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PREFACE

The first edition of the *Handbook of Modern Pharmaceutical Analysis* addressed a need for a text that highlighted the importance of analytical chemistry during the entire life cycle of a pharmaceutical drug product, from discovery of an active molecule, through the various phases of clinical development, product registration, and technical transfer from R&D to the quality and manufacturing arena. We are highly gratified that the text has been widely embraced over the past nine years, and because of the process-oriented arrangement of the subject material, it has remained fairly current in that regard.

The pharmaceutical industry has continued to evolve. New regulatory guidelines have had their effect on all facets of drug development and commercialization. The socioeconomic trends in the emerging markets of the world have also changed the development paradigm, as companies have more carefully considered the demand for new medicines to treat unmet medical needs in these markets. The routine development of biopharmaceutical proteins has increased dramatically over the past several years. Finally, technology has played a major role in altering the business of drug development. More sophisticated instrumentation with higher sensitivity has allowed the routine quantification of trace and ultratrace level impurities in both active pharmaceutical ingredients and dosage forms. Spectroscopic techniques with the capability of monitoring synthetic reactions and drug product processing steps have led to increased understanding of such operations. And the trend toward electronic and paperless systems in every area of the industry, from laboratory notebooks to regulatory filings, has caused a reexamination of processes based on the usage of paper.

Careful considerations of the changes in the industry have influenced the structure and content of this edition. The chapters repeated in this text from the first edition are still relevant today and have been updated in terms of literature references; and they cite any pertinent changes to regulatory authority guidance

documents. The chapter covering dissolution adds a focus on modeling, while the stability studies section has been enlarged in scope to consider requirements of countries other than the United States. The chapter on analysis of novel drug delivery systems has also been expanded to reflect the variety of new approaches being considered to increase bioequivalence, especially in the case of low-solubility active ingredients. Given the increased scrutiny by the authorities and quality of in-process control methods, a separate chapter devoted to in-process testing has been added. The chapter on technical transfer pays more attention to the requirements of "rest of the world" countries.

Notable additions to the text by way of new chapters include the important subjects of quality by design (QbD) and process analytical technology (PAT), genotoxic impurities (GTIs), method development of chiral compounds, and characterization and analysis of biopharmaceutical proteins. QbD has been the subject of numerous meetings, seminars, and publications over the past several years. Embracement of the QbD paradigm relies heavily on the movement away from empirical thinking to one that puts an increased emphasis on modeling and PAT. A greater understanding of the relevant guidance documents is necessary to allow an analyst (working with process development) to implement a sound control strategy that can be defended with the regulatory authorities. It is expected that QbD and PAT will play an ever-increasing role in pharmaceutical development and testing in the years to come.

The discussion of GTIs incorporates the regulatory requirements as well as analytical approaches for the determination of these analytes. It is felt that a better background in the reality of the expectations of the authorities is required for a pharmaceutical analyst to make the best choices with regard to techniques. Greater knowledge of the guidance documents will encourage informed decisions. The importance of chiral compounds both in terms of pharmacological and toxicological activity cannot be overstated. Chiral methods present unique challenges in that the molecules have the same physical and chemical properties, except their optical activity. Readers will find this chapter fascinating. Given the increased importance of biomolecules, a separate chapter has been devoted to the analytical challenges associated with the characterization and analysis of biopharmaceutical proteins.

We believe that the additions and changes made in the second edition of *The Handbook of Modern Pharmaceutical Analysis* will enhance its stance as a useful and informative text for those engaged in pharmaceutical drug discovery, development, manufacturing, and quality control and assurance.

