

Preface

Sterile products represent a significant fraction of parenteral products and encompass a variety of challenging dosage forms. Development of sterile products poses multifaceted challenges which can be broadly categorized into three areas: formulation dosage form development, processing and manufacturing and assurance of purity, safety and efficacy of the manufactured product. The chapters in this book are structured along this theme and offer a useful guide for scientists and personnel working on commercialization of sterile drug products.

The first part of the book covers the formulation aspects of sterile product development including basic principles of formulation development, formulation selection via molecule and manufacturability assessments, and formulation approaches for polymer, lipid-based systems, PEGylated biotherapeutics, nasal delivery, vaccines and adjuvant systems. The second part focuses on manufacturing process, container closure, and delivery considerations. This section covers freeze-thaw processing, technology transfer of sterile products, transfer across barrier systems, in addition, it focuses on recent innovations in aseptic filling, and approaches for developing lyophilized parenterals. The part also emphasizes on recent innovations in pen and autoinjector drug delivery devices and the methods available to establish container closure integrity (CCI). The last part of this book expands on quality and regulatory aspects of sterile products including particulate issues and appearance defects in sterile products, sterile filtration, and intravenous admixture compatibility. As sterilization process is an essential component of aseptic processing, the last four chapters cover the basic principles behind commonly used sterilization techniques, associated validation strategies along with an overview of microbial measurement methods.

The book commences with an introduction to basic principles of sterile product formulation development. This chapter presents cogent approaches on development of injectable products and discusses formulation development considerations such as solubility, challenges for lipophilic formulations, nanoparticles, suspensions and dry formulations. Furthermore general considerations for compatibility with primary packaging and manufacturing are provided.

Chapter 2 discusses an approach for selection of molecules based on manufacturability assessment so that robust commercial formulation can be developed for protein products. This chapter covers aspects of protein sequence analysis from product quality standpoint and identifying “hot spots” for degradation and approaches for initial formulation screening through assessment of physical and chemical stability. This chapter dives deeper into considerations for manufacturability assessment through various process studies by subjecting molecule to stresses experienced during manufacturing process.

Chapter 3 provides a snapshot of polymer- and lipid-based drug delivery technologies. Drug delivery technologies, especially controlled drug release technologies have come a long way and their use in commercial drugs highlights the utility of such technologies. This chapter reviews the matured technologies that are being used in parenteral drug delivery and focuses on in situ forming gel depot formulations and lipid-based drug delivery technologies. Authors have also provided insights into the considerations for the development of newer technologies.

Chapter 4 touches upon an important area of PEGylated biotherapeutics where a comprehensive review of commercial products and clinical products in development has been provided for readers. Authors initiate the discussion with chemistry of PEGylation and go into the details of manufacturing and formulation aspects such as issues during reaction, process considerations and characterization for drug substance, and stability aspects to consider during formulation development followed by delivery challenges for PEGylated products due to viscosity issues.

Chapter 5 shifts the attention to nasal delivery aspects for sterile products. This chapter navigates readers through nasal physiology and mechanism of delivery, provides good review of local and systemic acting nasal products, discusses various challenges encountered during nasal drug delivery, and provides a comprehensive approach for formulation development and characterization. One of the important aspects in nasal delivery is the consideration for delivery devices. This chapter also provides an in-depth discussion on delivery devices, analytical testing, regulatory expectations, and manufacturing aspects through relevant case studies.

Chapter 6 focuses on considerations for vaccine formulation development which include antigen and adjuvant formulation development. This chapter differentiates between the protein formulation vs. vaccine formulations and guides readers to the important aspect of immune response and how it is achieved in vaccines. The chapter reviews formulation considerations and available adjuvants for vaccines. In addition, authors discuss the impact of route of delivery and challenges in stability and analytical characterization of vaccines.

Part II begins with a chapter on freeze-thaw processing of bulk protein solutions. This chapter provides excellent insight into mechanistic aspects of freezing process for protein solutions, impact of freezing on proteins through cold denaturation, ice-liquid interface, and implications of cryoconcentration effects through solute crystallization and phase separation. Furthermore considerations for formulation and protection against freezing induced stress, design of freeze-thaw process parameters, scale down studies, and container closure aspects are discussed.

Chapter 8 is a comprehensive collection of case studies by the author on best practices for technology transfer of sterile products. This chapter provides outstanding overview of requirements for material release testing for API and excipients with underlying case studies. The author discusses production aspect preparations, compounding operation, lyophilization, and sterilization elucidated with case studies. Product release testing approach is explained through visual inspection, particulate matter testing, and sterility testing.

Chapter 9 discusses transfer of material across barrier systems in aseptic fill finish operations. It outlines topics such as requirements based on type of material being transferred, methods of transfer for solids, liquids, and suspensions. A comprehensive discussion on selection of appropriate transfer process is presented with illustrating case studies with isolator for potent compounds, biotech products in prefilled syringes, and for sterile suspensions for vaccines.

