# Part One

# STATISTICS IN THE DEVELOPMENT OF PHARMACEUTICAL PRODUCTS

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# 1

# Statistical aspects in ICH, FDA and EMA guidelines

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## Synopsis

This chapter introduces the regulatory guidelines affecting drug product development and manufacturing that were published by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and other regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Authority (EMA). The focus of the chapter is on statistical aspects of these documents, thereby setting the stage for the whole book. These guidelines, collectively, deal with quality, safety and efficacy issues in clinical and pre-clinical research, chemistry, manufacturing and controls (CMC). In essence, they link patient clinical outcomes, drug product critical quality attributes, process parameters and raw material attributes. Establishing the link between patient, product and process is the most important challenge of biopharmaceutical companies and regulatory agencies for ensuring safe, effective and economic healthcare. This challenge is being addressed by the recent Quality by Design (QbD) initiatives of the FDA and ICH, which are also discussed.

## 1.1 Introduction

Healthcare is the treatment and prevention of illness. Healthcare delivery requires both innovators and manufacturers of drug products and medical devices, as well as healthcare providers

*Statistical Methods in Healthcare*, First Edition. Edited by Frederick W. Faltin, Ron S. Kenett and Fabrizio Ruggeri.
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such as hospitals and family medicine. This book, *Statistical Methods in Healthcare*, covers a wide range of activities where statistics impacts on the quality of healthcare, starting with the development of drug products and medical devices, followed by the handling of clinical trials, surveillance and statistical process control of health-related outcomes, economics of healthcare, and healthcare management. The book consists of five parts:

Part One: Statistics in Development of Pharmaceutical Products

Part Two: Statistics in Outcomes Analysis

Part Three: Statistical Process Control in Healthcare

Part Four: Applications to Healthcare Policy and Implementation

Part Five: Applications to Healthcare Management.

This chapter is about the fundamentals in drug development and manufacturing as defined by the regulatory agencies that determine what can be marketed to healthcare consumers. We begin with a general introduction to the organizations that produce such guidelines and regulations.

The pharmaceutical industry became more global in the 1960s and 1970s in parallel with worldwide development of pharmaceutical regulations. Moreover, contemporaneous with these developments, increased societal concerns were voiced for faster development of new biopharmaceutical compounds and for reduction of costs of healthcare and new drug development. One of the perceived roadblocks for expeditiously and efficiently developed new drugs was the fragmentation of pharmaceutical regulations among the United States, Japan and Europe. In the 1980s, the European Community initiated harmonization of European national drug regulations and demonstrated that harmonization of national regulations is possible.

In 1989, under the sponsorship of the United Nations World Health Organization (WHO), a meeting of the International Conference of Drug Regulatory Authorities was held in Paris to plan the harmonization of regulations among Europe, Japan and the USA. In a subsequent 1990 meeting in Brussels, under the auspices of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the steering committee of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH; http://www.ich.org) was established.

The purpose and terms of reference of the ICH were first declared by the steering committee in 1990, and later revised in 1997and 2000. The terms of reference of the ICH declare its purpose to be (1) to provide a forum for dialogue among industry and regulatory authorities of Europe, Japan and the USA; (2) to contribute to international public health; (3) to monitor and update harmonization documents; (4) to avoid divergent regulations with the development of new therapeutic advances and new technologies; (5) to facilitate adoption of new technologies to safely improve resource utilization; and (6) to foster dissemination and communication about harmonization.

As originally established and currently retained, the steering committee of the ICH consists of two members each from the EU, the European Federation of Pharmaceutical Industries and Associations, the Ministry of Health, Labour and Welfare of Japan, the Japan Pharmaceutical Manufacturers Association, the US Food and Drug Administration (FDA) and the Pharmaceutical Research and Manufacturers of America. The WHO, the European Free Trade Association and Health Canada each contribute one non-voting observer to the Steering Committee. The ICH secretariat, which is housed by the IFPMA, supports the ICH steering committee.

A key decision reached at the first ICH steering committee meeting was to divide the technical topics to be harmonized into three natural groupings: Safety, Quality and Efficacy. A fourth group of Multidisciplinary Topics has since been added. Currently, there are: 9 topics under Safety; 10 topics under Quality; 16 topics under Efficacy; and 5 Multidisciplinary topics. A number of these topics have multiple sub-topics, and several new topics are in their final stages of approval.

The collective impact of these guidelines on the multinational pharmaceutical industry cannot be overstated, particularly in Europe, Japan and the USA. Moreover, any pharmaceutical company that wants to reach these markets needs to pay attention to these guidelines. Individuals working in any aspect of drug development, drug manufacturing or post-marketing monitoring are typically well versed in those guidelines pertinent to their work.

Examples of the guidelines include the Multidisciplinary Guideline M4 and Quality Guideline Q8. Organizations responsible for compiling a new drug application closely follow the format and structure described in M4 concerning the Common Technical Document (CTD). The ICH community recognizes that quality cannot be tested into products and should be built in by design using the information from pharmaceutical development studies as the basis for quality risk management. In that context, the Q8 guideline on 'Pharmaceutical Development' highlights the importance of quality by design (QbD) in pharmaceutical development.

Throughout, statisticians are involved in a variety of drug development, drug manufacturing and healthcare delivery activities. As such, they need to know the statistical aspects of all of those guidelines pertinent to their responsibilities (Peterson *et al*., 2009a).

