

SECOND EDITION

Advances in Large-Scale

Biopharmaceutical Manufacturing

and Scale-Up Production

A COMPREHENSIVE STUDY OF THE SCIENCE, TECHNOLOGY
AND BUSINESS OF BIOPHARMACEUTICAL MANUFACTURING



PART 1: Emerging Technologies, Scientific Advancements

PART 2: Business, Capacity and Regulatory Issues

Eric S. Langer, Editor

Advances in Large-Scale Biopharmaceutical Manufacturing and Scale-Up Production Second Edition

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PART 1
Emerging Technologies, Scientific Advancements

PART 2
Business, Capacity and Regulatory Issues

Foreword by Wolfgang Noe, Ph.D.

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Eric S. Langer
Managing Editor

Preface

This is the second edition of our extensive research into current advances in biopharmaceutical manufacturing and scale-up production. It has been updated as a result of requests from the industry to ensure a single resource that tracks and presents trends in this fast-changing scientific area. The study was undertaken, managed and coordinated by BioPlan Associates, Inc., a biopharmaceutical management and marketing research consulting firm in Rockville, MD, based on its 18 years experience and knowledge of the market segment. BioPlan surveyed the industry to identify required content, and then selected subject matter experts to author relevant chapters for this study.

The American Society for Microbiology, in recognizing the importance of applied sciences in biotechnology processes, has lent its name to this endeavor. ASM's mission is to promote research and research training in the microbiological sciences and to assist communication between scientists, policy makers, and the public to improve health, protect the environment, and foster economic well-being. This study provides a platform from which both basic and applied research scientists can share findings and novel technologies associated with biopharmaceutical manufacturing. The findings of this report may also support public, health and economic policy.

Each chapter provides a unique, unbiased view of the current state of the science and technology associated with biopharmaceutical manufacturing and scale-up production. While no single body of work can encompass all the advances being made in the field, this work offers the most comprehensive information to date on technologies and processes that will be leading the next decade.

Included are sections on biopharmaceutical manufacturing technologies for human therapeutics, including mammalian, microbial, and yeast systems, and other novel technologies. We have evaluated the entire production process, from early scale-up through purification and downstream production. Each chapter includes extensive technical information and quantifiable data, as well as including real-world situations and relevant case studies that provide context for the discussions.

The intended audiences are decision-makers at biopharmaceutical organizations, contract manufacturing organizations, suppliers to the industry, and international entities evaluating this market. As the industry progresses, we plan to keep this study current by providing regular updates as technologies evolve.

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Foreword

As I am writing these lines, the biotechnology industries, and the products made by 'biotech' processes, continue to flourish and mature. Products based on microbial processes have been made for more than fifty years in large-, and very large-scale reactors ($> 100,000$ L). A multi-ton industry for biotech products, like amino acids, has developed over the past decades, and is still growing and prospering. This bio-based industry has become well established over the years and is now making significant contributions to food industry related products as well.

However, over the past 20 to 30 years, much of biotechnology's focus has been drawn to large scale manufacturing of biotherapeutics; and there has been much success to report regarding progress in biologics manufacturing. Biotechnically manufactured therapeutic processes are now a multi-billion dollar, world-wide market!

Since the mid 1970s, vaccines derived primary from human or primate cells, such as vero-based Interferon production, were the primary focus for biologics manufacturing processes. Shortly afterward the first recombinant based biotherapeutics appeared. Erythropoietin, rt-PA, and Rituxan are just a few examples of the innumerable biotherapeutic products that followed. While many organizations in the mid 1980s were proud to achieve mg/L quantities, we currently are finding it necessary to target multi-grams per L for biologics in routine operation.

Today, standard manufacturing is accomplished in bioreactors for mammalian cells that can now produce 10,000 to 25,000 L working volumes. A mere 15 years ago, the fact that a complex biological could successfully be produced in a cell based system was astonishing. Today, our challenges are more of related to economics, quality and consistency. In addition, a growing challenge involves the creation of global markets using worldwide manufacturing capability outside Europe and the US, which are currently the major producers of therapeutically used biologics. Still, questions around product consistency, quality and robustness need to be addressed for regulatory acceptance, stability, the supply chain distribution, marketing and market maintenance of biologically manufactured therapeutics worldwide.

Despite intensive efforts in individualized therapeutic approaches, the most important therapeutic applications in major therapeutic areas, such as immunology, oncology and neurology, are still recombinant protein-based, and will continue to be that way in the near future. These protein products are generally manufactured using cell culture based systems (mainly antibody therapeutics), while many recombinant growth factors are based on microbial systems.

Finally, the question is, are we prepared for the challenges of the future? For example, are we prepared for the economic pressure to make biologics for less than \$100/gr? Are we able, at the same time to maintain focus on quality, consistency and efficacy for those 'well characterized biologics' that are produced in multi-product facilities around the world? And to intensify this equation, how will the question of quality be put on the table as biogenerics/biosimilars, which are expected to populate the market, be handled?

To give a comprehensive overview of the current biologics market and related manufacturing areas, the BioPlan/ASM Press has compiled its second edition of *Advances in Large-Scale Biopharmaceutical Manufacturing and Scale-Up production*. In this edition you will find an inclusive summary of individual chapters written by bioprocess experts. Topics include: productivity, large-scale microbiological manufacturing, vaccine production, as well as protein recovery and protein stability-related topics, with actual details on new approaches. In addition, you will find an excellent summary of business perspectives including facility design, disposable technology, regulatory considerations on biogenerics, and follow-up on biologics and post-approval changes for biologics. At the conclusion of this comprehensive summary of up-to-date biotech manufacturing, you will find coverage of legal and IP issues, worldwide production capacity, and economics considerations.

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