in considerably more detail in Chapter 8.

1.6 BENEFIT-RISK ESTIMATES

As noted in Section 1.2.3, while not addressed in this book, the assessment of efficacy is needed in the process of benefit-risk estimation. The term benefit-risk estimate addresses precisely the same concept as the term benefit-risk ratio, but does so in a more meaningful manner in the present context. While the mathematical calculation that compares benefit to risk is correctly thought of as a ratio since we wish to compare benefit (the numerator) with harm (the denominator), the term ratio can imply a degree of precision that is not actually possible in benefit-risk assessment.

The calculation that is performed here can be more meaningfully expressed as

$$\text{Benefit-risk estimate} = \frac{\text{Estimate (probability and degree) of benefit}}{\text{Estimate (probability and degree) of harm}} \quad (1.3)$$

This expression of the calculation that is conducted makes explicit that the two values that are placed into the equation and hence used in the ensuing calculation (the numerator and the denominator) are estimates, not precisely known quantities. Therefore, the result of this calculation is also an estimate. It is certainly true that, for any two values placed into this formula, a precise mathematical answer will be given, but since this answer is the result of a computation involving two estimates the answer is an estimate too.¹

The term benefit-risk balance is also used in this book. A favorable benefit-risk balance is one in which the estimate of benefit is sufficiently greater than the estimate of harm, and an unfavorable benefit-risk balance is one in which the estimate of benefit is not sufficiently greater than the estimate of harm. To be considered reasonably safe, a drug needs to have a favorable, or acceptable, benefit-risk balance, whatever acceptable is deemed to be by a regulatory agency or a physician (see the following two sections).

It should also be noted here that a drug's benefit-risk balance can vary across time. Several occurrences can prompt a reevaluation of the benefit-risk balance. Identification of additional risk at a later time point (perhaps from postmarketing surveillance) reduces the benefit-risk estimate (the denominator in Equation 1.3 becomes greater). This is probably the occurrence that comes more readily to mind when considering this topic. However, the benefit-risk estimate can also be reduced, i.e., the benefit-risk balance made less favorable or acceptable, if the benefit decreases (the numerator in Equation 1.3 becomes smaller). This occurrence prompts the question: in what circumstances would the estimate of benefit be considered to have become reduced? One possibility is that postmarketing surveillance reveals that the effectiveness of the drug in the large population of patients taking it is less than was expected on the basis of the efficacy seen in the preapproval clinical trials that led to the drug's marketing approval.

Another scenario in which a drug's benefit-risk estimate can be reduced is the subsequent availability of a second drug with an equal benefit estimate and a lower

¹This logic is analogous to that for using the term sample-size estimation rather than sample-size calculation when determining how many participants to employ in a clinical trial (see Turner, 2007, pp. 127–135).

risk estimate. This means that the original drug no longer offers a unique therapeutic benefit. Therefore, while the estimate of risk for the original drug remains the same, the estimate of its relative benefit is decreased by the availability of the second drug that possesses an equal benefit estimate and a lower risk estimate. In this scenario, as in the previous one, the original drug's benefit-risk estimate is decreased by a numerator that is smaller. However, the reason for the decrease in the benefit estimate is different.

Benefit-risk determinations, i.e., benefit-risk estimations in our nomenclature, are central and critical components of both regulatory and clinical decisions. Regulatory decisions have an impact on a potentially extremely large patient population, i.e., they have public health implications, and clinical decisions have an impact on individual patients on a case-by-case basis. Both kinds of decisions are extremely important. The scenarios in the previous paragraph attest to the need to consider several factors in benefit-risk estimations. In real life, this process is far less clear-cut than indicated in these scenarios, and far less clear-cut than frequently intimated in (often sensationalist and inaccurate) media coverage of pharmaceutical topics.

1.6.1 Benefit-risk Estimations by Regulatory Agencies

Once an NDA is submitted to a regulatory agency at the end of a clinical development program, the regulatory agency is faced with a decision: does it approve the drug for marketing? As will be discussed in considerably more detail in Section 8.10, the information that the regulatory agency must use to make this decision, while gathered from a seemingly large number of subjects, cannot be definitive.

