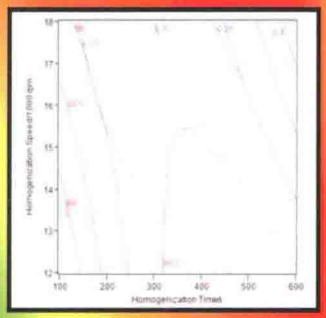
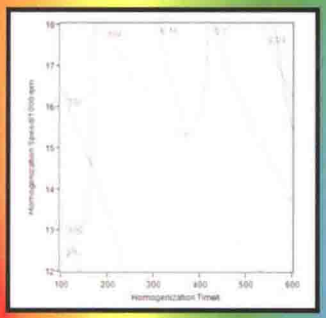
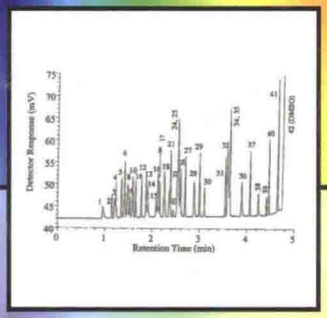
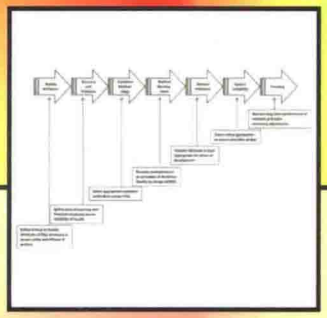
SPECIFICATION OF DRUG SUBSTANCES AND PRODUCTS

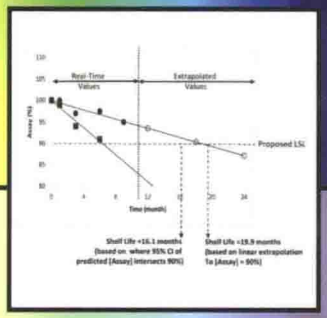
DEVELOPMENT AND VALIDATION OF ANALYTICAL METHODS











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Introduction

1

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CHAPTER OUTLINE

When the first version of this book was published in 1996,[1] The International Conference on Harmonization (ICH), which is an effort by the USA, the EU and Japan to harmonize new drug applications, was still in its infancy. Since then, all the key ICH Quality Guidelines[2–26] covering specification setting (e.g. ICH Q1,[2–8] Q3–Q6)[9–21] and method validation (ICH Q2)[6] have been published, and some have been revised at least once. The ICH Guidelines, together with some of the more recent changes in regional guidelines and compendial requirements will form the general framework for this book. Where the Quality (Q1–Q11) ICH Guidelines fit into the general drug development framework is shown in Fig. 1.1.

The introduction of the earlier ICH Quality Guidelines (Q1–Q6),[2–21] which describe most of the general requirements for the analytical content of the Common Technical Document (CTD, ICH M4Q(R1))[22] and its electronic counterpart (eCTD), was followed by a series of guidelines (Q7–Q10) addressing some of the key approaches to drug development that are also to be included in the CTD. Although there are some regional differences, the CTD is the generally harmonized document used in the ICH regions for marketing authorization applications. The general framework of the CTD is also used, with appropriate modifications, for clinical trials applications. The CTD is also accepted in many non-ICH countries, such as Canada and Australia.

According to the ICH definition, the specification(s) for a new drug substance or a drug product (Q6A and Q6B) contain three elements: (1) the quality attributes (or tests), (2) references to the associated methods and (3) the acceptance criteria. The primary objective of this book is to provide a critical and comprehensive assessment of the approaches used to identify what are the key quality attributes that impact safety, efficacy, and manufacturability, select appropriate analytical methods based on the accuracy and precision needed to adequately measure and control the identified quality attributes and determine how the analytical methods are developed and validated for their intended use. The general principles of the specification-setting process are surveyed in Chapter 2 and explored in greater detail in Chapters 5–15. Chapter 16 deals with the development and validation of bioanalytical methods.