This chapter highlights statistical concerns in the four sets of ICH guidelines, and other major regulatory documents with strong statistical focus. The intention is to generate awareness of the breadth and depth of the statistical aspects of these guidelines and not be necessarily fully inclusive.

In addition, we briefly review the guidance documents developed by the FDA and European Medicines Authority (EMA). In general, the FDA and EMA guidance documents are more extensive than the ICH guidelines.

The FDA guidance documents, for example, address some specific statistical concerns not currently covered in the ICH guidelines. For example, the FDA has published a draft guidance on Adaptive Design Clinical Trials for Drugs and Biologics; a topic covered in Chapters 2 and 5 of this book.

However, in addition to these particulars, the FDA has also incorporated the ICH guidelines as guidances. While the role of guidance documents and guidelines in national regulatory policies and procedures is generally overlapping, there are differences among regions. The FDA specifically points out that guidance documents and guidelines 'do not create or confer any rights for or on any person and do not operate to bind FDA or the public'. On the other hand, the Japanese Pharmaceutical Affairs Law includes specifically some of the ICH guidelines (for example, The CTD guideline of M4). The next section provides an overview of the ICH guidelines.

## 1.2 ICH guidelines overview

The list of topics covered by the ICH guidelines is continuously expanding. New topics or revisions of existing documents can be officially proposed by many forums such as scientific

societies or ICH regional guideline workshops. Official requests, however, must be channeled through one of the six parties in the steering committee, or by one of the observers on the committee. The next step is the preparation of a short concept paper which may trigger the steering committee to appoint an official Working Group (WG) to proceed with development of the topic. The WG then works to produce a draft guideline with the help of technical experts and the three regions' regulatory authorities (the EMA, the Pharmaceutical and Medical Devices Agency, Japan (JPMDA) and the FDA). The draft is published by the three regulatory authorities for further discussion and broad input. Based on the subsequent regulatory input, the WG then moves to prepare a final document which requires sign off from each of the three regions. With this task completed, the steering committee signs off and thus finalizes the new or revised guideline. Should there be disagreements in any part of this multi-step process, there are established procedures for resolving them.

The four sets of ICH Guidelines cover the development of a new biopharmaceutical product: Quality, Safety, Efficacy and Multidisciplinary. The 10 Quality topics focus on chemical and pharmaceutical quality assurance. The 9 Safety topics relate to *in vitro* and *in vivo* pre-clinical studies, and the 16 Efficacy topics concern clinical studies in human subjects. The Multidisciplinary topics deal with five issues that do not fall clearly into one of the other three sets of topics. Chapters 2–5 in this book provide in-depth studies of statistical and modeling aspects in pre-clinical and clinical research in the spirit of these guidelines.

The Quality guidelines, designated Q1, . . . , Q10 are, respectively: (1) stability; (2) analytic validation; (3) impurities; (4) pharmacopoeias; (5) biotechnology quality; (6) specifications; (7) Good Manufacturing Practice (GMP); (8) pharmaceutical development; (9) quality risk management; and (10) pharmaceutical quality systems.

A number of the quality guidelines are multi-part; for example, Q1 has six sub-guidelines. These guidelines and details of their statistical content are discussed in Section 1.4 of this chapter. Due to their impact, the three guidelines Q8, Q9 and Q10 are our primary focus. Guideline Q8 encourages new drug applications to include a design space and risk-based control strategies. The basic idea of Q8 is that drug product developers should study the behavior of critical quality parameters with an impact on critical quality attributes (CQAs) and determine a control strategy in their proposed new products, under variations in the raw material and process control parameters.

The Safety Guidelines, designated S1, . . . , S9 are, respectively: (1) carcinogenicity studies; (2) genotoxicity studies; (3) toxicokinetics and pharmacokinetics; (4) toxicity testing; (5) reproductive toxicology; (6) biotechnological products; (7) pharmacology studies; and (8) immunotoxicology studies. Topics (1) through (7) correspond to S1 through S7, while topic (8) consists of S8 and S9.

These guidelines are not discussed further in this chapter, and the reader is referred to the ICH website for more details.

The sixteen Efficacy guidelines, designated, E1, . . . , E16 are grouped into sets of related topics. Namely: clinical safety; clinical study reports; dose-response studies; ethnic factors; Good Clinical Practice (GCP); clinical trials; clinical evaluation by therapeutic category; clinical evaluation; and pharmacogenomics. Within some of these groupings there is a single guideline; while in others, there can be as many as four guidelines, and again some of the individual guidelines may be multi-part. For example, Q2 has six sub-topics, one of which has undergone two revisions. Section 1.3 of this chapter delves into the statistical details of many of the Efficacy guidelines.

In addition to these specific ICH guidelines, a substantial literature has developed offering commentary on many of the individual guidelines. As appropriate, some of this literature is noted in this chapter.

The ICH Guidelines are all available on the web at http://www.ich.org/products/guidelines.html, and as such are not individually cited in this chapter.

## 1.3 ICH guidelines for determining efficacy

The efficacy guidelines that are most focused on statistical issues are E9 and E10. The remaining guidelines deal with various statistical concerns, from suggested designs and inference requirements to statistical reporting.

Guideline E1, entitled 'Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-life Threatening Conditions', as its title indicates, discusses the rationale for sample sizes for various studies to characterize adverse drug experience (ADE) rates both in the short term (less than six months from treatment start) and in the longer term. The long-term concern in the guideline is defined to be chronic or repeated intermittent use for longer than six months. Short-term (three to six months) ADE rates of 1% or more are expected to be 'well characterized'; while rates of 0.1% or less are 'not expected' to be characterized. There is a need to examine the time-varying nature of these short-term rates, and E1 notes that 'usually 300–600 patients should be adequate'. This sample size is also adequate for detecting ADEs in the range of 0.5 to 5.0% that occur following short-term delays. In addition, to guard against ADEs that occur after six months, there is a requirement that at least 100 patients be treated and studied for at least one year.