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1 OVERVIEW OF MODERN PHARMACEUTICAL ANALYSIS

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I. INTRODUCTION

Modern pharmaceutical analysis encompasses much more than analysis of active pharmaceutical ingredients (APIs), inert ingredients (excipients), or formulated drug product (DP). The primary goal of pharmaceutical analysis is to assure drug quality. It is well known that quality cannot be tested into a product; however, well-planned testing with suitable methodology and instrumentation can help build quality into a DP.[1] A thorough understanding of interactions of drug substances with excipients is necessary, especially when residual solvents (including moisture) are present. It is also essential to understand potential degradation reactions that may occur in the formulated product under various stress conditions that might be encountered during storage and in shipment of the final package. And dissolution tests should correlate well with the bioavailability. In short, the aim of pharmaceutical analysis is to help build and assure quality

of DPs. Recognition of these principles has encouraged the Food and Drug Administration (FDA) to issue the new initiative quality by design (QbD) outlined in the May 2007 FDA report "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach." The focus of this concept is that quality should be built into a product by means of a thorough understanding of the product and the process by which it is developed and manufactured, along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks through continuous product improvement.

This second edition of *Handbook of Modern Pharmaceutical Analysis* addresses QbD and other new developments such as the best ways to monitor genotoxic impurities (GTIs), separations of chiral compounds, and characterization and analysis of biopharmaceutical proteins. The first edition published in 2001 has been a popular text among individuals in the pharmaceutical industry who are involved in drug development and the associated analytical function area. That book provided a journey through the drug development process, with emphasis on the role of analytical chemistry. It covered various separation methods such as thin layer chromatography (TLC), gas chromatography (GC), high-pressure or high-performance liquid chromatography (HPLC), and capillary electrophoresis (CE) that are commonly used in the pharmaceutical industry for the evaluation of a large variety of samples. These methods still remain the methods of choice for checking purity of new drug candidates, monitoring changes or scaleup of synthetic procedures, evaluating new formulations, and implementing quality control/assurance of final DPs. Hyphenated methods that combine a chromatographic method with spectroscopic methods such as mass spectrometry (MS) or nuclear magnetic resonance (NMR) have been found useful for characterizing impurities; these methods are fully covered in that text. The aim of this second edition is to supplement and complement the first edition and other complementary volumes on pharmaceutical analysis[2–4] and to provide a comprehensive text of modern pharmaceutical analysis that incorporates various relevant requirements and new initiatives to address DP quality. The key features of the second edition are listed below:

- Provides the latest analytical technology that allows greater sensitivity and selectivity.
- Includes methods for monitoring GTIs.
- Highlights implications for pharmaceutical analysis based on the new paradigm, "Quality by Design."
- Covers characterization and analysis of biopharmaceutical proteins, as these molecules are gaining significance.
- Provides up-to-date information on documentation in light of regulatory guidance, technology, and industry trends.

This book has been designed to be particularly useful for both novice and experienced method development chemists in the pharmaceutical industry who are seeking to update their knowledge. It should continue to serve as a definitive reference source on pharmaceutical analysis for researchers, analysts, managers, and pharmaceutical industry regulators.

II. SOLID-STATE STUDIES

A systematic approach to the physical characterization of pharmaceutical solids outlined in Chapter 2 serves as a useful pedagogical device for the classification of the many available methods of physical characterization. Within this system, physical properties are classified as being associated with the molecular level (those associated with individual molecules), the particulate level (those pertaining to individual solid particles), or the bulk level (those associated with an assembly of particulate species). One of the areas where the physical characterization of solids has become extremely important is in the study of polymorphs and solvatomorphs. The nature of the crystal structure adopted by a given compound upon crystallization exerts a profound effect on the solid-state properties of that system, and these variations can translate into significant differences in properties of pharmaceutical importance. It is now accepted that an evaluation of the polymorphism available to a drug substance must be thoroughly investigated in the early stages of development. The results of these studies must be included in the chemistry, manufacturing, and control section of a new drug application (NDA), and this information is required to demonstrate control over the manufacturing process.

