Chapter 1
Introduction

Kim Huynh-Ba

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Abstract The purpose of this chapter is introducing the goal of stability testing and its role in the Drug Development Process. It gives a brief overview of how stability studies are designed to support the development and commercialization of a new medicine. This chapter also acquaints the reader to the content of this book.

1.1 Stability

Stability is a critical quality attribute of pharmaceutical products; therefore, stability testing plays a crucial role in the drug development process. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environment factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf-life for the drug product and recommended storage conditions [1]. Therefore, it encompasses all the phases of the drug development process. A testing program for stability samples requires a tremendous amount of

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resources and expertise; however, many stability analysts are not aware of the purposes of these studies and how these studies support the decision-making activities during the drug development process. This chapter will discuss the purposes of the development phases of pharmaceutical products and how they affect the stability program.

1.2 Drug Development Process

The drug development process is a time-consuming process. It would take over 10 years to bring a new chemical entity (NCE) to the market. The drug development process generally consists of three periods: discovery/toxicology, clinical development, and commercialization.

1.2.1 Toxicological Phase

An Investigational New Drug (IND) application is the first regulatory step in the drug development process. The discovery/toxicology (pre-IND) period is where studies are conducted on animals with the purpose to understand the safety and biological activity of the NCE. This phase mainly consists of appropriate animal studies. Characterization of the Active Pharmaceutical Ingredient (API) and drug product must also be well studied to support the IND submission.

1.2.2 Clinical Phases

After the IND submission, the clinical development period starts with four main phases. Phase I concentrates on evaluating the safety and tolerability of the drug product on healthy volunteers. Phase II, focusing on patients, studies efficacy, and extended safety assessment. End of Phase II marks an important go/no-go decision. If promising, Phase III will be initiated on a larger scale with patients to link safety, efficacy, and effectiveness. A New Drug Application (NDA) will be submitted at the end of Phase III to the FDA. Phase IV may start after approval to study long-term side effects, side effects that occur after approval, or to support post-approval changes.

Table 1.1 introduces the development of a pharmaceutical product in several phases. The toxicological phases contain numerous laboratory and animal studies. The purpose of this phase is to study the safety, biological activity, and formulation of the drug substance. Due to recent developments in technology such as high throughput evaluation, genomics development, etc., many compounds have been nominated to enter this phase. After successful review of toxicological data, an IND application is filed to initiate clinical study phases.

Table 1.1 Purpose of drug development phases

Phase	Purpose	Test population
Toxicological (pre-Clinical) phase	Safety, biological activity and formulation	Laboratory and Animal Studies
	IND SUBMISSION	
Phase I	Determine safety and dosage	20–100 Healthy volunteers
Phase II	Evaluate effectiveness and look for side effects	100–500 Patient volunteers
	End-of-Phase II meeting	
Phase III	Confirm effectiveness, monitor adverse reactions from long-term use	1000–5000 Patient volunteers
	NDA/MAA SUBMISSION	
Phase IV	Additional post-marketing testing	
Commercial support	Annual Product Monitoring Post-Approval Changes	

The clinical phases are phases when API is being tested in humans. There are usually three clinical phases: Phase I, Phase II, and Phase III. These phases serve different purposes which are illustrated in Table 1.1.

Phase I studies are usually small studies, thus a stability study supporting this phase is relatively small in number of patients and short study duration. The subjects in this clinical phase are healthy volunteers and the population could range from 20 to 100 subjects. The main purpose of this phase is to determine the safety of the API and dosage form.

If successful, the API will proceed to Phase II. Phase II studies are larger and involving patient volunteers. The size of these studies is approximately 100–500 patients. The purpose of this study is to evaluate effectiveness and look for side effects. At the end of Phase II, companies are usually have an End-of-Phase II meeting with the regulatory agency to discuss the filing strategy. This is advisable before going into Phase III as Phase III usually takes up more resources and investments. Many compounds are dropped at this phase.

Phase III is an expansion of Phase II to a larger population with regards to age, gender, culture, etc. . . It involves patient volunteers at a range of 1000–5000 subjects. The purpose is to confirm effectiveness and monitor adverse reactions from long-term usage.

1.2.3 Registration Phase

Once Phase III is completed successfully, an NDA or Marketing Authorization Application (MAA) is filed with the regulatory agency. It normally takes from 6 months to a year for the review process to be completed. In general, one out of five

applications may get approved. Once approved, additional post-marketing testing may still be needed. This testing could be required by the regulatory agencies or by the company. Companies may want to expand the packaging configuration or to a different dosage strength.

Stability testing plays an important role in the drug development process. The safety and efficacy of drug products are established during development via clinical studies. If the drug product stability profile changes beyond established acceptance criteria, established safety and efficacy are no longer applicable, and thus, the safety and efficacy of the drug product may need to be re-established. This leads to additional stability studies. During the life of a drug product, there are inevitable changes, which may affect the drug product stability, thus additional studies will be necessary and further data will be needed to support these changes.