Guideline E1 notes that, with no occurrences of a serious ADE in one year and based on 100 treated patients, there is 'reasonable' assurance that the true incidence is less than 3%. Direct calculation shows that a one-sided exact 95% confidence interval for the probability of a specific serious ADE is less than 0.03 when no events are observed among 100 patients. Overall, E1 expects that at least 1500 patients will be needed during drug development to adequately characterize the ADE concerns.

There are six guidelines that comprise the E2 series, designated E2A, . . . , E2F. They deal with safety issues for drugs under development, as well as for marketed drugs. Guidelines E2A and E2D deal respectively with pre- and post-approval expedited reporting of adverse events and adverse drug reactions; while E2C and E2F deal with pre- and post-approval periodic safety update reports. Electronic formatting issues are discussed in E2B, and requirements for pharmacovigilance planning are discussed in E2E.

The pharmacovigilance planning is designed to aid sponsors in developing post-marketing safety surveillance plans that could be submitted with a new drug license application (NDA). At a minimum, the plan should describe the routine pharmacovigilance that is conducted for all products, with attention to the regional requirements. In terms of product-specific plans, E2E describes a variety of methods in an attached annex. These methods include designs for passive surveillance, stimulated reporting, active surveillance, comparative observational studies, targeted clinical evaluations and descriptive studies. Collectively these methodologies provide a wide range of approaches to monitor the safety of a new compound after approval, and the pharmacovigilance plan included in the NDA is an integral part of the regulatory review process.

Guideline E3, entitled 'Structure and Content of Clinical Study Reports', is a highly detailed guideline. While the context of this guideline is broad, there are several subsections of the report focused on statistics. Section 9.7 of E3 details with planned statistical analyses and justification of the study's sample size, and Section 9.8 addresses changes to the planned analyses that occurred during the study. Interestingly, E3's Section 11.4.2 of the efficacy results presents analytic features that are important for the regulatory statistical review; namely, adjustments for covariates, handling of dropouts and missing data, interim analyses, multiplicity issues and subgroup issues. Annexes III and IV of E3 provide useful approaches to schematically depict study designs and patient disposition.

Guideline E4, entitled 'Dose-Response Information to Support Drug Registration', is a relative short document focusing on the importance of obtaining dose-response information based on the totality of studies comprising the licensing application. Other than presenting several designs, there are few specifics on data analysis. In some sense the most compelling statistical statement is that, beyond the individual study analyses, 'the entire database should be examined intensively for possible dose-response effects'. This suggests that, when a sponsor prepares a clinical plan, there should be focused statistical consideration about how the studies' data will ultimately be integrated to provide accurate dose-response estimates for both efficacy and safety. Moreover, in light of the perceived high failure rate of Phase III trials (Kola and Landis, 2004), planned cumulative integration of dose-response data during drug development may be a helpful tool to improve this situation. Chapters 3 and 4 deal with phenomenological and physiological modeling, and cover dose-response modeling issues. These chapters cover the relatively new domain of pharmacometrics and fundamental biomathematical systems that combine disease progression models with toxicity, pharmacodynamics and pharmacokinetics to determine optimal treatment regimens and uncover mechanisms of action of the drug compound under investigation.

One of the more conceptually challenging guidelines is E5, entitled 'Ethnic Factors in the Acceptability of Foreign Clinical Data'. This guideline's purpose is to facilitate the use of 'foreign' clinical data obtained in one ICH region to gain approval for the study compound in another ICH region where there are differences between regions in characteristics such as genetics, physiology, culture or environment, which E5 terms collectively 'ethnic factors'. A bridging data package consists of the relevant information from the approved package and the necessary bridging studies to allow extrapolation to the new region. The guideline suggests a spectrum of ethnic factors ranging from intrinsic (e.g., genetics, gender) to extrinsic (e.g., medical practice, socioeconomic factors, climate), with a range of factors in between. There are general suggestions about the kinds of bridging studies that might be used depending on the study compound's class and sensitivity to ethnic factors and the kind of ethnic differences between the two ICH regions. There are circumstances where no bridging studies seem to be required. In other cases a pharmacodynamic study or dose-response study is required, and in still other cases a new, controlled clinical trial is required.

The need arising from E5 for statistical development is indicated by phrasing such as 'if the bridging study shows that the dose response, safety and efficacy in the new region are similar, then the study ... is capable of "bridging" the foreign data'. Little is explicitly said about what constitutes similar or equivalent evidence. From a statistical viewpoint, the question arises about how methodology that was developed in other settings to handle equivalence and non-inferiority studies might apply in this context.

The implementation of E5 has raised questions, and the ICH subsequently issued a supplement to E5 entitled 'Ethnic Factors in the Acceptability of Foreign Clinical Data: Questions

and Answers'. There have been a number of statistical and design papers written focusing on various aspects of E5; for example, Uyama *et al*. (2005) or Tsou *et al*. (2010), as well as a series of four papers by varying authors in an issue of the *Journal of Biopharmaceutical Statistics* (2002).