III. DEGRADATION AND IMPURITIES STUDIES

Forced degradation studies are used to develop stability-indicating analytical methodology, to gain a better understanding of API and DP stability, and to provide information about degradation products and pathways. To fulfill development and regulatory needs, Chapter 3 provides a road map for performing these studies, helpful tools in designing rugged scientific studies, and guidance on how to record and communicate results. The primary goal of stress testing is efficiently producing degradation samples realistic of those formed during manufacture, handling, and normal storage conditions (as specified by the International Conference on Harmonization—ICH) of the API and DP. Overstressing can destroy degradation products (degradants) that are relevant or generates unrealistic degradants, whereas understressing may fail to generate important degradation products. From a regulatory perspective, forced degradation studies should provide data to support the following:

- Identification of possible degradants
- Degradation pathways and intrinsic stability of the drug molecule
- Validation of stability-indicating analytical procedures

Specific issues addressed in regulatory guidances related to forced degradation are provided by the US FDA and from private industry on regulatory requirements for investigational new drug (IND) and NDA filings. It should be noted that regulatory guidance does not specifically address issues such as exact experimental conditions for forced degradation studies (temperatures, duration, extent of degradation, etc.) and experimental design.

IV. ANALYTICAL CONSIDERATIONS FOR GENOTOXIC AND OTHER IMPURITIES

The assessment and control of GTIs in pharmaceutical products is of great importance (Chapter 4). Shortly after the ICH formally adopted the drug substance quality guidance, ICH Q3A(R), a number of health authorities raised the concern that this guidance document did not adequately address the issue of highly toxic impurities in APIs and did not provide guidance for safe levels. To address this gap, the European Medicines Agency (EMEA) Safety Working Party (SWP) of the Committee for Medical Products for Human Use (CHMP) issued a draft position paper in late 2003 to provide guidance on the limits of GTIs. This position paper was the genesis for the eventual EMEA CHMP GTI guidance document that was issued in 2006. The EMEA guidance utilized an assessment procedure that is based on a concept of threshold of toxicological concern (TTC) to assign an acceptable exposure limit for GTIs in APIs. The successful implementation and execution of any GTI control strategy relies on the ability to adequately demonstrate that these impurities are controlled to a safe level in the final API. To accomplish this goal, the analytical methodologies used for the determination of GTIs at low levels should be very reliable.

V. QUALITY BY DESIGN AND PROCESS ANALYTICAL TECHNOLOGY

To achieve risk-based DP development and manufacturing, it is imperative to apply modern science-based principles throughout the entire life cycle of a DP (Chapter 5). Such modern approaches include the utilization of quality risk management principles, process analytical technology, and quality systems principles. In its entirety, the collective implementation of modern science-based principles will direct pharmaceutical development in a new direction that will build quality into products, as opposed to merely testing quality into products. This forms the core of QbD in that risks associated with pharmaceutical development and manufacturing will be addressed and mitigated throughout the life cycle of the product. After the release of the final draft of "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach," the FDA and the ICH have released various documents outlining the necessary components for the application of QbD. Such efforts to unify regulatory bodies and industry's direction in improving pharmaceutical quality provide the driving force and framework for modernizing pharmaceutical development and manufacturing to a state that ensures delivery of high-quality DPs to consumers.

VI. NOVEL DOSAGE FORMS

Novel pharmaceutical dosage forms cover a broad range of formulation delivery platforms such as tablets, capsules, cachets, sustained-release dosage forms, parenteral dosage forms, transdermal dosage forms, metered dose inhalants, solutions, emulsions, and suspensions that are designed to improve patients' acceptance and/or to assure maximum absorption following administration (Chapter 6). Excipients in the pharmaceutical processing operations may originate from a

wide variety of sources including plants (e.g., starches, sugars, celluloses), animals (e.g., gelatin, lactose, shellac), minerals (e.g., dicalcium phosphate dehydrate, magnesium stearate), and from synthetic origins (e.g., polyvinylpyrolidone, polysorbates, polyethylene glycols, EUDRAGIT®). Excipients exhibit a wide range of solubilities that influence the type of sample preparation technique that may be employed. Since the goal of any sample preparation technique is to get the drug substance into solution to achieve quantitative recovery (>98%) of the API, the number of sample treatment steps and choice of solvents used become a critical consideration. Sample treatment steps, whether manual or automated, involve laboratory sampling, weighing, sample extraction/dilution, and subsequent injection of an aliquot of the sample for analysis generally by HPLC. Unlike excipients, the API or drug substance (DS) is typically well characterized and may be organic acids or bases that exhibit different solubility in water. Solubility of the dosage form is a key factor when it comes to analysis. In view of the importance of API solubility in the HPLC analysis of pharmaceutical dosage forms, this chapter examines some of the strategies that may be employed to assure optimum quantitative recovery of the API during the sample preparation steps prior to HPLC analysis. In addition, emphasis on sample preparation strategies used for tablets and capsules has been exemplified, as they are the most commonly used delivery platforms for novel pharmaceutical dosage forms.