Challenges and recent innovations in aseptic filling technology are covered in Chap. 10. Aseptic filling requirements for clean room classifications, environmental monitoring, operator training, and gowning requirements are explained. An in-depth discussion on barrier system such as restricted access barriers (RABS) and isolators has been provided. Various filling containers and available filling processes are discussed which include ampoules, vials, prefilled syringes, cartridges, and Blow Fill Seal (BFS). This chapter concludes with case study on closed vial technology.

Because not all products have adequate stability in solution state, manufacturers rely on the lyophilization process to manufacture formulations, both biologics and small molecules, in freeze-dried state. Chapter 11 provides a detail overview of the scientific and technological advancements in the field of lyophilization. The chapter is an ideal resource for scientists involved with process design and qualification of freeze-dried products. Specific guidance on critical process parameters, critical quality attributes, and design space principles are covered that will help one to design process characterization studies. The author has also provided pertinent discussion on application of recent FDA guidance on process validation for this unit operation.

Assurance of CCI is critical to ensure safety of the final drug product presentation for the end user. Process development scientists should have a general understanding of the CCI testing and associated technical challenges in order to develop a robust drug product presentation. Chapter 12 provides an overview of regulatory expectations and Industry trend in CCI testing. A variety of CCI test methods are discussed along with considerations for method selection, development, and validation.

The ease and flexibility associated with the self-injection of parenteral drugs has also led to the increase in use of pens and autoinjectors as delivery devices. Chapter 13 provides an overview of the different types of injection devices as well as what the development of such a device entails. Regulatory requirements applicable to device development are discussed and examples are included to describe various steps associated with the injection device development and commercialization.

Part III brings the focus on regulatory and quality aspects of sterile product development. Chapter 14 reviews our understanding of the particulate matter as a critical quality attribute and the related concerns that impact product safety. The

origin of these particles as well as the available enumeration techniques are discussed in detail. The chapter also provides an overview of the pharmacopeial requirements and guidance on addressing regulatory queries related to subvisible particles in biopharmaceuticals. The discussion on product appearance is continued in Chap. 15. This chapter deals with the visual inspection of drug products with a focus on defects that are visible to eye—both cosmetic and functional. The chapter covers inspection attributes, regulatory expectations for manual and automated visual inspections, and related case studies.

The next chapter focuses on sterile filtration, a critical step in the manufacturing process needed to ensure sterility of the final product. The chapter covers the performance requirements for sterile filtration and membrane properties including pore size and material of construction that can affect the filtration process. Basic filtration concepts such as filter selection and filter sizing are included. Operational practices including installation, sterilization, flushing, and integrity testing are also covered, as well as the main components of filter validation including retention studies and filter integrity testing.

Intravenous (IV) admixture studies are an integral part of developing a safe and efficacious sterile drug product intended for IV administration. Chapter 17 discusses requirements and challenges associated with conducting IV admixture studies and the related regulatory guidance. A pharmaceutical admixture consists of a drug product mixed with an appropriate diluent in a suitable dosing/delivery device for the purpose of parenteral infusion to the patient. The discussion presented in the chapter will help researchers identify critical admixture issues for their products and gain insights into addressing those issues while meeting regulatory expectations.

The last four chapters of the book focus on sterilization process, microbiological methods, and the associated validation challenges. Chapter 18 deals with basics of sterilization methods commonly employed for sterile products. This chapter discusses requirements for sterilization methods that are subject to review by regulatory agencies when a sterile product is filed for approval. The author provides a summary of requirements for sterilization process, sterilization method details, and considerations for validation of sterilization methods including heat sterilization, radiation sterilization, and ethylene oxide sterilization. In addition the author discusses aseptic processing requirements which include filters, clean room consideration, personnel qualification, and aseptic process validation.

Chapter 19 discusses the common errors made during investigation of microbial contamination events. Several thought patterns and behavior that prevents one from finding the source of contamination and the associated root cause are covered. Multiple case studies are provided to aid the reader in conducting the best possible root cause investigation for a sterility assurance failure. Microbiological testing used to assess product sterility as well as microbiological quality of components, ingredients, environment and utilities, is foundational to the operation of pharmaceutical facilities. Given the slow turnaround time associated with the conventional methods, there has been an increasing interest in the use of rapid microbiological methods (RMMs). Chapter 20 discusses different types of available RMMs and provides guidance on the validation of such RMMs. A detailed

discussion of the validation strategy is provided including the user requirements, vendor assessments, documentation, and other qualification activities needed to meet regulatory expectations.

Chapter 21 describes the current expectations for validation of dry and moist heat sterilization cycles. The chapter explains the basic concepts behind dry and moist heat sterilization including the mechanism of sterilization, determination of worst case conditions, and the relevant loading configurations. References to key literature from Parenteral Drug Association and the International Organization for Standardization are provided to the reader for further details. The chapter also covers assessment of biological and physical aspects of sterilization process and provides guidance on strategy for validation of sterilization cycles.

Overall this book covers essential aspects of sterile product development with excellent contributions, including several case studies, made by key experts in the field. We trust that this book serves as reference guide for researchers, process engineers, pharmaceutical and biotechnology scientists as well as academic students.

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