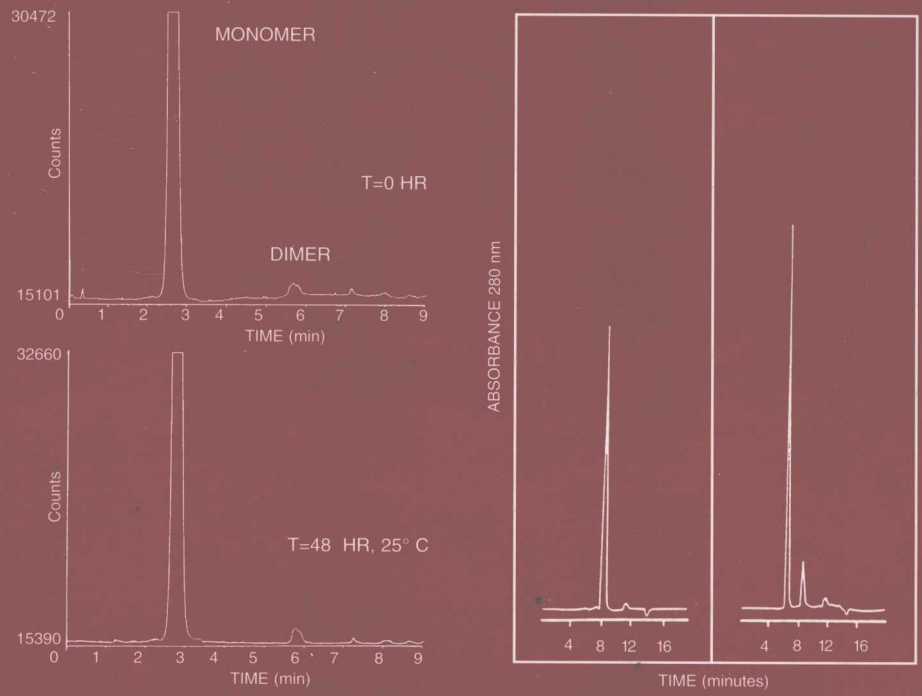
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 85

Development of Biopharmaceutical Parenteral Dosage Forms



edited by
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Development of Biopharmaceutical Parenteral Dosage Forms

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Preface

Successful sterile product development of modern parenteral biopharmaceutical therapeutic agents demands the close interaction of interdisciplinary sciences encompassing molecular biology, fermentation, process development, protein chemistry, analytical biochemistry, pharmacology, toxicology, preformulation, formulation, clinical development, quality assurance, bulk manufacturing, packaging, sterile manufacturing, regulatory affairs, and marketing.

The physicochemical properties of proteins constitute the building blocks for preformulations and formulations development. Elucidation of these properties facilitates educated selection of compatible excipients to extend the shelf life of protein drugs.

The objective of formulation scientists is to make biopharmaceutical parenteral products that are safe, effective, pure, stable, suitable for production, cost effective, and marketable, and elegant. We cover liquid parenteral formulations of biopharmaceuticals. Lyophilized formulation development of similar biopharmaceuticals are more properly the focus and interest of other pharmaceutical scientists.

This book describes fundamentals and essential pathways for various formulation techniques, their purpose and function, and how each method

is fundamentally related to and integrates with the other approaches to successful product development.

The book covers six key areas of the development of biopharmaceuticals for human use, and each chapter is written by one or more industrial scientists involved with the state-of-the-art techniques. Building on the key areas allows the formulator to incorporate specific tasks into biopharmaceutical design in order to reach the next plateau of development. The result is an understanding of the product development formulation process.

Following the introductory Chapter 1, Chapter 2 covers biopharmaceuticals currently licensed or in clinical development, including genetically engineered cells and engineered vectors. The fermentation process, the first key step in product development, is a key scientific and economic model. Once the goals of this process are defined, fermentation and harvest can begin. Quality must be designed into each step of the process to ensure success.

Chapter 3 discusses the purification and characterization techniques employed to produce a highly purified, economically focused, flexible process that can be transferred, scaled up for manufacturing, and validated to current regulatory standards. Several types of unit operations for isolation, purification, and characterization are also discussed. These are essential for the formulator to understand the biochemical structure of the active drug substance and to ensure quality of the final product.

