Handbook of Stability Testing in Pharmaceutical Development

Kim Huynh-Ba
Editor

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Regulations, Methodologies, and Best Practices

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A dream you dream alone is only a dream
A dream you dream together is reality
John Lennon

Preface

In my professional career as a pharmaceutical scientist, I have been involved with several aspects of the drug development process from pre-IND to commercialization and, somehow, I usually found myself coming back to a stability-related issue. The stability area seemed to draw my utmost interest because in my day-to-day work, my opportunities involved more than one product, and none of the issues were the same. Each situation posed challenges that usually required an exercise of judgment, an understanding of regulations, a knowledge of science, a grasp of compliance, and an appreciation of common practices.

Since early 2000, I have also been involved with several training opportunities and I struggled to find good, concise, practical resources, one of which I could just hand to a new scientist who wishes to gain a greater understanding of stability sciences. In addition, I encountered the same questions posted over and over on different stability best practices discussion forums.

As a book lover, I also have a good collection of technical books. Unfortunately, most of the stability related volumes are outdated. Many of these materials are theoretical and do not contain much practical information. I understand that the pharmaceutical industry during this period is quite volatile, and guidelines are changing rapidly while regulatory agencies are working closely with the pharmaceutical industry to accommodate these changes; however, the fundamental information continues to remain quite the same, just as current Good Manufacturing Practices (cGMP) continue to be the standard industry practice. Therefore, I hoped to assemble a practical handbook to fill this void.

Handbook of Stability Testing in Pharmaceutical Development is a product of several dedicated stability scientists. Collectively, we have over 300 years of experience working in all aspects of the pharmaceutical industry. This volume is intended to bring together a comprehensive overview of a stability program coupled with practical best practices. It can be used to serve the stability community as a handbook to train new scientists who find themselves involved with stability sciences in multidisciplinary functions. It can also be used in an academic setting so students can gain more practical understanding of the pharmaceutical industry.It contains

essential information to guide best practices for development and management of a compliant stability program.

July 2008 Kim Huynh-Ba

Editorial Notes

Contributing authors are responsible for the content and ideas included in their chapters. Although much information is presented and recommendations are drawn based on scientific knowledge of the experts, review perspectives may vary depending on technical background, personal experiences, and discussion preference. In addition, many references are cited from web links that appear to be valid at time of press. Great efforts were made to assure the book is as accurate as possible; however, the editor wishes to hold no responsibility for, nor can she endorse, the material published in this publication.

Acknowledgments

This project would not be possible without support from the following individuals. To them, I am in debt with appreciation.

I would like to thank all contributors for their work. They exemplify the expertise of their field and I am humble to have the privilege of editing and coordinating their work. Many of them have been my mentors, colleagues, and friends who provide enormous support throughout my professional career. I honor their trust in me leading this important project.

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Last but not least, I would like to thank my family – my husband Thai, my sons John and James – for their encouragement and for putting up with me while getting this important work done. My appreciation also goes to my parents, Mr. Hong Nguon Cao and Mrs. Kimhoa Ngoc Bach, for their unconditional support.

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Chapter 1
Introduction

Kim Huynh-Ba

Contents

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)

Part I
Stability Regulations

Chapter 2
Critical Regulatory Requirements for a Stability Program

Alvin J. Melveger and Kim Huynh-Ba

Contents

Abstract This chapter addresses the principles of stability studies in the drug development process. It gives an overview of different types of stability studies that support the entire drug development phases. It also discusses the purpose that one wants to achieve with the data set that these studies generate.

This chapter also discusses stability issues within the framework of the FDA cGMP guidelines as expressed in 21CFR Part 211. This review of cGMP regulations that tie to the stability program as well as to the testing laboratory is essential for pharmaceutical analysts to understand the process. This applies to all phases of stability studies including set up, testing, data review, and follow up on out-of-specification results.

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Details of FDA and ICH regulations are found in Chapter 3 – Understanding ICH Guidelines Applicable to Stability Testing. Other details on how to manage a stability program are addressed in subsequent chapters of this book.

2.1 Stability Role in the Drug Development Process

Stability plays an important role in the drug development process. It explains several factors that affect the expiration dating of drug products, including the chemical and physical stability during the pre-clinical formulation stages, process development, packaging development, and post-marketing life. The evaluation of the physicochemical stability of a given product requires an understanding of the physical and chemical properties of the drug substance [1]. Lack of drug substance or drug product stability may affect the purity, potency, and safety of the drug product.

