SECOND EDITION

BIOTECHNOLOGY OPERATIONS

Principles and Practices

John M. Centanni • Michael J. Roy

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Principles and Practices

Although our passion is in the expeditious development of biomedical products, it is also important to recognize the selflessness of research volunteers and patients who have the compassion and strength to participate in human clinical research studies for the betterment of others and in the hope of advancing medicine; without this, the development of new treatments would not be possible.

Preface

This book resulted from the authors' experiences gained while working in biotechnology development at industry, government, and academia, and while teaching a graduate course titled biotechnology operations. This course is offered to graduate students in the master of science (MS) in Biotechnology Program at the University of Wisconsin-Madison (http://www.ms-biotech.wisc.edu/). In this course, we examine the undertaking of developing biotechnology products, focusing on the scientific and management skills of biomanufacturing, clinical trials, nonclinical studies, project management, quality assurance, quality control, and regulatory affairs. The course emphasizes both operational planning for success and integration of plans and efforts in these seven functional areas. The instructors realized from their experience in the biotechnology industry the great need to carefully plan and fully integrate biotechnology development projects. The course is taught in that manner and this book reflects that philosophy; thus, this book is a practical guide for students and for those employed or interested in biotechnology.

This book is intended to meet a need and to fill a gap. Despite the wealth of experience with operations in the biotechnology industry, there was no single comprehensive and practical, yet fundamental, guide available. Many books and most individual scientific or trade publications are highly technical and focused on a specific aspect of biotechnology. They do not emphasize the themes of planning and integrating the seven operational endeavors. *Biotechnology Operations: Principles and Practices* is written with the objective of presenting a roadmap and reference for biotechnology operations, integrating these functional areas through the processes of product planning and design, and the practice of project management. It applies lessons learned in the biotechnology industry over past decades as novel products have been developed from emerging scientific discoveries. The lessons highlight development principles that could help the industry to bring to market more efficiently and quickly the safe and effective biotechnology products of the future. While focused largely on biopharmaceuticals, this book also reflects development of other biotechnology products. It is anticipated that this book will provide the reader a clear understanding of basic principles and practices, and assist in reducing risks and in resolving problems as future biotechnology discoveries are developed into products.

In preparation of the 2nd edition of this book, and at the request of the readers, we have enhanced our use of examples by including additional text boxes, diagrams, and figures. This 2nd edition now includes up-to-date methodologies associated with current biotechnology industry practices; incorporated are examples of tissue engineering, stem cell technologies, and the

use of alternative bioreactors. Chapter 2 now includes additional schematics to better depict abstract concepts. Chapter 3 is expanded to include current thinking of the FDA on various topics, and now includes specific information on submission formats and processes such as Common Technical Document format and electronic submissions. Chapters 2, 5, and 6 contain additional illustrations and examples of design and change control, management responsibilities, quality audit process, biomanufacturing facilities, whole animal bioreactors, and stem cell manufacturing processes. Chapter 7 is updated and includes depictions of testing equipment, figures outlining new concepts, and examples of trending and trend analysis. Chapter 8 now includes specific study design examples that have been used successfully to support translation of new biopharmaceutical products into human clinical trials. Finally, Chapter 9 includes an emphasis on the practical use of Good Clinical Practice (GCP) and how it directly applies to human clinical study management.

The target audience for this book is advanced undergraduates or postgraduate students pursuing an advanced degree in biotechnology and individuals working in any aspect of biotechnology product development. This book should be particularly relevant to students interested in biotechnology, biopharmaceutical product development, and those already working in biotechnology. The information presented in this book can be used to expand upon one's current experience while providing an additional level of appreciation and overview of the product development process. For those in the biotechnology industry, this book provides guidance on planning a new development program or managing an ongoing program. Noting that irrespective of the nature of the new biomedical product, the principles and practices outlined in this book are essential for the success of developing and marketing of a new product.

Acknowledgments

The authors sincerely hope the experiences, ideas, and examples related in *Biotechnology Operations: Principles and Practices* will inspire the reader to plan and implement meaningful strategies and thereby expedite the development of desperately needed new medical products. Many of the examples and suggestions in this book represent challenges and successes that we've experienced throughout our careers. It is our passion to contribute ways that facilitate the transition of new therapies from the discovery or research environment into the clinic.