Good Clinical Practices are documented in E6 and, as such, have little direct involvement with statistical concerns. The primary sections of this guideline deal with practices for Institutional Review Boards (also called Helsinki Committees), for investigators and for sponsors. Also considered are the structures of the clinical trial protocol and the Investigator's Brochure.

Guidelines for studies in special populations are considered in E7 and in E11. The former deals with geriatric populations and the latter with pediatric populations. Guideline E7 suggests that for compounds prescribed, but not uniquely, to the elderly, a minimum of 100 geriatric patients suffices, and for compounds which are for diseases uncommon in geriatric populations, smaller numbers are sufficient. Clearly for compounds intended for a primarily geriatric population, these patients should be a major portion of the data. Specific studies, such as pharmacokinetic or dose response, can explicitly model the effects of age; while, more broadly, for most compounds the entire clinical database should be examined for age-related effects.

Guideline E11 points out the importance of there being more products available for pediatric populations, and at the same time indicates many of the issues and difficulties in conducting studies in this population. Clearly this is a dynamic population, with substantial physiological, cognitive and developmental differences between the preterm and term newborns and adolescents. Pharmacodynamic and pharmacokinetic studies need to account for age and physiology (e.g., weight) and, if efficacy studies are needed, the sponsor may need to develop and validate endpoint measurements appropriate to the patients' cognitive development. Overlaying all the usual safety concerns, is the concern that the compound might affect growth and development, which may not be seen until a later age in the patient. (For more on this topic see Chapter 3.)

The ICH guideline E8, 'General Considerations for Clinical Trials', is a well-written overview document providing the principles for clinical trials and, more broadly, clinical development plans. While the design and statistical principles described in this guideline are ones many statisticians are aware of, the document as a whole makes excellent reading for a clinician designing a clinical trial or program.

For statisticians, the ICH Efficacy guideline with the most direct impact is E9, 'Statistical Principles for Clinical Trials', completed in 1998. The breadth of topics and the soundness of the material encompass much of what a clinical trials statistician faces in developing new drugs. Moreover, the principles considered are equally applicable to many types of clinical trials beyond those in the biopharmaceutical industry.

The introductory material of E9 (section I) espouses two important principles: one being that all trial statistical work is the responsibility of 'an appropriately qualified and experienced statistician', and the other being how important it is 'to evaluate the robustness of the results' in light of their 'sensitivity ... to various limitations of data assumptions'. This lengthy guideline divides the more technical considerations into five major components: overall clinical development, trial design, trial conduct, data analysis, and safety and tolerability. Due to the extensive nature of the material we can only highlight in this chapter select ideas.

The considerations for clinical development section (II) of E9 focuses on the overall plan, clinical trial purposes, issues concerning and types of response variables, and blinding and

randomization. There is a rather complete discussion of the different aspects of handling multiple primary variables when a suitable composite variable cannot be constructed based on them. Guideline E9 notes that 'it should be clear whether an impact on any of the variables, some minimum number of them, or all of them would be necessary', and describes the handling of type I error in each case. Regarding randomization, dynamic allocation of patients to treatments is discussed with the warning that 'the complexity of the logistics and the potential impact should be carefully evaluated when considering dynamic allocation'. The trial designs section (III) of E9, after considering various trial types, discusses fairly comprehensively how to model and analyze multicentre trials. It describes the value of having centers with comparably balanced numbers of patients and also indicates that treatment effect can be obtained from a model without a treatment-by-centre interaction. However, the homogeneity of treatment effect must be examined through, for example, graphical or analytic methods, and, if it is found, the possible causes carefully explained. Equivalence trials and non-inferiority trials are covered, but more complete discussion of many of the statistical issues for these can be found in two later EMA (2000, 2004) Points to Consider documents. The issues concerning switching non-inferiority and superiority objectives in the same trial are not discussed in E9, but in EMA (2000).

The trial conduct section (IV) of E9 considers issues concerning the monitoring of ongoing clinical trials. It basically dichotomizes the types of monitoring that might be considered into those which use only the blinded data and those which use suitably unblinded data. Blinded monitoring may involve modifying the inclusion/exclusion criteria in response to external information or in response to ongoing study results such as accrual rates. Other types of blinded monitoring can lead to adjusting an ongoing trial's sample size based on estimates of a response variance or overall survival rate. As pointed out by E9, blinded adjusted sample size procedures should be documented in the protocol or in an amendment, including a description of what effects there might be on type I error. Unblinded monitoring focuses primarily on group sequential designs, and E9 does not discuss the more recently developed adaptive designs based on unblinded data. The cautions that E9 presents for using group sequential designs equally apply to adaptive designs. The trial conduct section concludes with a discussion of the role of Independent Data Monitoring Committees (IDMCs). Throughout this section is the theme of the importance of preserving the trial's integrity with suitable protection in place if unblinded data are examined during the trial.

Section V of E9 is focused on data analysis and can be seen as a highly abbreviated text of statistical methods for analyzing clinical trials, and only a few of its features are highlighted here. Guideline E9 notes that the main analysis details should be in the study protocol, while the more complete statistical analysis plan may be a separate document (that needs to be completed before the blind is broken). The intention-to-treat and per-protocol analysis sets are discussed and their relative uses compared. Missing data considerations are given with the conclusion that 'unfortunately, no universally applicable methods of handling missing values can be recommended'. Standard advice is given concerning the careful specification of the primary efficacy variable(s) and the corresponding primary analytic model for them. There is also a short discussion of handling covariates, subgroups and interactions.