The fourth and fifth chapters cover key phases of successful product development. Considerations are reviewed for drug delivery, formulation, stability studies programs, routes of deactivation and denaturation, aggregations, protein stabilizers, excipients, requirements of preservatives, and physicochemical properties of therapeutics. Attention is paid to how each is accomplished by the pharmaceutical scientists in order to enhance the success of the formulation.

The sixth chapter addresses basic concepts in analytical techniques, methods development, separation methods employing chromatographic and electrophoretic techniques, bioactivity methods covering bioassays, and immunoassays. The methods selected will show how to measure stability of biological activity.

Chapter 7 covers basic filtration theories, filter classifications and characteristics, filter performance criteria, validation and regulatory requirements, filtration systems, filter separation specific for recombinant protein and peptide processing, and future trends in filtration technology. This chapter will inform the formulator how to select the proper filters for

each drug substance to maximize compatibility and minimize adsorption and inactivation.

The eighth chapter explains the physical, chemical, and toxicological properties of closures for parenteral products; protein adsorption on various elastomeric surfaces; strategies to reduce or eliminate adsorption; and specialized containers for biotechnological applications. The formulator is given a menu from which to select the most compatible elastomeric closure for a specific drug substance.

Our approach informs students, molecular biologists, protein chemists, process engineers, purification scientists, pharmaceutical formulators and manufacturing personnel, and those involved in QA/QC and regulatory affairs *how to perform* appropriate, systematic, sequential steps of formulation development.

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I wish to express my sincerest appreciation to each of the contributors. I fully understand their overwhelming achievement in balancing the demands of their own work with fulfilling the additional responsibility that I asked of them for the successful completion of this book. My sincerest thanks to Tony, Paula, Basant, and Forrest for making this book possible.

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My special thanks also go to Drs. Patty Kiang (The West Co.), Y. John Wang (Scios Nova), and Pai Kao (Mayo Clinic), for giving me permission to include some of their work on protein adsorption on elastomeric surfaces. This addition made the book more complete.

Last but not least, my very personal gratitude and thanks to my wife, Loretta. Her skills in preparing my chapters were invaluable—considering the corrections, changes, deletions, and additions—as was her huge amount of patience and understanding. I dedicate this book to my friend, my wife. Thank you, Loretta.

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Introduction to the Development of Biopharmaceutical Parenteral Dosage Forms

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I. INTRODUCTION

Successful sterile product development of modern parenteral biopharmaceutical therapeutic agents demands close interactions of interdisciplinary sciences encompassing molecular biology, fermentation, process development, protein chemistry, analytical biochemistry, pharmacology, toxicology, preformulation, formulation, clinical development, quality assurance, bulk manufacturing, packaging, sterile manufacturing, regulatory affairs, marketing, and others.

The objectives of formulation scientists are to make biopharmaceutical parenteral products for human and veterinary use which are safe, effective, pure, stable, elegant, suitable for production, cost effective, and marketable.

Our goals in this book are to describe fundamentals and essential pathways for each scientific section, its purpose, function, and how each section is fundamentally related and how it integrates with the next section in the successful product development efforts.

This book covers six key areas with several chapters. Each of these are addressed by one or more industrial scientists involved with the "state-of-the-art" development of biopharmaceuticals for human use. Dividing the scientific contents into key areas allows the formulators to incorporate specific tasks into the biopharmaceutical design and allows them to reach the next plateau of development. When incorporated sequentially, this will result in the scientific understanding of the product development formulation process.

Chapter 2, Fermentation Process Events Affecting Biopharmaceutical Quality, covers in detail biopharmaceuticals currently licensed or in clinical development that include genetically engineered cell and engineered vectors. The fermentation process, the first key step in product development, is a key scientific and economic model. Once this target is defined, the fermentation and harvest system can begin. Quality is designed into each step of the process to ensure success.

Chapter 3, Development of Recovery Processes for Recombinant Proteins and Peptides, covers in detail the purification and characterization techniques and approaches to produce a highly purified, economically focused, flexible process that can be transferred, scaled up to manufacturing, and validated to current regulatory standards. Several types of unit operations, for isolation and purifications and characterization, are discussed which are essential for the formulator in the understanding of the biochemical