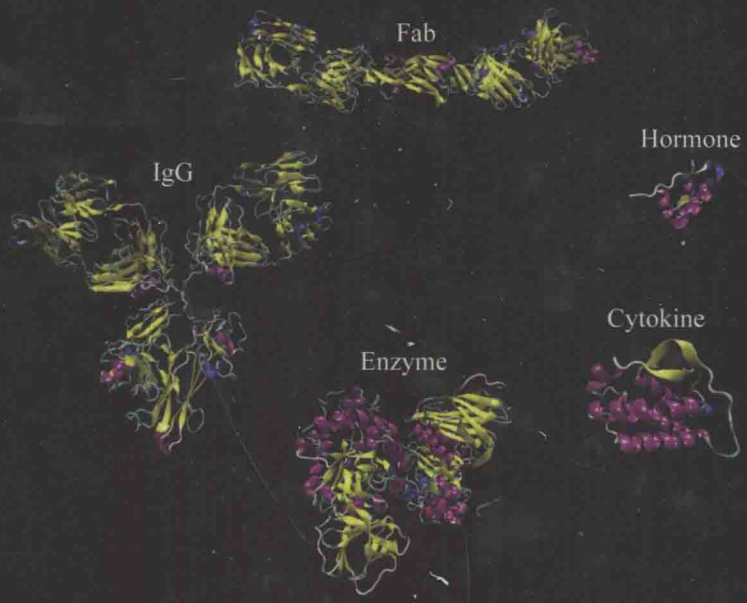
Formulation and Process Development Strategies for Manufacturing Biopharmaceuticals



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FORMULATION AND PROCESS DEVELOPMENT STRATEGIES FOR MANUFACTURING BIOPHARMACEUTICALS

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FORMULATION AND PROCESS DEVELOPMENT STRATEGIES FOR MANUFACTURING BIOPHARMACEUTICALS

FOREWORD

Since the introduction of recombinant therapeutic proteins in the 1980s, dozens of products have been successfully commercialized, and hundreds of new ones are currently in clinical trials. These products provide uniquely effective treatments for numerous human diseases and disorders. They have revolutionized the practice of medicine, saving and improving countless lives. But the most promising protein-based drug will not be of benefit to patients unless it can be manufactured, shipped, stored, and delivered to the patient, while minimizing degradation of the protein. This is a daunting challenge because proteins can readily aggregate, even under solution conditions that greatly favor the native state. Also, proteins are susceptible to numerous pathways of chemical degradation. Adding to the challenge is the potential that even if a small fraction of the protein molecules in a dose is degraded, an immunogenic response may be triggered with the potential to cause adverse effects in patients. Furthermore, the therapeutic protein must be produced at commercial scale using a complicated process that has been developed and documented to consistently result in a high-quality product. Also, the appropriate analytical methods must be developed and validated to ensure that degradation products can be quantified accurately and precisely. Clearly, the successful development of a commercialized therapeutic protein product requires multidisciplinary efforts of experienced, skilled scientists, engineers, and managers, and tremendous expenditure of capital. It is critically important for management to be cognizant of these challenges and to provide the appropriate resources to the development efforts for therapeutic proteins, as well as to establish reasonable timelines for this work, which is so vital to ensuring product quality and protecting patients' safety.

Over the years, as recombinant therapeutic proteins have been developed, the field as a whole has had to learn how to do this properly, and many of the important guiding principles and practical strategies had to be learned "on the job" as products were being developed. There were no established academic or industrial foundations for these efforts, because never before had recombinant proteins been used to treat human diseases and disorders. Fortunately, during this time, many of the leaders in the key disciplines published papers and books describing the continually improving, state-of-the-art approaches to stabilizing proteins, analyzing degradation products, and developing successful formulations.

An example of this type of on-the-job training was the research focusing on developing stable lyophilized formulations of proteins. In the early to mid-1980s, expertise from parenteral sciences and process engineering were applied to formulation and

process development for freeze-dried therapeutic proteins. The results of early efforts were often commercially viable freeze-drying cycles and formulations that provided good cake structure but did not stabilize the protein very well. At the same time, researchers from materials sciences, food sciences, and even zoology were working to understand the mechanisms by which various excipients succeeded or failed to stabilize proteins during freezing, drying, and storage in the dried solid. Combined efforts from all of these disciplines gradually led to determination of these mechanisms as well as to the discernment of the key physical properties (and associated analytical methods) that govern long-term storage stability of dried proteins. As a result, we now have fairly straightforward, rational approaches to development of stable freeze-dried protein formulations. But many challenges remain, particularly understanding the quantitative linkages between different degradation pathways (e.g., oxidation, aggregation) and physical properties of the dried formulation (e.g., glassy-state dynamics, protein structure).