In E9, section VI deals with evaluation of safety and tolerability and section VII with reporting. The safety population is usually considered as those who received one dose of a trial compound, and there is the strong recommendation that safety data be collected consistently across all the trials in a clinical program, so as to facilitate an integrated summary of safety

and tolerability. In many cases, it is suggested that descriptive statistics and graphics suffice to analyze safety where *p*-values and confidence intervals for 'flagging' and aiding interpretation are used as needed. The reporting section of E9 is intrinsically a shortened version of E3 which describes in detail the clinical report.

The ICH E10 is an intriguing and extensive guideline entitled 'Choice of Control Group in Clinical Trials'. It discusses a broad array of designs for clinical trials with an emphasis on the control group(s) in a trial. Guideline E10 classifies trials by five types of control groups: placebo, no-treatment concurrent control, dose-response concurrent control, active control and external control (which includes historical controls). Within each category, there is a detailed presentation of their uses, advantages and disadvantages, ethics, and variations of the designs in that category. For example, in the presentation of the modifications of placebo controls, there are discussions of add-on designs, 'early escape' designs, limited placebo period designs, and randomized withdrawal designs. Guideline E10 also provides two schematics; one indicating design types based upon trial objectives and the other being a flowchart which helps in choosing the concurrent control. While the designs are well described, little is given about methods for analyzing the various designs (for more on this topic see Chapter 2).

The more recent ICH Efficacy documents deal with specific therapeutic classes and modern topics arising from genetic considerations. Document E12 is termed 'Principles for Clinical Evaluation of New Antihypertensive Drugs' and E14 is entitled 'The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs'. Guidelines E15 and E16 are entitled, respectively, 'Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories' and 'Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions'. Interestingly, the ICH considers E12 a principle document rather than a guideline.

## 1.4 ICH quality guidelines

The ICH Quality guidelines concern designing and ensuring manufacture and delivery of quality drug products. While Q1–Q7 have impact, we focus on the three quality guidelines which are of substantial impact to the healthcare industry – Q8(R2) Pharmaceutical Development,Q9 Quality Risk Management and Q10 Pharmaceutical Quality System – and a concept paper, Q11 Development and Manufacture of Drug Substances.

The key concept behind these three guidelines is that quality of drug products is determined by their underlying design, development, manufacturing and supply processes. Crucially Q8 notes that 'it is important to recognize that quality cannot be tested into products; that is, quality should be built in by design'. A process is well understood when all critical sources of variability are identified and explained, variability is proactively managed by the process, and product quality attributes can be accurately and reliably predicted over the space of design parameters.

Processes must meet current good manufacturing practices to ensure that drug products meet safety and efficacy requirements. In the past, this requirement has been met by performing process validation studies on three batches; however, the ICH Quality guidelines recognize that this approach is unlikely to fully represent routine manufacturing and therefore unlikely to cover all potential sources of variability (e.g., raw materials, operators, shifts,

reactor vessels). In addition, the FDA has identified this issue as a challenge to the regulatory process and described the traditional approach as a 'focus on process validation and not process understanding' (Nasr, 2007). Quality by Design is about changing this approach (Kenett and Kenett, 2008).

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives, that emphasizes product and process understanding and sets up process control based on sound science and quality risk management. In the traditional approach, product quality and performance is achieved by restricting flexibility in the manufacturing process and by end product testing. Under the QbD paradigm, pharmaceutical quality is assured by understanding and controlling manufacturing and formulation variables. End product testing is used to confirm the quality of the product and is not considered part of the ongoing consistency assurance and/or process control (Yu, 2008). A key element in the QbD paradigm is the design space. A design space is defined by Q8 as 'the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality'. Q8 further notes that: 'Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post-approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval'.

The determination of a design space requires a combination of experimental data and mechanistic knowledge of chemistry, physics and engineering to model and predict performance. Statistical design of experiments (DOE) is used for setting up a design space. DOE is an efficient method used in industrial statistics for determining impact of multiple parameters and their interactions (Kenett and Zacks, 1998). Setting up a design space also involves scaling up studies to translate operating conditions between different scales or pieces of equipment.

Statistical analysis in product development includes model building. This consists of kinetic models such as rates of reaction or degradation, transport models of movement and mixing of mass or heat, models for manufacturing development including computational fluid dynamics, scale-up correlations and models for process monitoring or control such as chemometric models and control models. Chemometrics is the science of relating measurements made on a chemical system or process to the state of the system via application of mathematical or statistical methods. Measurements are integrated in a process control strategy that involves modeling, multivariate analysis and Statistical Process Control (Kenett and Zacks, 1998; Fuchs and Kenett, 1998). All such models require verification through statistical analysis.

The following provides more details concerning the ICH Q8, Q9 and Q10 Quality guidelines.

Guideline Q8, entitled Pharmaceutical Development, has been revised twice up to August 2009. The guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 CTD format. This section is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product. The pharmaceutical development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

The Q8 guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well.

Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support the establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful.

Guideline Q8 notes that 'At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.'

The elements of pharmaceutical development consist of a quality target product profile (QTPP), critical quality attributes (CQAs), a risk assessment linking material attributes and critical process parameters (CPPs) to drug product CQAs, a design Space and a control Strategy. The definitions of these terms are given in Q8 as follows. *QTPP*: 'A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.'; *CQA*: 'A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality'; and *CPP*: 'A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality'.