Special thanks go

- To the many students in the Master of Science in Biotechnology Program for helpful discussions and feedback on the best way to present this wealth of information.
- To Eric Schmuck and Derek J. Hei for their assistance with developing ideas and materials for this 2nd edition.
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Our special thanks go to Kurt Zimmerman, program director of the Master of Science in Biotechnology Program at the University of Wisconsin-Madison, for his continuing support and for providing a program in which the students are trained and encouraged to become industry leaders.

Authors

John M. Centanni, MS, has a faculty associate appointment in the School of Medicine and Public Health at the University of Wisconsin-Madison, in the Master of Science in Biotechnology Program. He has firsthand experience of leading functional groups in biotechnology firms as a project manager. His strong scientific background has allowed him to serve multiple scientific R&D roles in the biotech industry contributing to the development of preclinical safety studies, quality control assays, and animal models. Centanni has participated in the development and implementation of quality systems to meet regulatory compliance in both the industry and academic environments. He has directly overseen the regulatory and clinical operations associated with a number of early phase, multicenter, human clinical trials. Centanni has worked in the pharmaceutical and biotechnology industry since 1987 and has more than 20 years of product development experience for drugs, biologics, and devices. He has instructed and trained basic scientists and clinical researchers in regulatory compliance and expectations associated with clinical product development (Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Tissue Practice (GTP), and Good Clinical Practice). Centanni is experienced in preclinical research, regulatory, quality, clinical development, and project management, and has been involved in the development and registration of pharmaceutical products across a number of therapeutic categories.

Centanni is the director of the Investigational New Drug (IND)/ Investigational Device Exemption (IDE) Consultation Services, where he leads a team of consultants at the University of Wisconsin-Madison, Institutes for Clinical and Translational Research. In this role, he provides campus-wide support to clinical investigators advancing their investigational product from the research environment into the clinic. This support ranges from strategic support for the selection of viable product development candidates to characterization of products and design and implementation of human clinical trials.

Centanni is also an active participant in the Stem Cell and Regenerative Medicine Center and Cardiovascular Regeneration Focus Group at the University of Wisconsin. He serves on a number of grant review panels that include California Institute for Regenerative Medicine (CIRM), Institute for Clinical and Translational Research (ICTR) Novel Therapeutics Pilot Awards, and American Burn Association (ABA) Multicenter Clinical Trials Group.

Before joining the University of Wisconsin, Centanni directed the regulatory, quality, and clinical efforts of a small biotechnology firm in Madison, Wisconsin. As an accomplished molecular and cellular biologist, Centanni has successfully directed multimillion dollar translational and clinical

research projects as principal investigator. Additional professional attributes of Centanni include a notable patent portfolio as an inventor on more than a half dozen intellectual property filings and authorship of several scientific journal articles and book chapters.

Centanni is a graduate of Hood College, Frederick, Maryland, with a master's degree in biomedical sciences supported by a thesis and defense. Prior to graduate school, Centanni earned a BS in biology at the University of Wisconsin-Oshkosh, Wisconsin. In his free time, Centanni enjoys saltwater fishing, snorkeling, traveling, and playing racquet ball.

Michael J. Roy, PhD, is an emeritus professor at the University of Wisconsin-Madison, where he previously taught in the Master of Science in Biotechnology Program in the School of Medicine and Public Health. He has successfully developed biopharmaceutical products and medical devices for private and publically held firms, nongovernmental organizations, and the federal government for more than 27 years, serving as a consultant in biotechnology development over the past decade. Many of his efforts, including product development planning, regulatory affairs, quality systems, project management, biomanufacturing, quality control, and clinical studies, focus on early development of novel biotechnology products, notably vaccines and antimicrobial agents.

He is a graduate of the University of Wisconsin-Madison with a PhD in pathology, of Louisiana State University Medical Center, New Orleans, with an MS in tropical medicine and medical parasitology, and of the University of Wisconsin-Platteville with a BS in biology. Colonel Roy is retired from the U.S. Army Reserves, where he was involved in developing in vitro diagnostic devices and vaccines and in establishing quality systems at the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick. He also enjoys hiking, raising hardwood trees in southwestern Wisconsin, and has archeological interests of that region.

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