Chapter 1
Introduction

Keywords Chemistry, Manufacturing, and Controls (CMC) statistics • Clinical statistics • Pharmaceutical activities • Regulatory guidance • Statistical methods

1.1 Objectives

The motivation for this book came from an American Association of Pharmaceutical Scientists (AAPS) short course on statistical methods applied to Chemistry, Manufacturing, and Controls (CMC) applications presented by four of the authors. One of the course participants asked us for a good reference book, and the only book we could recommend was written over 20 years ago by Chow and Liu (1995). We agreed that a more recent book would serve a need in our industry. This book presents statistical techniques that are critically important to CMC activities.

Statistical methods are presented with a focus on applications unique to the CMC pharmaceutical industry. The target audience consists of statisticians and other scientists who are responsible for performing statistical analyses within a CMC environment. Basic statistical concepts are addressed in Chap. 2 followed by applications to specific topics related to development and manufacturing. The mathematical level assumes an elementary understanding of statistical methods. The ability to use Excel or statistical packages such as Minitab, JMP, or *R* will provide more value to the reader.

Since we began this project, an edited book has been published on the same topic by Zhang (2016). The chapters in Zhang discuss statistical methods for CMC as well as drug discovery and nonclinical development. We believe our book complements Zhang by providing more detailed statistical analyses and examples.

1.2 Regulatory Guidance for CMC Applications

Persons responsible for statistical analyses in CMC applications should be familiar with guidance and regulations that pertain to the pharmaceutical industry. The legality of CMC issues is covered in the Code of Federal Regulations (CFR),

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Title 21, Food and Drugs Administration (FDA). Several relevant sections of this code are reported in Table 1.1.

In addition to the CFR, regulatory agencies have produced a number of useful documents that direct the approaches used in statistical analysis. Tables 1.2, 1.3, 1.4, and 1.5 report documents referenced and discussed in this book.

1.3 Use of Statistical Tools in Pharmaceutical Development and Manufacturing

This book focuses on statistical methods used in the development and manufacturting of pharmaceutical products. An excellent description of this area is presented by Peterson et al. (2009). Pharmaceutical products are developed over five parallel activities:

1. Clinical trials,
2. Preclinical assessment,
3. Active pharmaceutical ingredient (API) development,
4. Drug product (DP) formulation, and
5. Analytical method development.

Table 1.1 Important sections of 21 CFR

Source	Title
Code of Federal Regulations, Title 21, Food and Drugs Administration (FDA), Part 210 (21 CFR 210)	Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs
21 CFR 211	Current good manufacturing practice for finished pharmaceuticals
21 CFR 600	Biological products: general
21 CFR 820	Quality system regulations

Table 1.2 Useful regulatory statistical guidance ASTM international

Title	Chapter
E29: Standard practice for using significant digits in test data to determine conformance to specifications	2
E2281: Standard practice for process capability and performance measurement	5
E2475: Standard guide for process understanding related to pharmaceutical manufacture and control	4
E2587: Standard practice for use of control charts in statistical process control	5
E2709: Standard practice for demonstrating capability to comply with an acceptance procedure	7
E2810: Standard practice for demonstrating capability to comply with the test for uniformity of dosage units	7

Table 1.3 Useful regulatory statistical guidance Food and Drug Administration, Center for Drugs Evaluation Research (FDA,CDER)

Title	Chapter
Guidance for industry: immediate release solid oral dosage forms, scale-up and postapproval changes: chemistry, manufacturing and controls, in vitro dissolution testing, and in vivo bioequivalence documentation (1995)	7
Guidance for industry: demonstration of comparability of human biological products, including therapeutic biotechnology-derived products (1996)	9
Guidance for industry: SUPAC-MR modified release solid oral dosage forms, scale-up and postapproval changes: chemistry, manufacturing and controls, in vitro dissolution testing, and in vivo bioequivalence documentation (1997a)	7
Guidance for industry: dissolution testing of immediate release solid oral dosage forms (1997b)	7
Guidance for industry: ANDAs: blend uniformity analysis (1999 withdrawn 2002)	7
Guidance for industry: powder blend and finished dosage units—stratified in-process dosage unit sampling and assessment (October 2003 withdrawn 2013)	7
Guidance for industry: process validation: general principles and practices (2011)	3, 5, 6, 9
Guidance for industry: quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product (2015a)	9
Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product (2015b)	9
Guidance for industry: biosimilars: questions and answers regarding implementation of the biologics price competition and innovation act of 2009 (2015c)	9
Guidance for industry: analytical procedures and methods validation for drugs and biologics (2015d)	6

Figure 1.1 from Peterson et al. displays the timeline for these activities.