Also, during the years of development of therapeutic proteins the types of degradation products that could be studied, and the quality and resolution of analytical methods have vastly improved. These improvements allow for better understanding of causes and pathways for degradation. However, they also lead to more stringent criteria for the definition of a stable protein product. There are still many analytical challenges. For example, size exclusion chromatography (SEC) is the key method used to quantify levels of protein aggregates and monomer. But this method can provide misleading results because aggregates can dissociate or form during SEC and/or adsorb to the column resin. Thus, values obtained from SEC may not actually represent the true aggregate levels in the protein drug container, so there is a continued effort to investigate methods that can be used to corroborate results from SEC. Currently the most promising approach is analytical ultracentrifugation (AUC). But this method has its own challenges in proper sample handling, data analysis, and appropriate training of personnel. The field must continue to strive to improve SEC and AUC methods for aggregate quantification and to explore new methods (e.g., field flow fractionation).

Today we benefit from the numerous advances in the field that have been made over the last few decades. But we also face many new challenges to developing safe and effective therapeutic proteins. For example, monoclonal antibody products that have doses with relatively high protein concentrations (e.g., $\geq$100 mg/mL) can be difficult to manufacture, stabilize sufficiently, and analyze properly. Additionally, the use of prefilled syringes as product containers has recently led to new issues with protein stability that had to be resolved. In general, we must conduct research to gain more fundamental insights into the effects of the various product containers and their component materials on protein stability. Similarly, we must work to understand how various key processes steps (e.g., filling vials or syringes with pumps) affect protein stability, to increase awareness of these issues, and to create effective strategies to investigate these potential problems and to mitigate them.

Another challenge facing many companies is the need to develop consistent approaches for protein formulation studies, characterizing analytical methods, and studying protein stability during various processing steps. This does not mean that

there should be "platform" formulations for drug product or platform analytical methods; indeed, any platform approach must be confirmed for each individual molecule, and there are many examples of surprising results. Rather, it is important to incorporate the scientific knowledge that has been gained across the industry in rational approaches that are developed and agreed on by educated and experienced personnel to ensure product quality and safety. As more companies develop global operations, such an approach may have the added benefits of promoting best practices between sites and individual researchers, minimizing unproductive conflicts, and speeding product development.

As has been the case throughout the history of working with recombinant therapeutic proteins, the field will take on current and future challenges and learn how to overcome them. Certainly, with future insights into disease pathologies and creation of new therapeutic protein categories, delivery approaches, and analytical methods, even more challenges will arise. With the strong foundation of excellence in therapeutic protein product development and rational approaches to delineate and solve problems, the field will successfully overcome these barriers, and new medicines will be made available for the benefit of patients.

In this book, experts from around the world provide comprehensive overviews of the many important steps involved in—and the critical insights needed for—the successful development of therapeutic proteins. The book is a state-of-the-art summary of what we have learned together as a field as we have worked to define the theory and practice of proper development of safe and effective medicines based on biotechnology. Moreover, it documents how researchers from numerous companies and universities contribute to furthering our insights and expertise for developing therapeutic proteins. The editors and authors are to be congratulated for their leadership in these efforts and their willingness to continue to communicate openly about where we are as a field and where we are going.

JOHN CARPENTER

PREFACE

The unraveling of the human genome, the concomitant explosion of proteomics, and an ever-increasing interest in proteins to treat an expanding range of medical indications have lead to growing interest in the development and production of biomolecules for therapeutic use. The identification of a new candidate drug compound is preceded by substantial scientific efforts and considerable capital investment. In order to realize the value to patients and the healthcare industry, the new drug molecule must be formulated and manufactured in an appropriate dosage form that can be conveniently used by the patient. Understanding the underlying challenges at each step of development and commercialization of the drug product dosage form is central to the successful launch of a biological therapeutic.

In order for proteins to manifest their proper biological and therapeutic effect, their conformational and structural integrity must be maintained at all stages of the development and commercialization process. Biomolecules are generally very sensitive to their microenvironment due to their complex and fragile structures. Once a new biologic has been identified for therapeutic use and product development, the first steps in the development process are determination of the physical and chemical properties of the molecule, identification of the major degradation pathways, and development of stability-indicating analytical methods as well as other biophysical characterization techniques. The information gathered from these early studies is used to identify excipients and conditions that will keep the protein therapeutic molecule in the native conformation and promote long-term product stability. Several chapters in this book discuss the latest biophysical and biochemical characterization techniques, as well as approaches to conducting the early physicochemical characterization studies.