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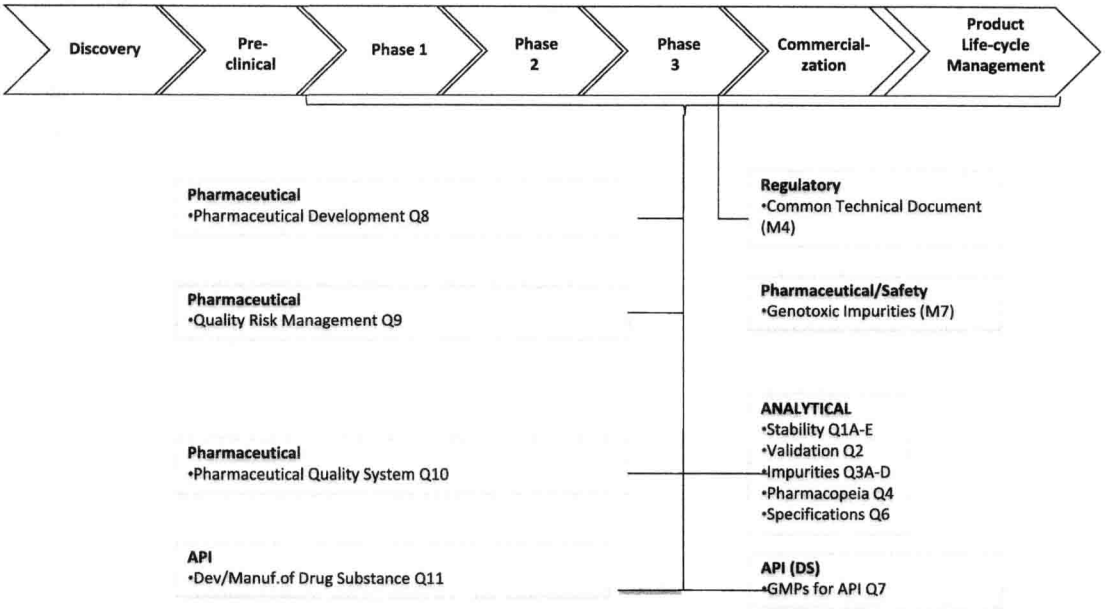

FIGURE 1.1

Summary of the ICH Guidelines applicable to pharmaceutical analysis (see also Refs 2–25) and where they fit into the drug development process.

The concept of Quality by Design (QbD) was introduced into the drug development process through the more recent ICH Guidelines (Q8–Q10)[23–25] with the primary aim of increasing the understanding and the knowledge base of the processes for the manufacturing of drug substances and products. However, the principles of QbD are equally applicable to pharmaceutical analysis. Therefore, the concept of Analytical Quality by Design (AQbD) is introduced in Chapter 3 and expanded in later chapters. Since the publication of the first version of this book, the key ICH Quality Guidelines have matured and now form the general framework for the application of worldwide marketing approvals of new drug products.

Whereas the guidelines dealing with specification setting (most notably ICH Q6A and Q6B) and Method Validation (Q2) describe what information regulators expect to see in a new drug application, they provide very little detail on how the guidelines are to be implemented at the technical level. The absence of specific direction on the implementation of the ICH Quality Guidelines allows for the application of new and improved analytical technologies targeted to the critical quality attributes which impact product performance. The use of statistical approaches to better correlate method performance with respect to control limits for critical quality attributes and to monitor long-term analytical method performance is an area which is not discussed within the guidances, but is critical to the development and maintenance of analytical methods. Whereas Chapters 2 and 3 survey the general principles of specification setting and QbD, respectively, Chapter 4 discusses conventional approaches to method validation. The ICH Guideline on Method

Validation (Q2(R1)) was primarily developed with separation techniques in mind and the following tests in particular:

- Identification tests
- Quantitative tests for impurities content
- Limit tests for the control of impurities
- Quantitative tests of the active moiety in samples of drug substance and drug product or other selected components in the drug product (e.g. preservatives, antioxidants)

Subsequent chapters will discuss how the principles of method validation set forth in Q2(R1) have been adapted to techniques as diverse as solid characterization and microbiological methods.

In keeping with the spirit of the first version of this book, this version is not intended as merely a review of existing regulatory guidance and industry practices. Rather, in addition to discussing conventional approaches, each chapter will address critical issues and novel approaches. The authors have been carefully selected as being former members of the ICH Expert Working Groups charged with developing the ICH guidelines, and/or subject-matter experts in the industry, academia and government laboratories. Thus, the book will provide the reader with not only an understanding of industry best practices and future directions, but also an insight into how international guidelines were developed and the rationale behind them.