While the most common area for statisticians to work is in the clinical area (activities 1 and 2), the focus of this book is on paths 3–5 in Fig. 1.1. Key research questions and statistical methods used to help answer them are shown in Table 1.6.

Statistical quality control methods are applied throughout all activities in Phase IV. These methods are discussed in Chap. 5.

1.4 Differences Between Clinical and CMC Statisticians

To better understand the nature of CMC statisical analysis, it is useful to contrast this work to that of the clinical statistician. The role of a clinical statistician is well established. It is required and integrated into regulations and internal business processes. Often, these predefined roles and responsibilities are outlined in company procedures. Given the key role they play in the clinical drug development process, the clinical statistician is well linked into clinical project teams with strong management support. Among their many responsibilities, clinical statisticians are responsible for statistical design of clinical trials and statistical analysis plans included in protocols which are sent to the FDA for review. These protocols are

Table 1.4 Useful regulatory statistical guidance International Conference on Harmonization (ICH)

Title	Chapter
Q5C stability testing of biotechnological/biological products (1995)	8
Q1B photostability testing of new drug substances and products (1996)	8
Q1C stability testing for new dosage forms (1997)	8
Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances (1999a)	3, 7, 8
Q6B specifications: test procedures and acceptance criteria for biotechnological/biological products (1999b)	7, 8
Q7 good manufacturing practice guide for active pharmaceutical ingredients (2000)	4
Q1D bracketing and matrixing designs for stability testing of new drug substances and products (2002)	8
Q1A(R2) stability testing of new drug substances and products (2003a)	8
Q1E evaluation for stability data (2003b)	7, 8
Q3A impurities in new drug substances (2003c)	8
Q3B (revised) impurities in new drug products (2003d)	8
Q5E comparability of biotechnological/biological products subject to changes in their manufacturing process (2004)	2, 9
Q2(R1) validation of analytical procedures: text and methodology (2005a)	6, 8
Q9 quality risk management (2005b)	3–5
Q10 pharmaceutical quality system (2008)	3, 5
Q8(R2) pharmaceutical development (2009)	3, 5
Q11 development and manufacture of drug substances (chemical entities and biotechnological/biological entities) (2012)	3

Table 1.5 Useful regulatory statistical guidance United States US Pharmacopeial (USP)

Title	Chapter
⟨905⟩ Uniformity of dosage units	7
⟨1010⟩ Analytical data—interpretation and treatment	2, 6
⟨1030⟩ Biological assay chapters—overview and glossary	6
⟨1032⟩ Design and development of biological assays	6
⟨1033⟩ Biological assay validation	6
⟨1160⟩ Pharmaceutical calculations in prescription compounding	8
⟨1223⟩ Validation of alternative microbiological methods	6
⟨1224⟩ Transfer of analytical procedures	6
⟨1225⟩ Validation of compendial procedures	6
General notices 3.10: conformance to standards, applicability of standards	7
General notices 7.20: rounding rules	2, 7

very detailed and provide clear articulation of the exact analyses to be followed and the specific endpoints that must be met for clinical success. These protocols typically are based on regulatory requirements. The FDA has a team of statistical reviewers that evaluates the protocols and the definitive pass/fail nature of these