Document Q9, entitled Quality Risk Management, is designed to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents, and complements existing quality practices, requirements, standards and guidelines within the pharmaceutical industry and regulatory environment. Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. The basic activities concerning risk management include: *risk assessment*, which consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards; *risk identification*, which is a systematic use of information to identify hazards referring to the risk question or problem description (information can include historical data, theoretical analysis, informed opinions and the concerns of stakeholders; *risk analysis*, which is the estimation of the risk associated with the identified hazards (it is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms); *risk evaluation*, which compares the identified and analyzed risk against given risk criteria; *risk control*, which includes decision making to reduce and/or accept risks (the purpose of risk control is to reduce the risk to an acceptable level); and *risk communication*, which is the sharing of information about risk and risk management between the decision makers and others. (See Chapter 6 in this book and Kenett and Raanan, 2010.)

Document Q10, entitled Pharmaceutical Quality System, is a comprehensive model for an effective pharmaceutical quality system that is based on International Organization for Standardization (ISO) quality concepts, includes applicable GMP regulations, and complements Q8 and Q9. The ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle.

The Q10 guideline promotes a lifecycle approach to product quality by focusing on four elements: (1) process performance and product quality monitoring system; (2) corrective action and preventive action (CAPA) system; (3) change management system; and (4) management review of process performance and product quality.

Specifically, CAPA methodology should result in product and process improvements and enhanced product and process understanding. It applies to pharmaceutical development, technology transfer, commercial manufacturing and product discontinuation. Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review. The management review system should include: (1) the results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities; (2) periodic quality reviews (that can include (i) measures of customer satisfaction such as product quality complaints and recalls; (ii) conclusions of process performance and product quality monitoring; and (iii)the effectiveness of process and product changes including those arising from corrective action and preventive actions); (3) any follow-up actions from previous management reviews.

The management review system should identify appropriate actions, such as: (1) improvements to manufacturing processes and products; (2) provision, training and/or realignment of resources; and (3) capture and dissemination of knowledge.

The ICH, in the Q8, Q9 and Q10 guidelines, as well as the FDA, have been strongly promoting QbD in an attempt to curb rising development costs and regulatory barriers to innovation and creativity (FDA, 2006). The introduction of QbD offers to statisticians a level of involvement beyond the traditional role of statisticians in clinical trials (Nasr, 2007, 2009; Kenett and Kenett, 2008; Peterson *et al*., 2009a). Moreover, QbD will certainly have an impact on modern statistical methodology, bringing forth new and challenging problems that require new statistical methodologies. It is patently clear that, in addition to the key roles that statisticians play in drug discovery and development, abundant opportunities exist for statistical involvement in QbD. With QbD, statisticians can now play a key role throughout the life cycle of drug products. These opportunities are expanded upon in Section 1.6.

## 1.5 Other guidelines

The preceding sections have primarily focused on the ICH Guidelines and in particular their statistical impact and challenges. However, there is an abundance of other guidelines and documents produced by each of the three regulatory regions that deal with design or analysis issues of biopharmaceutical trials, as well as related manufacturing issues. Due to the extent of these guidelines, we only highlight a small fraction of them in this document.

The EMA has published a large number of scientific guidelines categorized in six groupings: quality, biologics, non-clinical, clinical efficacy and safety, multidisciplinary and ICH. To gage a sense of their extensiveness, we note that within the quality topics, there are 11 sub-topics and, for example, in the sub-topic about manufacturing, there are 6 adopted guidelines including process validation, a 2010 concept paper on revisions of process validation, and manufacture of the finished dosage form. Within clinical efficacy, there are 16 sub-topics

with multiple guidelines within each of these and all mainly focused on treating specific medical conditions. In addition the EMA has published a number of concept papers in a series called 'Points to Consider'; some of which have later become EMA CHMP (Committee for Medicinal Products for Human Use) Guidelines. Among those of interest to statisticians are 'Points to Consider on Missing Data' (EMA, 2001), which in 2009 has been revised as a draft 'Guideline on Missing Data in Confirmatory Trials' (EMA, 2009); 'Guideline on the Choice of Non-inferiority Margin' (EMA, 2005; an earlier draft document on this topic is 'Points to Consider', EMA, 2004); 'Points to Consider on Applications with 1. Meta-analyses, 2. One Pivotal Study' (EMA, 2001); 'Points to Consider on Switching between Superiority and Non-inferiority' (EMA, 2000); 'Points to Consider on Multiplicity Issues in Clinical Trials' (EMA, 2002); 'Points to Consider on Adjustment for Baseline Covariates' (EMA, 2003); and 'Concept Paper on the Need for a Guideline on the Use of Subgroup Analyses in Randomized Controlled Trials' (EMA, 2010). While the primary EMA statistical documents are highlighted in the preceding, the many other documents in the 'Points to Consider' series and the 'Guideline' series, while focusing on other topics, do contain relevant statistical material. Collectively all these many documents are an excellent resource for those working in quality and efficacy aspects of biopharmaceutical development, although obviously with a focus on EU concerns.