Pharmaceutical stability may be applied in several ways; therefore, the performance of a drug will be evaluated depending on whether it assesses a drug substance, a formulation, a drug product, or a packaged product [2]. The safety and efficacy of a drug product are established during the development process via preclinical animal and human clinical studies. The quality attributes such as identity, concentration, and purity are defined, and testing is developed. Should drug properties change beyond the accepted criteria during a stability study, then the established safety and efficacy data may no longer be applicable. Changes in drug stability could risk patient safety, since the dosage amount to patient may be lower than expected. Instability may also lead to formation of toxic degradants.

If instability of a drug product leads to these unwelcome effects on patients, it could also lead to expensive costs to manufacturers as they attempt to discover the reasons for instability and methods of minimizing them. An unstable product would highlight an uncontrolled process, and could require a substantial product and process investigation with possible product recalls. FDA has authority to issue cGMP violations with follow-up warning letters and possible consent decrees and criminal prosecutions.

Stability testing therefore allows the establishment of recommended storage conditions, retest periods, and ultimately product shelf-life and expiry dating. Stability considerations will dictate the environment for drug substance preparation and storage, choice of packaging, and allowable shelf-life of the final drug product. Should a drug substance be sensitive to environmental factors such as temperature, humidity, pH, light and oxygen exposure, these must be considered and controlled when designing processing, storage, and final packaging of the drug product.

For example, a light-sensitive drug will require the minimization of exposure to certain light wavelengths during handling and the choice of final dispensing containers. Oxygen-sensitive materials will require handling under an inert atmosphere, such as nitrogen, and the addition of oxygen scavengers in the drug product container. In considering drug stability, attention must be paid to processes which may lead to instability of the product. The reactivity of the drug substance and the environment must be considered as well as potential interaction of all constituents in the drug product, excipients, and packaging. For liquid preparations, the possibility

of contamination by extractables from the container materials may occur during long-term storage. Container materials must be chosen to eliminate or minimize extractables.

2.2 Types of Stability Studies

Stability studies are used to provide data to support clinical trials, registration submission, or commercialization. There are different types of stability studies during the drug development process, which are diagrammed in Fig. 2.1.

Each phase of drug development requires addressing the time period that the drug product continues to maintain its specifications. This period is called *expiration dating* period of a drug product. Current GMP indicates that the purpose of stability testing of the final packaged drug product is to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use.

The use of stability testing is an integral part of the outlined development process and will be further described.

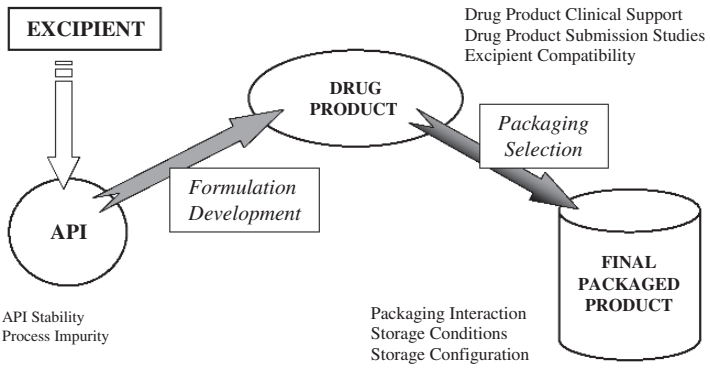

Fig. 2.1 Stability studies to support development of new drug product

2.2.1 Stability of Active Pharmaceutical Ingredient (API)

Before any formulation work is developed, it is necessary to determine the nature of the API. Its purity profile must be established and specifications set for the allowed levels of impurities. The change of impurities with storage time must be established by subjecting the API to various accelerated and stress storage conditions to establish conditions which minimize the formation of degradants. These early stability studies may determine that the API should be stored under non-ambient conditions such as low temperature, low humidity, and non-oxidizing and low-light environments. These stability studies should be continued to determine the optimum storage conditions for holding the bulk API before actual processing. Stability studies of

the API will provide data to establish a retest time for the raw materials used in the process. Stability indicating methods must be developed to monitor the purity of the API as well as identification and quantitation of impurities. If impurities are shown to be process related, then they may be monitored at release but do not need to be monitored during long-term stability. However, if any of these impurities are shown to increase during storage, or if new impurities are developed, these are referred to as "degradants" or "degradation products", and analytical methods must be developed to monitor these degradants during stability studies. Quality specifications and limits must also be set for the degradants as required by ICH.