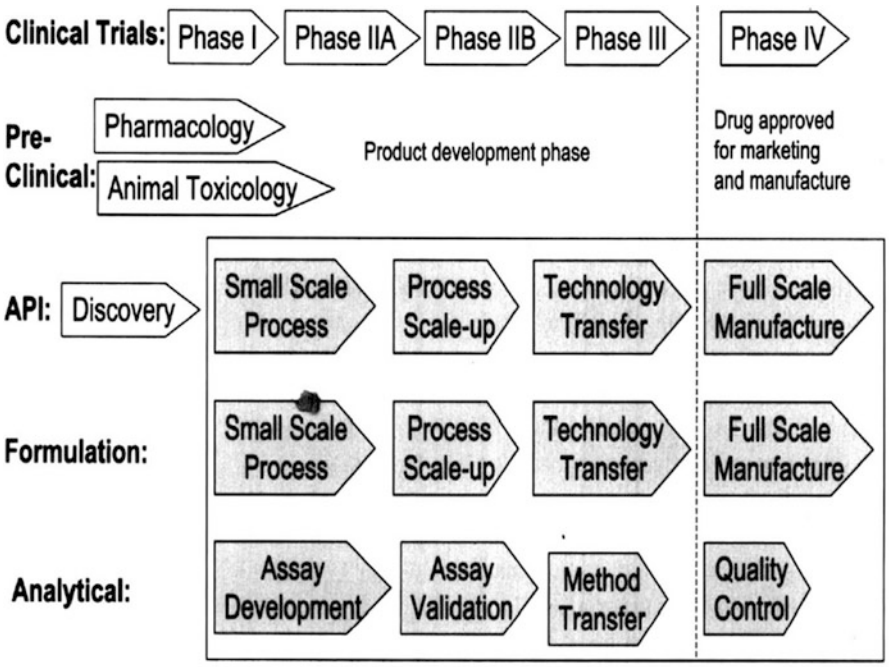

Fig. 1.1 Pharmaceutical activities

Table 1.6 Research questions and statistical methods

Activity	Research questions	Book chapter with application
API development	How can API be scaled to a level required for commercial market?	4
API development	How do we effectively characterize our product and develop a knowledge base for the API?	3, 4
DP formulation	What shelf life limits and specifications need to be established to ensure DP is safe and efficatious?	7, 8
DP formulation	If our process is transferred to another manufacturing site, how do we ensure product safety and efficacy are not impacted?	9
Analytical method development	How do we determine if analytical methods are fit for use?	6
Analytical method development	How do we know if a method will perform the same in two different labs?	6

criteria heightens the criticality of the statistician on the cross-functional team. There is much external guidance that must be followed and the clinical statisticians must follow strict documentation expectations. Data systems are well developed

and SAS and R are common data analysis tools. Other software packages are rarely used except for occasional exploratory work. Upon completion of the clinical study, the clinical statistician co-authors reports with clinical colleagues which are included in the regulatory submissions. Given the existing system, the clinical statistician does not spend a significant portion of time training their clinical colleagues to perform their own statistical analyses. Most of their interaction with colleagues involves discussions to help them understand and correctly interpret the statistical analyses completed by the statistician. In order to be the most successful, clinical statisticians must understand the science of the disease so that they can add value to the project team.

Although there are similarities between the roles of the CMC and clinical statisticians, there are differences in both type and degree. CMC statisticians work with scientists to help develop new drug substance and drug product manufacturing processes, develop and validate analytical procedures, improve existing processes and products, and troubleshoot systems when issues arise. Unlike the clinical statistician, the role of the CMC statistician does not have a regulatory requirement and as such, the nature of the role can vary both within and across companies. Factors impacting these differences include the technical and interpersonal skills of the statistician, the nature of management support, and the strength of the partnership with individual collaborators. Small, relatively short duration studies are common as opposed to large clinical trials and access to large data sets created to satisfy Good Manufacturing Practice (GMP) or regulatory requirements are the exception rather than the rule. Unlike the large and well-defined statistical departments in the clinical organization, CMC statisticians often work alone or in very small groups. The CMC statistician may report to management in the area they support, or to the broader clinical organization. Good documentation practices are important for the CMC statistician to adhere to GMP requirements but there are no statistical protocols sent to regulatory agencies for review. In the CMC area, studies are performed and documented internally so as to be available if requested by regulatory agencies. Documentation in these reports must be clear so that analyses can be explained and reproduced when necessary. Given that data sets are often small, data analysis packages such as Minitab and JMP are commonly used to perform calculations. SAS and R are also employed with larger data sets, or when requests are made from regulatory agencies. Because the CMC statistical workforce is relatively small, CMC statisticians spend time teaching their scientific collegues how to peform their own statistical analyses. This is one reason why statistical packages that do not require written code (e.g., JMP and Minitab) are often selected for analysis. Similar to the clinical statistician, the CMC statistician often contributes to the contents of a regulatory submission. CMC statisticians help write sections describing process and formulation development, stability, justification of specifications, process and product comparability, and analytical method validations. Similar to clinical statisticians, the CMC statistician must understand the science and engineering concepts of their collaborators in order to be successful.

1.5 How to Use This Book

It is possible to gain a working understanding of the methods in this book with no advanced statistical training. In fact, one objective of this book is to make these methods available for scientists who do not possess a degree in statistics. Professional statisticians will also find it helpful to have these methods in a single source for their own use and for training others.

Chapter 2 provides statistical methods that are useful for performing the analyses required to address research questions in the CMC manufacturing environment. We recommend that the reader begin by reading Sects. 2.1–2.5. This provides both a high level view of statistical applications and some specific examples for simple data sets. After reading this material, the reader may complete Chap. 2, or jump to any particular application of interest in Chaps. 3–9. Where needed, Chaps. 3–9 refer back to statistical methods in Chap. 2 where the reader is provided a more thorough understanding of the statistical method. Worked numerical examples are provided in all chapters.

The reader may use any number of statistical packages to help work the examples. Many of the examples can be performed using Excel. Some require user-friendly statistical packages, such as Minitab and JMP. Additionally, we have provided data sets and program codes written in SAS and R at the website for many of the examples. Discussions of the examples will focus on the output rather than specific code used to generate the output.

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