The EMA document on missing data (EMA, 2009) has an extensive review of the possible biases and effects that can be caused by ignoring or not properly taking into account missing data. While not espousing any universal approaches, it does provide rules that 'should be considered' in dealing with missing data. For example, mortality results should have relatively low missingness, but it recognizes that long-term studies in a psychiatric population may have relatively higher amounts of missing data. Methods for handling missing data need to be pre-specified and well documented in the final report. There is a full discussion of various ways to handle missing data based on modeling an understanding of the missing causes, as well as a discussion of multiple imputation and mixed models as approaches. The document concludes with a discussion of sensitivity analyses to assure that the results of the trial are not sensitive to a specific missing data approach. The EMA document on meta-analysis and one pivotal study (EMA, 2001) is really two documents in one with loose connections between the topics. The meta-analysis component discusses the issues about performing a meta-analysis on the studies included in an NDA. The reasons for doing such an analysis can be varied and include, for example, subgroup analyses or evaluating apparently conflicting study results. The document indicates that the meta-analysis should follow a detailed pre-specified protocol completed before any trial results are known; ideally prepared when developing the clinical development program. In those infrequent cases where the meta-analysis is not anticipated, but is carried out to integrate results from conflicting study results, the document addresses how to try to maintain credibility of the meta-analysis.

The FDA has a series of 'Guidances' that represent the FDA's current thinking on a topic. The list of guidance documents is extremely lengthy, with 30 subgroups, again with each subgroup consisting of multiple finalized and draft guidance documents. Three subgroups that directly deal with quality are 'Current Good Manufacturing Practices (CGMPs)/Compliance', 'CMC' (Chemistry, Manufacturing, and Control), and 'CMC – Microbiology'. The guidance on Process Validation: General Principles and Practices (FDA, 2011) outlines the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients. It incorporates principles and approaches that all manufacturers can

use to validate manufacturing processes. Process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. In this context, manufacturers should (1) understand the sources of variation, (2) detect the presence and degree of variation, (3) understand the impact of variation on the process and ultimately on product attributes, and (4) control the variation in a manner commensurate with the risk it represents to the process and product.

Guidances of substantial statistical interest concerning drug development can be found under a variety of topics. Illustrative of these guidance documents are 'Statistical Approaches to Establishing Bioequivalence' (FDA, 2001); 'Exposure-Response Relationships – Study Design, Data Analysis, and Implications for Dosing and Labeling' (FDA, 2003); 'Non-Inferiority Clinical Trials' (FDA, 2010a); and 'Adaptive Design Clinical Trials for Drugs and Biologics' (FDA, 2010b), where the last two are both in draft form.

The FDA draft guidance document concerning non-inferiority clinical trials is pertinent to such trials under the purvey of either the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER). This guidance begins with a general discussion of issues concerning non-inferiority trials, and then follows this section with a more detailed discussion of methodology to establish a non-inferiority margin and a comparison of methods, and ends with a section considering practical advice and an appendix providing examples of successful and unsuccessful non-inferiority trials. The first two sections provide a clear conceptual introduction to the rationale of non-inferiority designs, possible designs and methods, and approaches to obtain $M_2$, the largest clinically acceptable difference. Five interesting examples of non-inferiority trials drawn from public sources are given in the appendix.

The adaptive designs FDA draft guidance document is a major document discussing the important issues facing sponsors who are considering adaptive clinical trials to expedite drug development. Adaptive trials allow the change of the design of a clinical trial at interim points in the trial based on accumulating trials data, and are viewed as 'learning' as the trials proceeds. (For a general framework for sample size adaptive designs see Koyama, Sampson and Gleser, 2005a, and for adaptive designs in non-inferiority trials see Koyama, Sampson and Gleser, 2005b). There is a statistical cost for this trial-based gain in knowledge, and this FDA document requires characterizing this cost in a regulatory acceptable way. Besides providing general background and concerns about adaptive designs, the guidance dichotomizes adaptive designs into the two groups 'generally well-understood adaptive designs' and 'adaptive designs whose properties are less well understood'. Examples of the former are designs based on blinded interim analyses and, of the later, designs based on unblinded interim effect size estimates. For the well-understood designs there are valid implementation approaches, and for the less well-understood designs, this draft guidance discusses some relevant statistical considerations. Also discussed are the contents of an adaptive design protocol, as well as an indication of the interactions between a sponsor and the FDA when a sponsor is planning an adaptive design.

The Pharmaceuticals and Medical Devices Agency (PMDA) of Japan has some limited guidance documents in English, especially in terms of manufacturing and quality issues. The most relevant of these are 'Guideline for Descriptions on Application Forms for Marketing Approval of Drugs' (PFSB, 2007), which indicates the manufacturing method details to be included on marketing approval applications, and 'Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Drugs and Quasi-drugs' (MHLW, 2004).

Other than the ICH Guidelines there are very limited indications about statistical issues in any of the other guidance-type documents.

## 1.6 Statistical challenges in drug products development and manufacturing

This section highlights some key statistical challenges in the modern pharmaceutical industry. Context to these challenges is provided by the 2004 FDA Report 'Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products' (FDA, 2004). This report addresses in a clear way the challenges in overcoming the gap between scientific discoveries and their translation into modern medical treatments and also the opportunities to those involved with product development and manufacturing in transforming these processes to overcome this gap. Following the publication of this groundbreaking report, the FDA in 2006 issued a report entitled 'Critical Path Opportunities List'. The report lists specific examples where there are opportunities for innovation in the sciences and technology of product development. Some of the areas where the challenges clearly relate to statistics are in 'streamlining clinical trials', 'harvesting bioinformatics' and 'moving manufacturing into the 21st century'. Illustrative of these areas of statistical opportunities are furthering innovative trial designs concerning which the report focuses on active controlled trials, enrichment designs, integrating prior evidence for designs, adaptive designs, handling missing data, and dealing with multiple endpoints.

The challenges concerning manufacturing described in the 'Critical Path Opportunities List' report are grouped into manufacturing biologics, manufacturing devices, manufacturing drugs and dealing with nanotechnologies.