As noted in Section 1.2.3, the information before regulatory agencies at this point has been obtained from a relatively small number of subjects, on the order of 3,000–5,000. While this may initially seem a sizable number, it is dwarfed by the number of patients who may take the drug if it is approved for marketing. The regulatory agency therefore is placed in the position of having to decide, on the basis of how a relatively small number of participants responded to the drug in clinical trials, whether the drug is likely to be sufficiently more beneficial than harmful to the hundreds of thousands (or more) of patients who may take it. This decision is based on a benefit-risk estimate. The clinical trials provide an estimate of the likely benefit to these patients and also an estimate of the likely harm. These data are the information that forms the basis of the regulatory agency's benefit-risk estimate, and thus the basis of their decision to give or not to give marketing approval.

Regulatory agencies also have the responsibility of deciding if a marketed drug should be removed from the market on the basis of safety concerns (this topic is discussed in Chapters 10–12). Just like the decision to approve a drug for marketing, the decision to remove a drug from the market is not a decision that can be reached with absolute certainty. It is a relative decision based on the likely harm to patients, the likely benefit to patients, and the ramifications of removing the drug

from the market. Once it is removed, patients for whom the drug was effective and who suffered no ill effects do not have access to it. Depending on the availability or not of suitable alternative therapies, these patients may be harmed by no longer having access to beneficial treatment.

1.6.2 Benefit-risk Estimations by Physicians

Once a drug has been approved for marketing, it can be prescribed by physicians to their patients. When deciding upon a treatment regimen for an individual patient, a physician has to perform a benefit-risk estimation. Several pieces of information are used in the estimation process, including:

- All the available research data on a drug.
- The physician's knowledge of the patient's condition and medical history.
- The physician's clinical experience and clinical judgment in this situation.
- The patient's thoughts and feelings.

Having weighed the probability and degree of benefit to the patient against the probability and degree of harm, the physician has to decide, in conjunction with the patient, whether to prescribe the drug or not. That is, clinical decisions need to balance the relative weights of safety and efficacy considerations. If a higher dose of a given drug is considerably more effective than a lower dose and it only leads to a minimal increase in very mild side effects, a clinician may decide that, on balance, it is worth recommending the higher dose to the patient. Conversely, if a higher dose of a given drug is only minimally more effective than a lower dose and it leads to a considerable increase in moderate or severe side effects, a clinician may recommend the lower dose to the patient.

Clinical decisions involve an extra degree of complexity since, as noted, they are linked to the probability of the outcome occurring as well as the nature of a particular outcome. Consider the example of a physician and patient deciding together whether a new drug would be a useful therapy for the patient. Imagine that clinical research during the drug's development indicates that a particular side effect is likely to occur in 5% of patients who take the drug. If this drug would be particularly useful in the management of the patient's condition and the side effect is relatively benign (e.g., occasional moderate headaches), the clinician and the patient may decide that the risk of the side effect is worth taking. The side effect is relatively unlikely, and its occurrence would be manageable.

Consider now a similar scenario in which a different side effect also has a 5% probability of occurring, but that side effect is extremely debilitating. The patient and the clinician may make a different decision this time. On balance, the potential benefit of the drug may not outweigh the risk of experiencing the relatively unlikely but very undesirable side effect. The issue of balancing the probability of benefit with the probability of harm is a central element of clinical practice, and the probability

of benefit always needs to outweigh the probability of harm. Determining just how much the probability of benefit needs to outweigh the probability of harm in a given situation is the province of the physician's clinical judgment and the physician-patient relationship.

1.6.3 Similarities and Differences in Regulatory and Clinical Benefit-risk Estimation

While the basic process of using a benefit-risk estimate to make a decision is the same for a regulatory agency and for a physician, there is an important distinction. The regulatory agency is making a decision that it considers to be in the best interests of the whole population with the disease or condition that the drug is intended to treat, i.e., as noted earlier, it has public health as its focus. The physician is making a decision he or she considers to be in the best interests of a specific individual patient. While physicians have many patients, and are also interested in the larger picture of public health, they must practice their clinical interventions one patient at a time.

1.7 FORMALIZED DRUG SAFETY IS A RELATIVELY YOUNG DISCIPLINE

Orchestrated drug safety monitoring is still a relatively young discipline that can be traced to activities that followed the thalidomide tragedy in the 1960s. The drug thalidomide was first marketed in Germany for the treatment of insomnia and vomiting in early pregnancy in 1956. In 1961, there was a sizable increase in the incidence of congenital birth defects noted in that country. The defects typically noted were an absence or reduction of the long bones of the limbs in conjunction with normal or rudimentary hands and feet. Very unfortunately, however, the association of these defects with the use of thalidomide was not recognized for several years after the drug was marketed, and thousands of babies worldwide suffered from this congenital condition. This tragedy prompted widespread acceptance that greater control of medicines was necessary to prevent recurrences in the future (West, 1991).