The cost of taking an NCE through the drug development process ranges from $800 million to $1.2 billion. Therefore, optimizing the drug development process, fully understanding key factors affecting the stability profile of a drug product, and executing an effective stability program are very important for product commercialization.

1.3 Introduction of this Handbook

This handbook discusses many technical issues that impact a stability program to provide a reference to develop an effective stability program. It comprises several chapters covering topics from regulations to sciences. This book is divided into three main sections: Stability Regulations, Stability Methodologies and Best Practices, and other Stability Programs.

1.3.1 Stability Regulations

Chapter 2 introduces the critical current Good Manufacturing Practices (cGMP) regulations that are applicable to a stability program. It describes different types of stability studies to support the drug development process and discusses the GMP requirements surrounding the stability sciences.

Chapter 3 discusses International Conference of Harmonization (ICH) guidelines that are related to the stability sciences. It gives a brief history of how the Q1A was initiated. A summary of Q1A(R2) discusses thoroughly the current regulations that the industry supports and practices. While this handbook was being prepared, the FDA Stability Guidance was withdrawn; therefore, a brief discussion of the guidance status has been included. A discussion of mean kinetic temperature is included to have a basis of understanding stability testing conditions.

Chapter 4 discusses global expectations of a stability program. It includes a thorough discussion of stability requirements of non-ICH regions as well as a discussion on how the climatic requirements are implied in the world. This comprehensive chapter gives an introduction of stability requirements for countries around the

world. Discussions of World Health Organization (WHO) stability guidelines and Association of Southeast Asian Nations (ASEAN) stability requirements are also included.

Chapter 5 introduces the stability studies needed to support post-approval changes. This chapter also covers change control requirements as well as documentation needed for these changes.

Chapter 6 provides a thorough discussion of several factors that may impact the chemical stability of the API in its dosage form. Understanding these factors would help one to predict shelf-life of pharmaceutical products.

1.3.2 Stability Methodologies and Best Practices

Chapter 7 focuses on how to develop stability indicating methods for API as well as drug products. It also discusses forced degradation studies that challenge the stability indicating power of analytical methods.

Chapter 8 discusses requirements of method validation and transfer. It reviews critical validation characteristics as well as summarizes ICH Q2 Validation guidelines. It also includes strategies that one may take when performing method transfer.

Chapter 9 gives an overview of the Pharmacopeia of the United States of America (USP) and its USP-NF requirements for stability purposes. This chapter also discusses the development process for monographs, the goals for the general chapters, and relevant testing used for stability studies.

Chapter 10 covers non-chromatographic test methods used to monitor stability studies. This chapter also recommends practical practices for appropriate physical testing methods. An overview of dissolution testing is also included.

Chapter 11 introduces an overview of spectroscopic tests used to support stability studies. These types of testing have gained more attention in recent years to provide additional understanding of drug substance and drug product stability.

Chapter 12 provides a review of solid state characteristics. It discusses the major physical attributes and their impact on the stability of drug substances and drug products.

Chapter 13 discusses the collection and presentation of stability data. Evaluation of data (ICH Q1E) is also discussed as well as Out-of-Specification (OOS) and Out-of-Trend (OOT) investigations. In addition, it also introduces the stability report and data trending.

Chapter 14 introduces stability chambers. It also discusses factors to be considered for chamber validation, calibration, and maintenance. This chapter also elaborates on ICH Q1B guideline, which established the requirements for photostability condition.

Chapter 15 covers critical activities necessary to maintain an effective stability program. Best practices on day-to-day operational activities such as sample pulling, testing window, and chamber inventory are included in this section to provide guidance on current industrial practices. Development of a stability protocol is also integrated together with a discussion of ICH Q1D-Bracketing and Matrixing concepts.

1.3.3 Other Stability Programs

Chapter 16 provides a general discussion of stability program for combination products or drug in devices. It covers differences in working with this type of materials as well as applicable regulations in this area.

Chapter 17 gives a general discussion of the stability program for biologics and large molecules.

1.4 Conclusion

As you can see, these 17 chapters cover several different aspects surrounding the stability programs of pharmaceutical products from pre-IND stages to post-approval. It gives a generous overview of stability regulations in the United States and ICH regions as well as in all other climatic conditions around the world. It discusses methodologies to monitor physical as well as chemical stability of drug substance and drug products. It also gives practical information to build effective systems to support stability operations.

We hope that this book will help your journey to discovering the magnitude of Stability Sciences and its significant impact in the Drug Development Process of pharmaceutical products.

Reference

1. ICH Harmonized tripartite guidelines for stability testing of new drug substances and products – Q1A(R2)