VII. METHOD DEVELOPMENT FOR CHIRAL COMPOUNDS

Separation chemistry has progressed to a point where it can be used to resolve isomers that are identical except for their ability to rotate the plane of polarized light. In today's pharmaceutical industry, the vast majority of this work is now done by HPLC. Regardless of whether a traditional normal phase HPLC, reversed phase HPLC, or SFC (supercritical fluid chromatography) technique is used, routine analytical chiral method development screening is a very effective and efficient means for developing chiral selective methods in the pharmaceutical industry (Chapter 7). Of course, for preparative chromatography, normal and supercritical fluid chromatographic systems provide significant advantages in recovering enantiomers from the mobile phase. However, for analytical operations, analysts overwhelmingly prefer not to have to switch to normal phase modes for chiral analysis. Thus, chiral method development screening has become quite important in all these chromatographic formats. As a more diverse stream of chemical entities is being developed for market, the analytical chemist must continually look for ways to optimize the screening system. This is required to ensure the best opportunity for success in yielding a robust analytical method for the new chemical entities in development.

VIII. CHARACTERIZATION AND ANALYSIS OF BIOPHARMACEUTICAL PROTEINS

An analytical development program for biomolecules such as proteins comprises in-depth product characterization, assay development, and routine testing activities (Chapter 8). The goals of characterization efforts are to define the

structure of the major product substances and product-related impurities, to relate structure to function, and to identify and quantify protein/DNA impurities derived from the host cell.[3,5–7] In addition to fundamental product knowledge, a comprehensive characterization effort allows the future implementation of meaningful comparability protocols that support manufacturing changes. The goals of assay development are to develop and implement relevant, routine assays that address biological activity, safety, efficacy, and quality. These assays support process development efforts, manufacturing investigations, drug substance and DP release, and stability programs. Many assays evolve from the characterization activities. This chapter provides a brief overview of analytical methods commonly used to assess the structure, purity, safety, stability, and potency of recombinant protein pharmaceuticals. These methods are technically challenging to develop because the protein products are large in size, complex in structure and function, and marginally stable in aqueous solution. The basic biochemical, biophysical, and cell biological principles that support these methods are described in the chapter.

IX. PREFORMULATION AND EARLY PHASE METHOD DEVELOPMENT

The transition from discovering a new therapeutic agent to developing a new pharmaceutical product begins with an investigation of the physical and chemical properties of the API, a process commonly referred to as "preformulation" (Chapter 9). This is a key milestone in the drug development process, as the focus shifts from looking at the therapeutic agent as a molecular entity to how it can be effectively made into a product. Preformulation studies, when effectively conducted, can be accurate predictors of the challenges that will be encountered in combining the API with a suitable system that will deliver this new therapeutic agent in a safe and effective manner to a patient. Following preformulation, formulation development activities begin with the eventual goal of developing a robust bioavailable, efficacious, and safe dosage form that can be manufactured at a suitable scale for commercialization. Analytical chemists play an important role in the preformulation process by developing and validating the optimal methods to support these studies.

X. IN-PROCESS CONTROL TESTING

Most pharmaceutical analysts are very familiar with developing methods and analyzing the intermediates, APIs, and DPs of chemical, biological, or pharmaceutical processes. They are also very familiar with the challenges that working with these samples can provide. For the analyst dealing with in-process testing, there are some key additional challenges that include the many different sample matrices, sample or matrix instabilities, sample reactivities, and, in early development, the uncertainty of the sample matrix from batch to batch. The challenges can lead to having to modify the way we qualify and validate the methods and how the technical transfer performed. Chapter 10 deals with analyzing samples taken during a unit operation within a processing step and discusses a typical processing

step and how one can determine what, when, and how to test the samples, and the technical transfer of these test methods to a production facility.