In 2008 the FDA issued an additional report addressing safety monitoring; in particular, monitoring the safety of a product throughout its entire life cycle. The report entitled 'The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety' (FDA, 2008) addresses a breadth of concepts focusing on using modern information technology to identify, in a timely fashion, previously unknown risks of medical products, learn about their patterns of use, and assess the outcomes associated with them. The report discusses FDA activities in the context of risk identification, risk assessment and risk minimization. While statistical opportunities in this initiative are not overtly discussed, there are clearly opportunities for innovative statistical methods to detect and describe safety issues in a timely fashion.

Others, outside the regulatory arena, have also identified the challenges for statisticians. For instance, Peterson *et al*. (2009b) identified a number of factors that are converging to increase the need for sophisticated, statistics-driven approaches to quality and process understanding in the pharmaceutical industry. These include the following.

1. **Regulatory trends:** as clearly described in this chapter, a substantial driver is regulatory agencies that require new, more statistically rigorous and risk-based ways of conducting drug development and manufacturing.
2. **Inherent characteristics of pharmaceutical manufacturing:** in pharmaceuticals it is difficult to tightly connect product specifications to product performance. For example, 'tablet dissolution' rates cannot be clearly linked to drug efficacy and safety over a vast array of potential product users, each with different body size, age, lifestyle, genetics

and drug metabolism chemistries. Furthermore, pharmaceutical companies must maintain quality in a many-step production process that creates a complex molecule that must have the proper molecular structure and be free of serious chemical impurities or biological contaminants. In addition, up to now, there has been a lack of incentive for continuous improvement in pharmaceutical manufacturing after regulatory approval. This is due primarily to the fact that substantial changes in the manufacturing process or recipe required formal regulatory approval. Recently, QbD guidance has been introduced to provide more flexibility with regard to continuous improvement in manufacturing. However, pharmaceutical manufacturers will have to show clear process understanding and prediction ability in order to be granted such flexibility. To meet all these complex challenges, pharmaceutical companies need more, not less, statistical thinking and practice.

3. **Economic pressures:** many companies, faced with thin product pipelines, major patent expirations and downward pressure on pricing, attempt to cut their manufacturing costs, improve yield and productivity, and generate bottom-line savings that can be used to drive growth and innovation. Statistically driven improvement methodologies found in QbD are critical for success in these efforts. The same economic pressures drive the need for more efficient and adaptive designs, better ways of integrating and accumulating product performance during development, and innovative use of simulation and computer modeling.

4. **Increased need for effective technology transfer:** virtually every drug at some stage of its development or manufacture must be transferred from one site to another. Furthermore, mergers, acquisitions, the rise of 'global' generics, the ongoing rationalization of manufacturing and other factors have increased the frequency with which pharmaceutical manufacturing organizations must effectively and efficiently transfer products and manufacturing processes from one location to another. Successful transfer requires a degree of understanding of products and processes that can be greatly improved by statistical techniques.

The effects of multinationalism are also seen in the need for innovations in designing and analyzing multinational clinical trials, as well as developing the designs and statistical methods for bridging studies (as elaborated upon in ICH E5) in order to gain approval of a product in a new region based upon approvals in another region.

Peterson *et al*. (2009a) further note that 'As these trends continue and converge, the role of statistics and statisticians will only grow larger in the industry.'

## 1.7 Summary

This chapter reviewed guidelines and guidance documents regarding safety, efficacy and quality of drug products. These guidelines directly affect drug development, clinical research and drug product manufacturing. The Quality by Design initiative is providing an integrated view linking patients, products and processes in order to achieve safety, efficacy and quality in an economic way.

Section 1.3 described in detail the ICH guidelines concerning efficacy. These guidelines, adopted by the three major regulatory regions, directly impact how biopharmaceutical clinical

development is conducted. From a statistician's perspective, E9, 'Statistical Principles for Clinical Trials' provides a clear discussion of the statistical principles and methods for designing and analyzing pharmaceutical clinical trials. Since its completion in 1998, new analytical issues have arisen for clinical trials that present further challenges to regulators and statisticians. Some of these challenges were highlighted in Section 1.5.

In Section 1.4 we mentioned that a design space of a drug product is the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Including a design space in a new drug application is a key element of the Quality by Design initiative. Working within the design space is not considered a change requiring regulatory approval. Movement out of the design space is considered to be a change, and requires a regulatory post-approval change process. This difference has significant impact on the bilateral relationships between industry and the regulator. It requires shifting from a paradigm of 'Tell' and 'Do', where no preapproved change is allowed, to 'Do' and 'Tell', where industry has the freedom to improve products and processes, within the boundaries of the knowledge supported by evidence in the drug product application. Statisticians can play a significant role in gaining and documenting such knowledge.

Bayesian methodology is being employed in both development and quality. A Bayesian approach to setting up a design space was proposed by Peterson (2004, 2008). This approach accounts for model parameter uncertainty and correlation among the CQAs. The paper by Stockdale and Cheng (2009) includes examples where this approach is applied to identify a reliable operating range. Fuchs and Kenett (1998, 2007) describe multivariate methods for achieving process control and determining process capability, and Kenett and Kenett (2008) present Bayesian methods for combining information from simulation and physical experiments with expert opinions, in order to derive a comprehensive design space.

Incorporating modern statistical methods in the life cycle of a drug product, from its development to its manufacturing and delivery is what this whole book is about. This first chapter has set the regulatory context that is an essential pillar in the overall system which includes patients, the pharmaceutical industry and regulatory agencies.

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