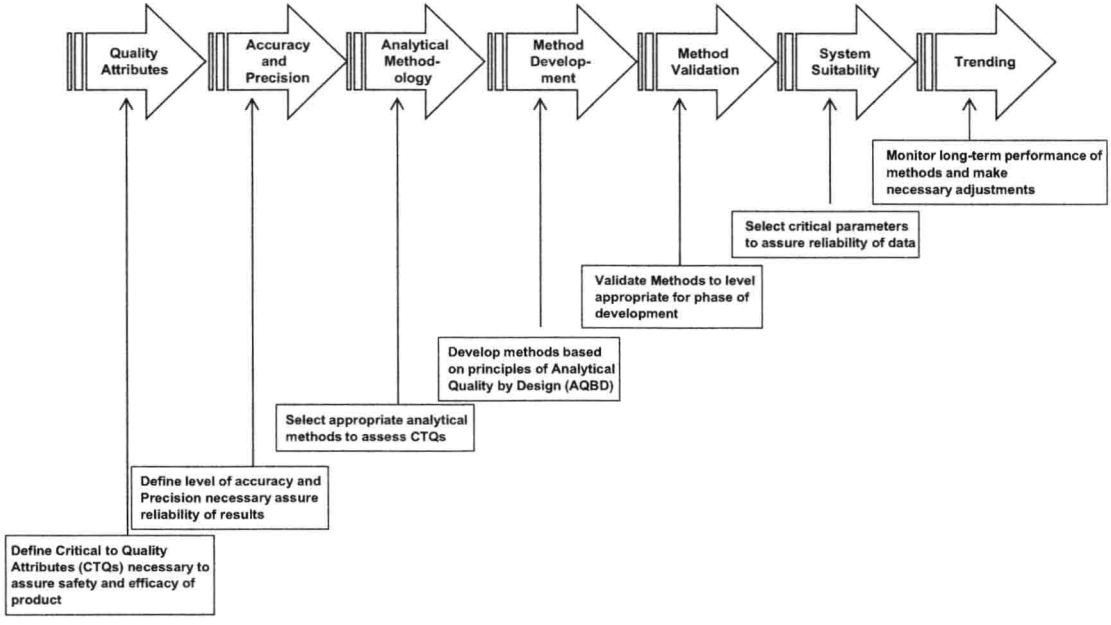

FIGURE 1.2

The evolution of analytical technology for the control of pharmaceuticals through the life cycle of the development process.

In addition to providing the "what" but not the "how" to set specifications and validate analytical methods, the ICH Quality Guidelines (Q1–Q6)[2–20] only define what is to be provided in a new drug application. They expressly exclude what is expected in the clinical stages of drug development (i.e. in an Investigational New Drug Application, IND). Therefore, a common theme throughout the book is how the methods are validated and specifications evolve over the drug development life cycle (Fig. 1.2). The intention in writing the second version of the book is to capture the many regulatory and technical advances that have occurred in the field since publication of the first version in 1996.

The "how" of the earlier Q1–Q6 Guidelines are to be applied is described in large part in subsequent guidelines (Q7–Q11). For example,[27] 16 attributes were identified for a polymeric excipient, derived from a natural product, and used in sustained release product to control the potentially variable performance of the excipient in the product. The only way to manage the 16 attributes and achieve acceptable product performance was to understand the contributions of the various attributes and the interactions between them—between each physical and chemical characteristic. By analytically measuring each of the attributes and then using statistical/chemometric approaches, it was possible to define a "design space" of all parameters which could deliver the overall desired effect of drug release.

Thus, this version is intended to be not only a review of the ICH Guidelines relating to the specification and method validation of new drugs, but also to provide a critical analysis of the regulatory guidelines and a comprehensive treatment of how those guidelines are applied to the development of new drugs. It is intended to be an educational tool and a reference source for those involved in the development and regulation of new drug products.

References

1. Development and Validation of Analytical Methods. In Riley, C. M., Rosanske, T. W., Eds.; *Progress in Pharmaceutical and Biomedical Analysis,* Vol. 3, Elsevier, 1996.
2. Stability Testing of New Substances and Products (Q1A(R2)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* Second Revision, 2003.
3. Stability Testing: Photostability Testing of New Drug Substances and Products (Q1B). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 1997.
4. Stability Testing: New Dosage Forms (Q1C). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 1997.
5. Bracketing and Matrixing Design for Stability Testing: New Drug Substances and Products (Q1D). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 2002.
6. Evaluation of Stability Data (Q1E). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 2003.
7. Stability Data Package for Registration Applications in Climatic Zones III and IV (Q1F). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 2006.
8. Validation of Analytical Procedures: Text and Methodology (Q2(R1)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* First Revision, 1995.
9. Impurities in New Drugs Substances (Q3A(R2)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* Second Revision, 2002.

10. Impurities in New Drugs Products (Q3B(R2)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* Second Revision, 2002.
11. Impurities: Guideline for Residual Solvents (Q3A(R5)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* Fifth Revision, 2010.
12. Impurities: Guideline for Metal Impurities (Q3D). Concept Paper. *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 2009.
13. Pharmacopeial Harmonization (Q4A). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, in development*, Unpublished.
14. Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions (Q4B). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 2007.
15. Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (Q5A(R1)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* First Revision, 1997.
16. Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (Q5B). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 1995.
17. Stability Testing of Biotechnology/Biological Products (Q5C). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, 1995.
18. Derivation and Characterization of Cell Substrates Used for Production of Biotechnology/Biological Products (Q5D). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 1997.
19. Comparability of Biotechnology/Biological Products Subject to Changes in their Manufacturing Process (Q5E). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 2004.
20. Specification: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Q6A). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 1999.
21. Specification: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products (Q6B). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* 1999.
22. The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use,* First Revision, 2002.
23. Pharmaceutical Development (Q8(R2)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.* Second Revision, 2009.
24. Quality Risk Management (Q9). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.* Second Revision, 2005.
25. Pharmaceutical Quality System (Q10(R4)). *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.* Fourth Revision, 2009.
26. Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceutical to Limit Carcinogenic Risk. *The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*, Final Concept Paper, 2010.
27. Brown, B.; Caster, D.; Clarke, B.; Hopkins, S.; Llewelyn, J.; Martin, L.; Meehan, E.; Timko, R.; Yang, H. *Extended Release Formulations Comprising Quetiapine and Methods for their Manufacture,* 2011. United States Patent Application, US 2011/0319383.