Over the next several years, many countries adopted new approaches to assessing drug safety. First, legislation was introduced requiring that a drug's safety be assessed before the drug was marketed: some companies conducted clinical trials on their new drugs, but this was not a legal requirement. Second, systems for collecting information concerning the occurrence of adverse drug reactions from both medical professionals and the pharmaceutical industry were established. West (1991, p. 89) described this activity as "the foundation stone of safety surveillance and the start of regulatory authorities playing a significant role in ensuring drug safety."

The last 40 years have seen a lot of progress in safety surveillance, and this progress is detailed in subsequent chapters. Many parts of this book adopt a chronological approach, providing a historical framework to show how this

progress came about and allowing us to see how and why we are where we are today. Most important, this perspective also allows us to look forward. It is fair to say that we still have room for many improvements in drug safety, and this historical approach is hopefully beneficial in facilitating discussions of where we would like to be in the future, and how best to get there in an effective and timely manner.

1.8 INTEGRATED CARDIAC SAFETY

This book brings together three domains of cardiac safety—proarrhythmic, generalized, and behavioral—that together form integrated cardiac safety. Such integration is not typical in texts addressing cardiac safety, and, perhaps of particular note, behavioral cardiac safety is not typically addressed in texts addressing proarrhythmic and/or generalized cardiac safety. It is a quite different aspect of integrated cardiac safety, and, like proarrhythmic cardiac safety, it is certainly broad enough and important enough to warrant its own dedicated texts. However, we have written this book in the belief that everyone concerned with and involved in the provision to patients of drugs that can improve their health (and their quality of life) can benefit from an awareness of all three facets of integrated cardiac safety.

1.8.1 Proarrhythmic Cardiac Safety

The history of formalized proarrhythmic cardiac safety is even shorter than that of overall orchestrated drug safety as discussed in the previous section. While individual articles in scientific journals have been published for several decades and have been increasingly published for the last 15 years or so, books bringing together various aspects of proarrhythmic cardiac safety are a recent phenomenon. Seven such books are listed here, and all of them are highly recommended (they are cited in full, and in the usual alphabetical order, in the References). The first four are:

- 2002: Yap and Camm, *Drug-induced long QT syndrome*.
- 2003: Gussak and Antzelevitch (Eds.), *Cardiac repolarization: Bridging basic and clinical science*.
- 2004: Camm, Malik, and Yap, *Acquired long QT syndrome*.
- 2005: Morganroth and Gussak (Eds.), *Cardiac safety of noncardiac drugs: Practical guidelines for clinical research and drug development*.

It is also instructive to quote a few lines from each. It should be noted that these quotes contain terms with which you may not be familiar at this time. This is Okay: you will be very familiar with them once you have read this book. Morganroth

and Gussak (2005, pp. vii and viii) noted that their book was “designed to present current preclinical, clinical, and regulatory principles to assess the cardiac safety of new drugs based primarily on their effects on the ECG” and to be “a primary reference for drug developers as well as academicians consulting in this arena.” The individual chapters in their edited book, like those in the Gussak and Antzelevitch (2003) volume, provided detailed discussions of many aspects of this field, and one of our book’s goals is to provide you with the background knowledge necessary to benefit fully from reading more advanced works in this research field.

In their Introduction, Yap and Camm (2002, p. 1) observed that:

Drug effects are the most common cause of acquired long QT syndrome (LQTS)...In recent years, it has become apparent that a spectrum of noncardiac drugs, such as nonsedating antihistamines, macrolide antibiotics, antipsychotics, and others can cause QT prolongation and aggravate torsades de pointes. Of concern is that the proarrhythmic risk of many of these drugs was not detected during the developmental phase and was recognized only after the drug had been marketed for many years.

In their Preface, Gussak and Antzelevitch (2003, p. ix) noted the following:

The past decade has seen an explosion of knowledge and radical changes in our understanding of ventricular repolarization as an integral part of the cardiac electrophysiologic matrix; a topic which, until now, has not been covered in depth. *Cardiac repolarization: Bridging basic and clinical science* presents comprehensively the latest developments in the field of cardiac electrophysiology with a focus on the clinical and experimental aspects of ventricular repolarization, newly discovered clinical repolarization syndromes, electrocardiographic phenomena, and their correlation with the most recent advances in basic science.