2.2.2 Stability Studies to Support Formulation Development

Excipients or non-active constituents may be added to an API to develop a formulation which meets the intended performance criteria of the drug product. These excipients may be necessary for purposes of adding color, or controlling pH, moisture, or oxygen content. Interaction of the excipients with one another or with the API will be determined, as well as the rates of these reactions, through stability studies. Data of these studies, so-called *excipient compatibility*, will be used to determine the appropriate formulation for the drug product. If interactions occur, then the products of these interactions (degradants) must be evaluated for safety, and analytical procedures for ID and quantitation must be developed. Krummen gave an overview of some issues which can arise in stability testing during preparation development. He indicated that stability testing is a continuous process as information on the drug substance and the first provisional dosage forms is synergistic and builds the basis for the development of the dosage form which will be marketed [3].

Many companies also manufacture small batches at the extreme of the manufacturing process capabilities. These batches are then placed on stability stations to determine the stability profiles of the drug product, to better understand the process capabilities.

2.2.3 Stability Studies to Support Production and Use of Pre-clinical and Clinical Supplies

During the formulation development studies, batches are made to support clinical studies. Pre-clinical stage formulations are usually used for testing in animals. Stability studies are performed to show that pre-clinical samples maintain their specifications over the entire time span of the animal study. The formulation being tested must be stable to assure that all animals receive the nominal dose and purity from start to finish of the study.

As the drug product enters subsequent clinical phases, materials are needed to support these clinical evaluations. Stability studies are necessary to support these materials. In most cases such studies would only require long-term storage; however, most companies conduct additional accelerated or stress studies on the clinical

materials to gain more understanding of the drug product. This data set is also used to set expiry of clinical supplies.

A stability survey was done in 2007 by AAPS Stability Focus Group, benchmarking industry standards and practices of their stability operations within the pharmaceutical and biopharmaceutical industry. It noted that the majority of the industry has used ambient room temperature as the long-term storage condition to conduct stability studies to support clinical trial application.

2.2.4 Stability Studies to Support Drug Registration

Final packaged product must be shown to be stable up to at least the expiry date. These stability data are obtained by actual testing through the expiry date and beyond. Early term stability data may be submitted to FDA or other regulatory bodies to support preliminary expiry dating. These data as well as data obtained under accelerated storage conditions may be utilized to predict ultimate stability and to establish rates and kinetics of degradation.

ICH requires at least 12 month long-term stability data of three batches of drug products as necessary for drug registration. In addition, accelerated and stress studies are also conducted to establish a tentative expiration date. More detailed information on ICH guidelines are covered in Chapter 3. Global regulations are also discussed in Chapter 4.

2.2.5 Stability Studies to Support Marketed Products

Expiry dating of a drug product must be determined on the actual packaged drug product over the period of time indicated by the expiry date. Although extrapolated stability data may be used to support product registration, real time data must be established to support actual product dating. In addition, sampling of newly manufactured production lots of product must be monitored on a continuing basis, at least to the projected expiration date or beyond, and data submitted to FDA.

After approval is received for the drug product, stability studies are continued to support commercialization of the drug product. Representative lots are put on stability station for annual product monitoring.

In addition, post-approval studies would also be necessary if there is any change to the processing or packaging of the drug product. More details of stability requirements and regulations are discussed in Chapter 5.

2.3 Scientific Principles of Stability Testing

Based on ICH Q1A(R2), *"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 environmental factors such as temperature, humidity and*

light" [4]. Therefore, stability studies provide data to justify the storage condition and shelf-life of the drug product. For drug substance, such studies establish the retest date in addition to the storage condition of raw material.

Stability of a drug substance or drug product during drug synthesis, formulation, and storage must be ascertained. Instability could lead to chemical degradation and loss of drug potency and the possible formation of new chemical species with potential toxic side effects. Therefore, early evaluation of a drug substance should include elucidation of stability under a number of environmental conditions. To aid in the prediction of drug stability, forced or accelerated degradation is performed to elucidate potential degradation products, determine their safety, and develop analytical procedures to quantitate these new chemical species. These forced degradation studies may be predictive of the degradation pathways of the drug under normal conditions. In fact, information learned from studying the kinetics of degradation may be used to extrapolate rates of degradation which might apply during normal storage conditions and could be utilized to predict long-term stability under these normal storage conditions [5].

The development of appropriate analytical methods will then aid in the development of purification schemes to remove degradants and to allow the development of drug impurity profiles which will be used for setting purity specifications and for defining the drug which is to be utilized in pre-clinical animal and later human studies.

