Preface

Upon completing a Ph.D. in chemical engineering, I chose an industrial career. Looking back, I remember my start in the biopharmaceutical industry as being mired in mistakes and characterized by a general lack of understanding of the methods and technologies used for production. I recall my boss at the time mentioning the need to perform an "OQ" (operational qualification) on a piece of equipment. I had no idea what OQ meant, much less what the equipment being "OQ'd" was used for. And I wasn't at all sure what I would do to figure out how to accomplish the task at hand.

Somehow, I managed to survive and even thrive in the biopharmaceutical industry. There is no doubt that my training in chemical engineering provided a solid foundation in topics such as fluid dynamics, heat transfer, mass transfer, and reactor design, all of which are fundamental to the unit operations used in a biopharmaceutical manufacturing environment. But I still had much to learn. I had only a modicum of familiarity in the practical and theoretical aspects of the unit operations common to the biopharmaceutical industry, such as cell culture, chromatography, or ultrafiltration. I had no knowledge of the stringent documentation rules, the importance of clear and detailed procedures, qualification and validation requirements, methods for addressing deviation root causes, and the numerous other expectations required under Good Manufacturing Practice (GMP) standards that govern production of biopharmaceutical products. And I had no understanding of the biological product landscape to help put my work into context – the variety of biological products on the market, how those products work, and the diseases that were being treated or prevented. When I speak with colleagues of a similar age about their early days in the industry, most have similar stories.

As I progressed in my career, it became clear to me that a university student who was offered an educational experience with even just a few courses tailored to biopharmaceutical production could really hit the ground running when he or she joined a biopharmaceutical company. My desire to work with others to create these learning opportunities led me to join the Golden LEAF Biomanufacturing Training and Education Center (BTEC) at North Carolina State University, which opened in July 2007 to provide education and training opportunities to develop skilled professionals in the biomanufacturing industry. This mission has led to the development of numerous courses – for both university students and professionals – in the area of GMP manufacturing of biopharmaceuticals. The curriculum that has been developed is unique and has produced a cadre of graduates who, by all accounts, have hit the ground running when they enter the biopharmaceutical industry. And our professional programs have helped to fill knowledge gaps for literally thousands of professionals affiliated with the industry in a variety of ways. BTEC – its mission, the many courses that have been developed, the many colleagues who have supported these efforts during the past decade, and the many students who have (hopefully) benefitted – is the inspiration for this book.

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As you read the book, I think it will become clear that the design and execution of biopharmaceutical processes is a multidisciplinary effort. For example, expertise in molecular biology is required to create the cell lines used to produce biopharmaceutical products. Cell culture and fermentation require training in microbiology, and chromatography is best undertaken with a background in biochemistry and/or chemical engineering. As a result, covering all the topics addressed in the book required three co-authors – myself, Charlie Rutter, and Becky McCuen. I took on the downstream processing material, Charlie shared his expertise in fermentation and cell culture, while Becky, who works in the industry, shared GMP/regulatory expertise.

Our vision for the book has been to provide concise, comprehensive coverage of the principles, processes, and practices underlying biopharmaceutical production. Our choice of the material included has been influenced by both our industry experience and teaching experience. We are especially grateful for the many questions posed over the years by university students looking at this topic with fresh eyes and by current professionals who bring more experience to the classroom. The questions from both groups have informed the topics covered here and the way they are covered. We hope that the book strikes the right balance between practical and theoretical information and the story it tells benefits a variety of audiences: students using it as a textbook for a course on biopharmaceutical manufacturing or professionals working in the biopharmaceutical (or a related) industry who simply need information on how biopharmaceutical production is done.

Chapter 1 provides an overview of biopharmaceutical products, explaining what they are, the components of a biopharmaceutical drug product, and what we mean by quality – a critical topic given that biopharmaceuticals are delivered to patients by some form of injection and products must be effective for the sake of the patient. This first chapter is intended to set the foundation for all subsequent discussion by clearly defining the product that is being produced. Chapter 2 provides an overview of the process steps used in production of biopharmaceutical products, how these process steps are designed, and the design of the facilities in which the products are made. It is intentionally written at a high level, as subsequent chapters provide greater detail on process steps (i.e., individual unit operations) and practices. An important theme in the chapter is the criticality of the manufacturing process and production facility to overall product quality. The discussion around quality continues in Chapter 3, which covers details on GMP requirements – the minimum requirements that ensure a product is safe for use and effective – that apply to biopharmaceutical manufacturing.

Chapters 4–9 take a deeper look at production processes by considering each of the unit operations commonly used to produce drug substance of the required quality. Those chapters are presented in the order that unit operations are likely to occur in a manufacturing process. Chapter 4 covers fermentation and cell culture, the steps in which most biopharmaceutical products are produced. Chapter 5 covers methods for cell lysis, a necessary step when a biopharmaceutical product remains within the host cell once produced. Chapters 6 (centrifugation) and 7 (filtration) look at solid-

liquid separations – required because, among a number of applications, the product must be separated from the cells used to produce it. Chapter 8 discusses chromatography, the unit operation commonly used for removing soluble impurities from the product, which at this point in a process is typically the active ingredient dissolved in an aqueous solution that also contains a number of undesirable soluble impurities that would cause harm to a patient. Chapter 9 focuses on ultrafiltration, a technology that can be used in a number of locations within a process but is almost always needed to formulate (e.g., exchange buffer systems) the final product. And, finally, we wrap up in Chapter 10 by summarizing some of the key concepts in the book and briefly considering some topics that were not able to be covered.

We have striven to make the concepts presented in each chapter clear and accurate. Despite our efforts, we suspect that there may be flaws – hopefully very few – that need to be fixed. We would be grateful if you would inform us of any such issues so that they can be corrected.

We would be remiss not to make special mention of vaccines, given the COVID-19 pandemic that has wreaked havoc on much of the world's population in a matter of months. The pandemic started two-thirds of the way into the writing of this book, and it has been fascinating to see the speed at which two vaccines (at the time of this writing) were developed, authorized for use, and manufactured for use in the United States. The fact that those vaccines rely on mRNA technology, when no mRNA vaccines had previously been licensed, makes the COVID-19 vaccine story even more interesting. The need to rapidly develop and manufacture billions of doses of COVID-19 vaccines highlights the importance and societal impact of biopharmaceutical manufacturing. Indeed, many aspects of biopharmaceutical manufacturing presented in this book apply to production of those mRNA vaccines used against COVID-19 and to production of other types of COVID-19 vaccines likely to be approved in the near future.

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On behalf of the authors,
Gary Gilleskie