The protein or peptide drug active must then be formulated for preclinical and clinical testing in conditions that preserve the chemical and physical integrity of the molecule, as well as render it in a form suitable for administration to patients. This is generally accomplished by screening the protein under a variety of excipients and conditions and monitoring stability as a function of time, temperature, and other stresses to identify/select the best conditions for further development. Liquid dosage forms may be preferred because of their greater convenience and lower manufacturing costs. However, lyophilized formulations may be required in some cases to attain adequate shelf-stability or where enhanced stability at higher temperatures or other special features are desired. At early stages, lyophilization may also offer a faster or more reliable path to develop an initial clinical formulation. This book contains a number of chapters relating to early formulation development strategies, platform

approaches for initial antibody formulations, high-throughput strategies based on statistical design, and design space considerations. Additional chapters focus on the challenges associated with stability and analysis in the development of high concentration antibody formulations, and the impact of high concentrations on manufacturing and dose delivery. Case examples are provided to illustrate these approaches and offer specific applications.

Concurrent with preclinical and clinical testing of the candidate drug compound, the process development group will typically evaluate additional options available for expression, recovery, purification, and characterization of the drug substance for commercial production. Alternative formulations of the drug product for commercial use will also typically be explored. At this stage, the requirements in terms of stability, shelf-life, and ruggedness are typically much greater than for the earlier stages of development. In addition the focus on minimizing cost of goods and increasing throughput and manufacturing ease and consistency are significantly greater at this stage. Robust conditions for storage and shipment of the bulk drug substance must be identified. During subsequent commercial manufacturing, the purified bulk drug substance needs to be processed and prepared for successful fill/finish of final dosage form and, may go through freeze-thawing, formulation, mixing, filtration and filling operations prior to finishing as a lyophilized or liquid dosage form. Although these unit operations have been studied during earlier stages, the stresses generated and the mechanisms of denaturation in a manufacturing setting may be different, depending on scale, equipment and facility. Chapters dedicated to drug product process development discuss in detail, illustrated with case studies, methodology to develop, characterize and "optimize for scalability" all the manufacturing processes relating to drug product prior to their transfer to manufacturing sites. Additionally, these chapters provide guidance on formulation design considerations to stabilize the drug against the stresses that typically arise during large-scale manufacturing and commercialization in the cGMP environment.

There is growing interest in devices to simplify injection, particularly for products that will be sent home with patients for self-administration. This has led to increased interest in more complex container closures, such as prefilled syringes, either as standalone injection devices or as a component of a more complex injection device such as an auto-injector. The more complex primary containers may introduce additional stresses for the protein drug, as well as increased manufacturing challenges. Several chapters address considerations common to all container closures, as well as specific issues related to the more complex primary containers such as prefilled syringes.

Once the commercial formulation and configuration have been recommended and all the process parameters are locked into, the process is transferred to manufacturing. In simple terms technology transfer is referred to as transfer of a new product design from development (internal or external) into an operational environment for validation and robust sustained production. It can be between sites at a single company or from company to company and may involve a scale change or adaptation to a different equipment train. It is very complex operation that demands in-depth understanding of manufacturing challenges associated with the design of the facility, equipment train,

scale, and operational procedures, besides development of robust processes and analytical methods. Chapters relating to technology transfer will discuss the manufacturing challenges and requirements and provide guidance to the reader as to when in the development phase these requirements need to be incorporated to mitigate the risk of failures and delays in getting the product to the market.

In recent years the field has evolved rapidly in many dimensions. The dramatic expansion in number and diversity of protein therapeutics, new scientific and technical approaches, the evolving regulatory landscape, and changes in marketing requirements and expectations for patient compliance make it imperative to update the available information. This book provides a comprehensive overview and guide to formulation and process development as well as manufacturing of biopharmaceutical drug product, covering both fundamentals and specialized considerations. Case histories are included to illustrate challenges and successful approaches for each phase as well as various classes of protein therapeutics, along with thoughtful analysis of lessons learned. Contributors have been selected from both industry and academia and have a wide range of experience and expertise in this area. The book will benefit scientists and engineers involved at various stages of product development, commercial production, project management, clinical, regulatory affairs, and quality assurance, and can serve as an introduction and reference for students who are contemplating a career in the biopharmaceutical industry.

Color versions of some of the text illustrations can be found at the following ftp site address:
ftp://ftp.wiley.com/public/sci_tech_med/formulation_biopharmaceutical

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