Camm, Malik, and Yap (2004, p. vi) noted similarly that:

This book is written with the intention of providing a detailed review on acquired long QT syndrome, from drug-induced QT prolongation to cardiac and noncardiac causes of QT prolongation. Detailed attention is paid to the mechanism of drug-induced QT prolongation and the clinical methodology of measuring myocardial repolarization which is crucial in the assessment of the proarrhythmic risk of a particular drug.

Likewise, Morganroth and Gussak (2005, p. vii) commented that:

Cardiac safety of noncardiac drugs: Practical guidelines for clinical research and drug development is designed to present the current preclinical, clinical, and regulatory principles to assess the cardiac safety of new drugs based primarily on their effects on the ECG. Practical guidance to define cardiac safety at all stages of clinical research and drug development are featured and discussed by internationally recognized experts with academic, industrial, and regulatory experience.

It is also informative here to note three other books. Two of these resulted from Novartis Foundation symposia, and the third is a volume in the Wiley-VCH book series entitled “Methods and Principles in Medicinal Chemistry.”

- 2003: Chadwick and Goode (Eds.), *Development of the cardiac conduction system*. (Novartis Foundation Symposium 250)
- 2005: Chadwick and Goode (Eds.), *The hERG cardiac potassium channel: Structure, function and long QT syndrome*. (Novartis Foundation Symposium 266)
- 2006: Triggle, Gopalakrishnan, Rampe, and Zheng (Eds.), *Voltage-gated ion channels as drug targets*.

In the early 1990s, Morganroth (1993) observed that “At present, our knowledge base about the relation of the QT interval and torsades de pointes is grossly incomplete.” Twelve years later, discussing a chapter by Morganroth and Gussak (2005), Shah (2005a, p. 259) referred to Morganroth’s observation and commented as follows:

Unfortunately, despite extensive research for more than a decade since, this still remains the same today. It is therefore not surprising that more than any other drug-induced adverse reaction, it has been responsible in recent times for the withdrawal of many drugs from the market.

1.8.2 Generalized Cardiac Safety

As noted in the Preface, the term generalized cardiac safety is used in this book to refer to all cardiac adverse drug reactions with the exception of arrhythmogenic events captured by the term proarrhythmic cardiac safety. Events falling within

our category called generalized cardiac safety include fatal heart attacks, major irreversible morbidity (e.g., nonfatal myocardial infarctions), debilitating cardiovascular symptoms or events (e.g., transient ischemic attacks, marked fluid retention, and palpitations), and various pathophysiological characteristics that increase the likelihood of cardiac and cardiovascular events (see Borer et al., 2007).

While cardiac and cardiovascular parameters are certainly monitored during preapproval drug development programs, formal generalized cardiac safety assessment typically starts once a drug is marketed (using essentially the same postmarketing surveillance methodologies used in proarrhythmic postmarketing surveillance). Chapter 12 addresses generalized cardiac safety by way of three case studies involving high-profile instances in the last few years where the cardiac safety of specific drugs was questioned. One of these case studies addresses drugs generally known as coxibs, anti-inflammatory agents, and another addresses drugs known as thiazolidinediones, agents used in the treatment of diabetes.

1.8.3 Behavioral Cardiac Safety

The third aspect of cardiac safety discussed in this book is termed behavioral cardiac safety. This term is used to refer to cardiac adverse events where behavioral factors are the primary instigating factor. This category includes medication errors whereby patients are prescribed, dispensed, and/or administered an unintended drug or drug regimen and patients' intentional or unintentional lack of adherence to legitimately prescribed drug regimens. Chapter 13 therefore discusses the roles of physicians, pharmacists, and nurses in pharmacotherapy: as Dowell (2004, p. 50) noted, "the term clinician can meaningfully be applied to professionals in each of these healthcare domains since each may be in the position of discussing the use of or authorising the supply of medicines." The category of behavioral cardiac safety also includes the behavior of the patient in terms of how he or she actually takes medication that has been accurately prescribed and dispensed. The term adherence is one term that is used to address this issue, and patients vary considerably in their adherence to an appropriately prescribed drug regimen.

