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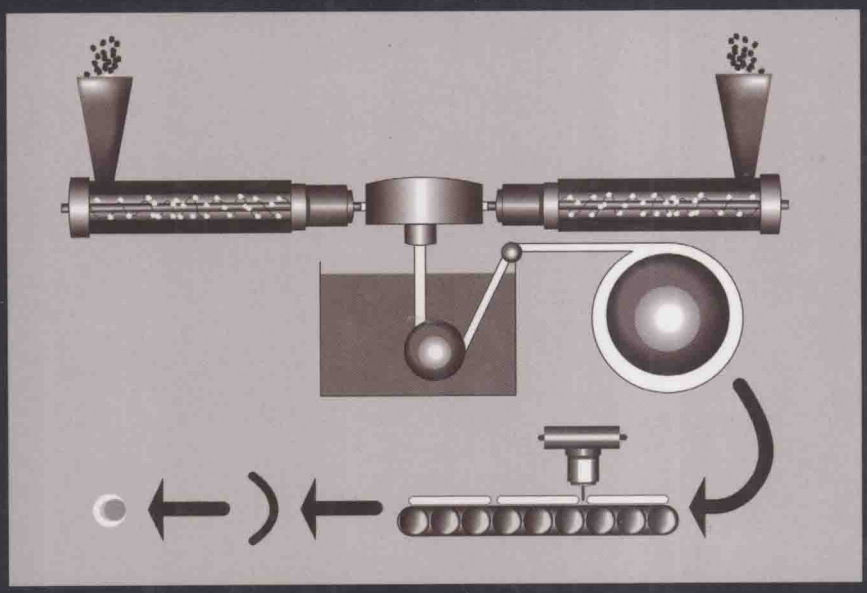
Pharmaceutical Manufacturing Handbook

Production and Processes



Edited by

Shayne Cox Gad

PHARMACEUTICAL MANUFACTURING HANDBOOK

Production and Processes

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PREFACE

This *Handbook of Manufacturing Techniques* focuses on a new aspect of the drug development challenge: producing and administering the physical drug products that we hope are going to provide valuable new pharmacotherapeutic tools in medicine. These 34 chapters cover the full range of approaches to developing and producing new formulations and new approaches to drug delivery. Also addressed are approaches to the issues of producing and packaging these drug products (that is, formulations). The area where the most progress is possible in improving therapeutic success with new drugs is that of better delivery of active drug molecules to the therapeutic target tissue. In this volume, we explore current and new approaches to just this issue across the full range of routes (oral, parenteral, topical, anal, nasal, aerosol. ocular, vaginal, and transdermal) using all sorts of forms of formulation. The current metrics for success of new drugs in development once they enter the clinic (estimated at ranging from as low as 2% for oncology drugs to as high as 10% for oral drugs) can likely be leveraged in the desired direction most readily by improvements in this area of drug delivery.

The *Handbook of Manufacturing Techniques* seeks to cover the entire range of available approaches to getting a pure drug (as opposed to a combination product) into the body and to its therapeutic tissue target. Thanks to the persistent efforts of Michael Leventhal, these 34 chapters, which are written by leading practitioners in each of these areas, provide coverage of the primary approaches to these fundamental problems that stand in the way of so many potentially successful pharmacotherapeutic interventions.

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SECTION 1

MANUFACTURING SPECIALTIES

1.1

BIOTECHNOLOGY-DERIVED DRUG PRODUCT DEVELOPMENT

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Pharmaceutical Manufacturing Handbook: Production and Processes, edited by Shayne Cox Gad

1.1.1 INTRODUCTION

Although the origins of the first biological and/or protein therapeutics can be traced to insulin in 1922, the first biotechnology-derived pharmaceutical drug product approved in the United States was Humulin in 1982. In the early stages of pharmaceutical biotechnology, companies that specialized primarily in the development of biologicals were the greatest source of research and development in this area. Recent advances in molecular and cellular biological techniques and the potential clinical benefits of biotechnology drug products have led to a substantial increase in their development by biotechnology and traditional pharmaceutical companies. In terms of pharmaceuticals, the International Conference on Harmonization (ICH) loosely defines biotechnology-derived products with biological origin products as those that are "well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology" [1]. In practical terms, biological and biotechnology-derived pharmaceutical agents encompass a number of therapeutic classes, including cytokines, erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines [1]. Additionally, short interfering and short hairpin ribonucleic acids (siRNA, shRNA) and antisense oligonucleotide therapies are generally characterized as biotechnology-derived products.

According to the biotechnology advocacy group, The Biotechnology Industry Organization (BIO), pharmaceutical-based biotechnology represents over a $30 billion dollar a year industry and is directly responsible for the production of greater than 160 drug therapeutics and vaccines [2]. Furthermore, there are more than 370 biotechnology-derived drug products and vaccines currently in clinical trials around the world, targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, acquired immunodeficiency syndrome (AIDS), and arthritis. While the clinical value of these products is well recognized, a far greater number of biotechnology-derived drug products with therapeutic potential for life-altering diseases have failed in development.