The analytical procedures to assess stability must encompass the elements common to validating analytical assays. The methods must be validated according to the parameters of accuracy, precision, robustness and specificity, limits of detection and quantitation, linearity of active ingredient assays, degradants, and other reaction products. More information on how to develop stability indicating methods is discussed in Chapter 7. Validation of these methods is discussed in Chapter 8.

These stability studies will expose the drug to potentially degrading conditions including moisture, oxygen, pH, temperature, and light. Discovery that a drug has a very restricted stability range will affect process and packaging development, and labeling for long-term shelf-life. Sensitivity to such environmental factors may also dictate the necessity for inclusion of stabilizers in the formulation and will dictate the choice of dosage form and packaging. It may turn out that such restricted stability and associated developmental costs to remedy the situation will be sufficient to eliminate a potentially viable drug product. For products which are expected to be sold and used worldwide, attention must be given to differing climate zones when considering expiry dating and long-term stability.

Drug stability must be assured during the critical pre-clinical animal testing and subsequent human testing. This requires that the drug that is used from beginning to end of a study be characterized for concentration and impurity levels throughout the study to assure that the drug has not changed. This characterization will then define the drug profile that is to be the specifications as to safety and efficacy.

For solid dosage forms, the solubility, efficacy, and stability of a drug may depend on the particular crystalline state of the drug. Many crystalline drugs can exist in different crystalline states called polymorphs. It is expected that characterization of the solid dosage forms include not only the chemical identity but the polymorphic

distribution as well. The polymorphic content may be characterized by techniques such as x-ray powder diffraction, Raman and infrared spectroscopy. The sensitivity to environmental conditions of different polymorphs of the same drug entity may differ and therefore polymorphic composition may play an important role in determining a drug's stability.

Once the drug sensitivities are determined and the product development process addresses these issues and defines the product, then the long-term official stability studies may begin. The conditions and protocols for these studies are well defined by FDA and ICH guidelines which are discussed in detail in subsequent chapters of this book.

2.4 Review of cGMP Stability Requirements

The development of a new medicine relies heavily on compliance with 21 CFR Part 211. The scope of these regulations indicates that the requirements listed in this section contain only the *minimum current* GMP practice for preparation of drug products for administration to humans or animals. Therefore, companies must adhere to cGMP regulations to avoid regulatory scrutiny. Violations of these regulations could lead to warning letters or even criminal penalties. Thus current GMP plays an important role in guiding development of new drug products. A few selected sections of CFR 211 are discussed in this chapter to clarify the requirements that impact the stability program and testing. It is not meant to be a comprehensive discussion of all applicable cGMP requirements.

2.4.1 Part 211.166 – Stability Testing

The cGMP requirements of a stability program reside in 21CFR Part 211.166. Table 2.1 lists a summary of components needed to support a stability testing program for pharmaceutical products.

Table 2.1 Requirements of stability program

211.166(a) Written program must include: • Sample size and test intervals, • Storage conditions for samples, • Reliable, meaningful, and specific test methods, • Testing of drug product in marketed container, • Testing of drug product for reconstitution at dispensing time and reconstituted time.

Every company must have a written stability program documented in a standard operating procedure (SOP). This program will define the requirements for stability studies to be put up to assess the stability profile and the expiry of the drug product. It is required to have the sample sizes and testing intervals defined along with storage

conditions. Chapter 3 will present in more detail the frequency of stability testing and the conditions under which samples will be stored.

Analytical methods must be developed to allow monitoring the critical characteristics of a drug product. These methods must be stability-indicating and validated. Subsequent chapters will discuss these issues in more detail. Importantly, methods to monitor impurities or degradation products must also be developed and utilized to establish the shelf-life of the drug product. Mass balance is also critical while developing stability indicating methods. This is quite a challenge for Research and Development, where analytical methods continue to evolve as the formulations are being developed.

Current cGMP requires that the drug product must be tested during stability storage in the same container and closure as proposed in the registration. Therefore, stability studies must be set up on stability station, which is the time point in each specific storage condition, in their actual storage container. This may be an issue if there is not enough material available to be placed on stability station. For drug substance, a functionally similar container may be used to mimic the cardboard or plastic drum that is usually used to store raw material.

Part 211.166 (b) stipulates that an *adequate number of batches must be tested to determine an appropriate expiration date*. However, the regulations do not specify what the number of batches is and the size of these batches. This information is further clarified with the issuance of ICH stability guidelines. Similar sets of samples are also placed at higher temperature and higher humidity conditions to speed up degradation. These accelerated conditions generate data that are used to establish *tentative* expiration dates. Most studies use 40°C/75% Relative Humidity (RH) as the accelerated condition. This condition is also the ICH-accelerated condition.