The assessment methodologies employed in the investigation of behavioral cardiac safety are applicable to behavioral drug safety in general, and so behavioral drug safety is discussed in general, but with specific examples related to cardiac safety. Behavioral safety is largely specific to postmarketing situations, since many of the behavioral factors of interest—errors in prescribing, dispensing, administration (e.g., by health care providers in in-patient settings and nursing homes), and taking one's own medication—occur once a drug is on the market. One area of behavioral safety that is not specific to postmarketing involves the preparation of clinical trial drug products, the pharmaceutical delivery vehicles via which the investigational drug and a comparator treatment (e.g., a placebo) are administered to participants in preapproval clinical trials.

As discussed in more detail in due course, one of the major problems in clinical medicine is that not everyone reacts in the same manner to the same approved and marketed drug. In the vast majority of cases, a very large percentage of patients will safely experience a beneficial therapeutic effect, a small percentage may safely experience no therapeutic benefit, and a (very) small percentage may experience an adverse drug reaction. This unfortunate occurrence can happen despite full due diligence on the part of the pharmaceutical company that developed the drug, the regulatory agency that approved the drug for marketing, and the physicians who prescribed the drug to patients who experienced the adverse drug reactions. As noted in the Institute of Medicine's report on the future of drug safety (2007b, p. 27), "The approval decision does not represent a singular moment of clarity about the risks and benefits associated with a drug—preapproval clinical trials do not obviate continuing formal evaluations after approval" (Part III of this book focuses on precisely such continuing formal evaluations). The main reasons that certain patients experience adverse drug reactions to drugs that were prescribed in full accordance with evidence available from all currently employed diagnostic tools, and with the highest degree of clinical judgment on the part of the prescribing physician, are individual genetic differences that influence the way a drug is metabolized and the degree to which a drug interacts with nontarget biological structures. These topics are discussed in due course: For now, the main point is that everyone involved in providing drugs to patients who experience proarrhythmic or generalized cardiac adverse drug reactions performed to the very best of their ability.

Unfortunately, this is not the case in behavioral cardiac adverse drug reactions. As noted previously, the field of behavioral cardiac safety includes studying the occurrence of medication errors, errors whereby patients are prescribed, dispensed, and/or administered an unintended drug or drug regimen that leads to a cardiac adverse drug reaction. Medication errors occur much more frequently than one might think: tens of thousands of people in the United States die each year from medication errors. Having made these statements, statements that can certainly appear harsh and judgmental—the word errors has a habit of sounding judgmental, an issue that is discussed in some depth in Chapter 13—it is extremely important to note that judgments are the last thing needed in this context. The physicians who prescribe, pharmacists who dispense, and nurses who administer drugs to patients are human beings, and human errors happen. Indeed, we should expect human errors to occur. The fundamental issue here is the design and implementation of safety systems that eliminate (or minimize to the greatest degree possible) the occurrence of errors by building in enough checks so that errors occurring early in the process are caught and rectified before the patient takes the drug at the end of the process. Health care is a high-risk field: patients can and do die from medication errors. However, it is not the only high-risk field (think about landing a military aircraft on the deck of an aircraft carrier on a pitch black night in very heavy seas). Safety systems have evolved to a much greater degree in other high-risk situations, and the need for the continuing evolution of health care safety systems is discussed in Chapter 13.

Chapter 13 also examines the role of the patient in medicine taking. This takes discussions into the realms of adherence—how closely the patient’s pattern of taking prescribed medication matches the prescribed regimen—and concordance, which focuses on the interaction between physician and patient at a holistic level. Patients’ psychosocial and behavioral characteristics can significantly influence which medicines they are willing to take and how they take them once prescribed, and the greater the degree of open discussion between the physician and the patient the better.

Some books that address these issues are listed here in chronological order (again, full details are provided in the References).

- 2000: Institute of Medicine, *To err is human: Building a safer health system*.
- 2003: World Health Organization, *Adherence to long-term therapies: Evidence for action*.
- 2004: Bond (Ed.), *Concordance*.
- 2004: Institute of Medicine, *Patient safety: Achieving a new standard for care*.
- 2005: Bosworth, Oddone, and Weinberger (Eds.), *Patient treatment adherence: Concepts, interventions, and measurement*.
- 2006: O’Donohue and Levensky (Eds.), *Promoting treatment adherence: A practical handbook for health care providers*.
- 2007: Park and Liu (Eds.), *Medical adherence and aging: Social and cognitive perspectives*.
- 2007: Cohen (Ed.), *Medication errors*, 2nd edition.
- 2007: Institute of Medicine, *Preventing medication errors*.