As the appreciation of the clinical importance and commercial potential for biological products grows, new challenges are arising based on the many technological limitations related to the development and marketing of these complex agents. Additionally, the intellectual property protection of an associated agent might not

provide a sufficient window to market and regain the costs associated with the discovery, research, development, and scale-up of these products. Therefore, to properly estimate the potential return on investment, a clear assessment of potential therapeutic advantages and disadvantages, such as the technological limitations in the rigorous characterization required of these complex therapeutic agents to gain Food and Drug Administration (FDA) approval, is needed prior to initiating research. Clearly, research focused on developing methodologies to minimize these technological limitations is needed. In doing so we hypothesize the attrition rate can be reduced and the number of companies engaged in the development of biotechnology-derived products and diversity of products will continue to expand.

Technological limitations have limited the development of follow-on, or generic biopharmaceutical products that have lost patent protection. In fact, the potential pitfalls associated with developing these compounds are so diverse that regulatory guidance concerning follow-on biologics is relatively obscure and essentially notes that products will be assessed on a case-by-case basis. The reader is encouraged to see Chapter 1.2 for a more detailed discussion concerning regulatory perspectives pertaining to follow-on biologics.

Many of the greatest challenges in producing biotechnology-derived pharmaceuticals are encountered in evaluating and validating the chemical and physical nature of the host expression system and the subsequent active pharmaceutical ingredient (API) as they are transferred from discovery through to the development and marketing stages. Although this area is currently a hotbed of research and is progressing steadily, limitations in analytical technologies are responsible for a high degree of attrition of these compounds. The problem is primarily associated with limited resolution of the analytical technologies utilized for product characterization. For example, without the ability to resolve small differences in secondary or tertiary structure, linking changes to product performance or clinical response is impossible. The biological activity of traditional small molecules is related directly to their structure and can be determined readily by nuclear magnetic resonance (NMR), X-Ray crystallography (X-ray), mass spectrometry (MS), and/or a combination of other spectroscopic techniques. However, methodologies utilized for characterizing biological agents are limited by resolution and reproducibility. For instance, circular dichroism (CD) is generally considered a good method to determine secondary structural elements and provides some information on the folding patterns (tertiary structure) of proteins. However, CD suffers from several limitations, including a lower resolution that is due in part to the sequence libraries used to deconvolute the spectra. To improve the reliability of determining the secondary and tertiary structural elements, these databases need to be developed further. An additional example is the utility of two-dimensional NMR (2D-NMR) for structural determination. While combining homonuclear and heteronuclear experimental techniques can prove useful in structural determination, there are challenges in that 2D-NMR for a protein could potentially generate thousands of signals. The ability to assign specific signals to each atom and their respective interactions is a daunting task. Resolution between the different amino acids in the primary sequence and their positioning in the covalent and folded structures become limited with increasing molecular weight. Higher dimensional techniques can be used to improve resolution; however, the resolution of these methods remains limited as the number of amino acids is increased.

Understanding the limitations of the analytical methodologies utilized for product characterization has led to the development of new experimental techniques as well as the refined application of well-established techniques to this emerging field. Only through application of a number of complementary techniques will development scientists be able to accurately characterize and develop clinically useful products. Unfortunately, much of the technology is still in its infancy and does not allow for a more in-depth understanding of the subtleties of peptide and protein processing and manufacturing. For instance, many of the analytical techniques utilized for characterization will evaluate changes to product conformation on the macroscopic level, such as potential denaturation or changes in folding, as observed with CD. However, these techniques do not afford the resolution to identify subtle changes in conformation that may either induce chemical or physical instabilities or unmask antigenic epitopes.

Further limiting successful product development is a lack of basic understanding as to critical manufacturing processes that have the potential to affect the structural integrity and activity of biopharmaceuticals. As with traditional small molecules, stresses associated with the different unit operations may affect biopharmaceutical products differently. In contrast to traditional small molecules, there is considerable difficulty in identifying potentially adverse affects, if any, that a particular unit operation may have on the clinically critical structural elements of a drug. Considering that many proteins exhibit a greater potential for degradation from shear stress, it is particularly important to assess any negative effects of mixing, transport through tubing, filtration, and filling operations. Essentially all unit operations for a given manufacturing process could create enough shear stress to induce minor structural changes that could lead to product failure. The difficulty is establishing what degree of change will have an impact on the stability, bioactivity, or immunogenic potential of the compound. Unfortunately, unless exhaustive formulation development studies are conducted, coupled with a comprehensive spectrum of analytical methodologies, these effects may not be readily evident until after scale-up of the manufacturing process or, worse yet, in the clinical setting. Moreover, modeling shear and stress using fluid dynamic structurally diverse molecules is a foreboding task. Extending these models to validate process analytical technologies (PAT) and incorporate critical quality by design (QbD) elements in the development process for a collection of biopharmaceuticals would be largely hindered by the daunting nature of the task at hand.

The use of biological systems to produce these agents results in additional variability. Slight changes in nutrient profile could affect growth patterns and protein expression of cultured cells. Furthermore, microbial contamination in the form of viruses, bacteria, fungi, and mycoplasma can be introduced during establishment of cell lines, cell culture/fermentation, capture and downstream processing steps, formulation and filling operations, or drug delivery [3]. Therefore, establishing the useful life span of purification media and separation columns remains a critical issue for consistently producing intermediates and final products that meet the defined quality and safety attributes of the product [4]. In short, understanding the proper processability and manufacturing controls needed has been a major hurdle that has kept broader development of biopharmaceutical products relatively limited.

Notwithstanding the many technological hurdles to successfully develop a pharmaceutically active biotechnology product, they offer many advantages in terms of