FDA suggests accelerated studies to support tentative expiration dates; however, the real time studies are to be ongoing and continue until the actual projected expiration date is achieved. FDA addresses separately those samples which are claimed to be sterile and/or pyrogen-free. Additional information of the storage conditions for accelerated and stress conditions are discussed in Chapters 3 and 4.

2.4.2 Part 211.170 – Reserve Samples

A sample retention program is required for drug substance and drug product. For drug substance, a representative set of samples of each lot in each shipment of each active ingredient is to be retained to support marketed products. The amount must be twice the quantity needed for all tests to determine whether the active ingredient meets established specifications. In general, these samples must be retained for 1 year after the expiration date of the last lot of manufactured drug product containing the active ingredient. Radioactive drug product, pyrogen-free/sterile, and over-the-counter (OTC) drugs have other requirements as listed in Part 211.170.

For drug product, a representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling, in the same container-closure system that is marketed. Again, the amount is at least twice the

quantity needed to perform all required tests, except for sterility and pyrogens. Similar to drug substance, these samples, in most cases, must be retained for 1 year after the expiration date of the drug product.

2.4.3 Part 211.137 – Expiration Dating

This section of cGMP indicates that the expiry of the drug product is established by the stability program described in Part 211.166. The stability program also establishes the conditions that the product must be stored, and this information must be included on the product label. A manufacture must assure that the product meets quality standards of identity, strength, quality, and purity at the time of use.

Section (g) of this section indicates that the drug product used for investigation does not need to follow cGMP providing that the company will meet their specifications set by stability testing of clinical materials. However, many companies choose to follow cGMP for their late-phase clinical studies.

2.5 Review of Part 211.160 – Laboratory Controls

The general requirement for laboratory controls applies to stability testing (Subpart 211.166) as well as the others. These controls apply to testing instruments, analytical instrumentation, storage chambers, documentation including SOPs, data reporting and storage, data analysis, and sample plans utilizing statistical methods.

This section indicates that the quality unit (QA) is responsible to review and approve all specifications, standards, sampling plans, analytical procedures. QA must also have a change control system to manage changes to the above activities.

This section requires that all activities in the laboratory must be documented at the time of performance. These approvals and sign-offs shall be documented at time of performance. Any deviations must be recorded and justified. Therefore, all activities from sample set-up, sample pulls, sample testing, etc., are included. It requires that the controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures.

These are to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

2.6 Part 211.165 – Testing and Release for Distribution

Stability studies run on drug product are useful in defining and establishing the product specifications such as concentration, identity, and purity. These specifications form the criteria for the QA unit's product release activities. This section also

indicates that testing must be done, as needed, for each batch of drug product to assure the absence of objectionable micro-organisms.

Product must be tested utilizing sampling and testing plans which are documented and approved in writing. The testing methods must utilize validated procedures according to pre-approved validation protocols.

2.7 Part 211.194 – Laboratory Records

Section 211.194 details how the testing results are to be documented and the testing methods validated. These criteria also apply to the testing procedures used to perform stability testing, as well as release testing. Table 2.2 lists the requirements of laboratory records specified in this cGMP section. Drug products are only to be released if the test results conform to pre-determined acceptance criteria.

The documentation relating to testing and release must include a complete description of the source of the sample, the amount sampled, the lot number, date received, and date tested. The testing procedures must be completely referenced and any method changes documented and approved by QA with reasons for the change.

All reagents, standards, and instrumentation must be referenced and appropriate documentation for standard and instrument calibrations available for examination.

This requirement is covered by Section 211.280 – General Requirements, which indicates that all the records generated must be available for inspection at any time. Companies must consider their extended laboratories, especially those that are a part of their outsourcing paradigm. For marketed products, these data must be reviewed annually.

Table 2.2 Summary of laboratory records requirements

211.194 Laboratory records
• Complete record of data
• Description of sample (location, quantity, lot, date received, etc.)
• Method used, modification, and reason
• Reagents, standards, and instrumentation
• Stability testing

2.8 Conclusion

The need for stability studies is clearly defined in the above cGMP requirements for the pharmaceutical industry. It forms the basis for the ICH guidelines of specific conditions for stability studies. These guidelines will be discussed in depth in this book in the next two chapters for ICH regions and global regions. Stability studies form an integral part of the drug development process. No drug can be introduced into commerce without a stability studies program which is ongoing. The data generated will assure the drug product's stability and consequent safety and efficacy through at least the expiry date on the label.