1.9 TEACHING AND LEARNING OBJECTIVES OF THIS BOOK

Differentiation between teaching and learning is an interesting philosophical challenge, and one that is beyond the scope of this book. In practical terms, we would like to convey certain information to our readers: we will try to teach you about, and we hope that you will learn about, research activities in the field of integrated cardiac safety. Whether one therefore regards the following points as teaching or learning objectives, we hope that reading this book will facilitate your appreciation of the following points that provide an effective agenda for subsequent discussions:

- Obtaining the full benefits from integrated cardiac safety assessment requires an integrated approach that makes use of optimum quality information to make optimum quality benefit-risk assessments throughout a drug's lifecycle. This assessment starts during drug design, occurs in nonclinical and clinical research, and extends throughout the drug's time on the market.
- *In silico* structure-function prediction research conducted during contemporary drug design aims to engineer safety into new molecular entities by engineering cardiotoxicity out of them.
- The ICH Guidance S7B, *The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals*, directs nonclinical cardiac safety research addressing a candidate drug's proarrhythmic liability.
- The ICH Guidance E14, *Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs*, directs clinical trials addressing an investigational drug's proarrhythmic liability.
- Postmarketing surveillance methodologies play a crucial role in monitoring for the occurrence of proarrhythmic and generalized cardiac adverse drug reactions.
- In addition to adverse drug reactions that can result from appropriately taken medication, medication errors (errors of prescription, dispensing, and administration) lead to a large number of adverse drug reactions. Developing and implementing safety systems throughout pharmaceutical (and all areas of) health care must be a high priority.

As noted on several occasions, the discussions in this book are at the introductory level. Accordingly, lists of Further Reading are provided at the ends of chapters for those of you who would like to take your study of integrated cardiac safety (or any component thereof) to the next level. The sources in the following section, the further reading for this chapter, are presented in the typical alphabetical order. In some of the subsequent chapters that focus on specific areas within integrated cardiac safety, the sources are presented in chronological order to provide a mini-history of developments in the respective areas.

1.10 FURTHER READING

Arnold, B.D.C., 2004, Regulatory aspects of pharmacovigilance. In Talbot, J. and Waller, P. (Eds.), *Stephens' detection of new adverse drug reactions*, 5th edition, Chichester, UK: John Wiley & Sons, 375-451.

[This chapter contains discussion of the Council for International Organizations of Medical Sciences, the ICH, and regulatory activities in the EU, France, Germany, the United Kingdom, Japan, and the United States.]

- Harman, R.J., 2004, *Development and control of medicines and medical devices*, London: Pharmaceutical Press.
[This book discusses the roles of UK and pan-European regulatory authorities.]
- Lee, C-J., Lee, L.H., Wu, C.L., Lee, B.R., and Chen, M.L, 2006, *Clinical trials of drugs and biopharmaceuticals*, Boca Raton, FL: CRC/Taylor & Francis.
- Mann, R. and Andrews, E. (Eds.), 2007, *Pharmacovigilance*, 2nd edition, Chichester, UK: John Wiley & Sons.
[This volume provides instructive information on regulatory activities in the EU, the United Kingdom, France, Germany, the Netherlands, New Zealand, Japan, and the United States.]
- Rang, H.P. (Ed.), 2006, *Drug discovery and development: Technology in transition*, Philadelphia: Churchill Livingstone/Elsevier.
- Regulatory Affairs Professionals Society, 2007, *Fundamentals of U.S. Regulatory Affairs*, 5th edition, Rockville, MD: Regulatory Affairs Professionals Society.
- Rogge, M.C. and Taft, D.R. (Eds.), 2005, *Preclinical drug development*, Boca Raton, FL: CRC/Taylor & Francis.
- Smith, C.G. and O'Donnell, J.T. (Eds.), *The process of new drug discovery and development*, 2nd edition, New York: Informa Healthcare.
- Talbot, J. and Waller, P. (Eds.), *Stephens' detection of new adverse drug reactions*, 5th edition, Chichester, UK: John Wiley & Sons.
- Turner, J.R., 2007, *New drug development: Design, methodology, and analysis*, Hoboken, NJ: John Wiley & Sons.