XI. METHOD VALIDATION

Because of the current accuracy and precision in analytical instrumentation, reagents, and capabilities of modern data processing systems, even poor methods may be acceptably validated; however, this does not necessarily certify a method as being "good," robust, or suitable for a control environment (Chapter 11). Ideally, the method validation should be integral to the development process and should be utilized for the method optimization. This chapter reviews a systematic and scientific approach to the method development and validation of analytical methods, which should demonstrate to regulatory agencies that methods used in the testing of pharmaceutical products at each stage of development, and ultimately at commercialization, are fit for the purpose. To ensure that the data are accurate and reliable, qualified and trained laboratory analysts should always perform methods on qualified equipment, using suitable standards. It should always be recognized that the validation of such methods is not required solely to comply with good laboratory practices or to satisfy regulatory guidance. In reality, it is done to ensure that data used to approve medicinal products are accurate and that patients can receive life-enhancing medicines without compromise to their welfare or safety.

XII. STABILITY STUDIES

Conducting a dynamic, compliant stability program requires more than merely knowing and adhering to regulatory requirements. It also requires management of the stability samples, the environmental chambers, and all the associated documentation. Standard operating procedures, processes for protocol amendments/deviations, and out-of-trend or out-of-specifications investigations are all key elements of a compliant stability program. Chapter 12 describes how to manage both the operational elements and the regulatory compliance issues to ensure a successful application and inspection by any regulatory agency. The ICH guidelines and the WHO guidelines related to stability are also discussed in detail.

XIII. METHOD TRANSFER

Presently, there is no technology transfer guidance available from either the FDA or from the ICH. Good analytical method transfer requires that a method or test procedure work in an equivalent fashion at two or more different sites or laboratories. This is evidenced by the results of the transfer meeting all predefined acceptance criteria (Chapter 13). The process is driven by compliance and governed by a statistical treatment of the resulting data. Method transfer can be

defined as "the introduction of a validated method into a designated laboratory so that it can be used in the same capacity for which it was originally developed." The second portion of the technology transfer process concerns the transfer of technical ownership from one laboratory to another. This latter type of transfer is usually associated with the movement of drug development projects from research and development (R&D) to the commercial release environment; however, it can also be associated with transfer to and from Contract Research Organizations (CROs) or Contract Manufacturing Organizations (CMOs). In many case studies involving technical transfer, the process of ensuring that the receiving laboratory is sufficiently familiar with all scientific aspects of the project is not carried through to fruition. In such cases, problems with the operation of the methods can manifest themselves later during testing of commercial products. Indeed, rapid and complete transfers are crucial to the success of process validation experiments for pharmaceutical dosage forms. The importance of analytical transfers is underscored by the incidence of 483 observations that laboratories have received from the FDA.

XIV. DOCUMENTATION

Pharmaceutical analytical documentation should accomplish the key mission of analytical R&D: to monitor and ensure the identity, purity, stability, and consistency of drug substances/APIs and dosage forms used during preclinical, clinical, and marketing phases in accord with the governing regulatory guidance and policies (Chapter 14). Analytical data are the foundation and backbone for pharmaceutical development leading to approval and production of new drugs for market. Analytical documentation provides the critical links during the evolution and life cycle of a new pharmaceutical product—beginning from earliest studies, enabling entry into humans, through product launch and postapproval changes. Prior to marketing approval, analytical R&D personnel support API synthesis and process development, as well as dosage form design, process development, and optimization activities. Following approval, quality control personnel provide the data to assure consistent quality and stability for the marketed product and to support the inevitable postapproval quality and stability for the marketed product and to support the necessary postapproval changes that occur in every product's life cycle. Analytical scientists have welcomed the concepts of ICH M4 Q—Common Technical Document (CTD) as a means of providing globally accepted information and scientific data in a common format. Analytical data generated with a better understanding of QbD can play a pivotal role in describing the API and DP, as well as at the interface. To concisely and effectively communicate the increased level of drug development phase-dependent information, scientifically sound, consistent, and compliant documents become essential elements of the development process. Good documentation of the product development also helps to assure that the continued quality of the marketed product is achieved.