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The first edition of this book was published when monoclonal antibodies had established themselves as a powerful force in medicine and already dominated mammalian cell culture processes. Antibodies have always offered a collective bargaining power brought about by their consistent properties, but their vast potential has grown as more successful second- and third-generation products have been launched, and with hundreds of candidates in preclinical and clinical development the need for state-of-the-art manufacturing technology is greater than ever before. Monoclonal antibodies have maintained and even consolidated their position as market leaders, and this will be sustained by waves of engineered antibody-related molecules that promise to fill the market for years to come.

I first came into contact with this field in 1986, when monoclonal antibody production was in its infancy, and a milligram of antibodies was worth far more than its weight in gold. At that time, my colleagues and I had visions of curing cancer by drug targeting, and we linked all sorts of cytotoxic agents to the antibodies we produced. Some of the expectations surrounding the medical use of antibodies turned out to be premature and unrealistic. Our awareness coincided with the first real downturn in the biotechnology sector, but antibodies survived in niche markets for diagnostics and research reagents. Years later, this market segment was reborn and monoclonal antibodies are now stronger than ever. Indeed, they are the fastest-growing class of biotherapeutics with nearly 50 products on the US market in 2016 and well-filled development pipelines [1].

Most commercial antibodies are still produced in cultured mammalian cells, and an entire subindustry has evolved around upstream production and downstream processing to ensure that manufacturing processes generate safe and efficacious products suitable for administration to humans. At the end of the 1980s, antibodies were produced commercially by cultivating mammalian cells in perfusion fermenters, but the yields rarely exceeded 100 mg/L. Huge volumes of culture broth needed to be processed to achieve even these yields, and the easiest way to bring the volume down was polyethylene glycol (PEG) precipitation with tons of material and endless centrifugation cycles. The yields
were poor and difficult to reproduce, but there were no alternatives. Since then, the productivity of cell cultures has increased significantly, with 5 g/L titers now routine and the real prospect of 10–20 g/L yields in the next decade. This increase in titers has heaped pressure on the downstream processes that we use to extract and purify antibodies from cell culture broth, and the technologies used in downstream processing have been forced to modernize and improve in the face of this increasing challenge.

When the first edition of this book was published, downstream processing meant packed-bed chromatography, a workhorse that had served the industry well since the first proteins were manufactured [2]. But even at that time, there were rumblings of doubt, with some even predicting that traditional chromatography was facing a terminal decline [3]. Unlike fermentation, chromatography steps in downstream processing do not benefit from an economy of scale. The bind-and-elute cycles in chromatography are driven by mass rather than by volume, and this means that increasing batch sizes translate directly and almost linearly into increasing costs. This phenomenon particularly affects the first column, which captures the product. This initial recovery step was therefore identified as the most serious potential bottleneck, with knock-on effects throughout the processing facility in terms of column sizes, buffer preparation areas, and hold tanks. Others predicted that packed-bed chromatography would survive and even flourish [4, 5]. This has indeed proven to be the case [6]. The revolution never happened, chromatography was never abandoned, and chromatography today has much the same central role in antibody manufacturing as it did a decade ago.

However, the industry has undergone and is still undergoing massive redevelopment. The exciting atmosphere of incipient change that inspired the first book has not abated, although the focus has moved. There are many new challenges that were distant or unheard of 10 years ago, including novel and more potent antibody formats, new treatment indications, the advent of personalized medicine, the drive toward distributed manufacturing, the increasing importance of flexibility, and finally the success of biosimilars, which will change the entire biopharmaceuticals market beyond recognition. In reaction to these developments, the market is becoming increasingly fragmented and decentralized, with the focus shifting from in-house production to outsourcing, and from dedicated single-product facilities to multiproduct contract manufacturers using disposable processing solutions.

This second edition, therefore, follows in the footsteps of the original, but has expanded to embrace diverse new technologies and products, and the trend toward making modern production facilities more adaptable and flexible (helped in no small way by the increasingly supportive initiatives of the regulatory agencies). Chapter 1 brings us right up to date with current practices in monoclonal antibody purification and makes the case for future developments in this area. This is complemented by Chapter 2, which provides an informative historical overview of the development of antibody purification technologies. Chapters 3–6 address historical and contemporary practices in antibody purification, beginning with harvest and recovery, capture by Protein A chromatography, and a summary of non-Protein A methods. Chapters 7 and 8 address hydrophobic interaction chromatography and mixed-mode chromatography as specific capture methods.

Chapter 9 begins with a summary of process development strategies before considering nonchromatography methods and their application in monoclonal antibody purification processes (Chapter 10), focusing on process-scale precipitation (Chapter 11) and the use of charged membranes (Chapter 12). Chapters 13 and 14 consider disposable packed-bed chromatography solutions and integrated polishing steps for antibody
purification. The focus then shifts to orthogonal methods for virus removal (Chapter 15), before we consider platform technologies that are used to integrate virus clearance with capture and purification (Chapter 16), and the evolution of platform technologies for antibody purification (Chapter 17). We then discuss the use of continuous chromatography for the high-resolution separation of antibodies (Chapters 18 and 19), and the development of accelerated seamless antibody purification (Chapter 20) as an industrial process.

Chapters 21–23 look at the economic perspectives of antibody manufacture, one from the standpoint of process economics, the next from the standpoint of process design and optimization, and finally from the perspective of designing an efficient facility using smart design principles. In Chapter 24, we consider process development by high-throughput screening and modeling, and the unique aspects of process development for antibody fragments (Chapter 25) and other derivatives (Chapter 26), including antibody–drug conjugates (Chapter 27) and IgM/IgA products (Chapter 28). We also consider the emerging field of antibody production in plants (Chapter 29), including the potential application of plants for very-large-scale antibody manufacturing (Chapter 30).

Chapter 31 considers the last stages of antibody manufacturing, namely formulation and filling. Finally, the book is wrapped up with Chapter 32, which looks to the future by considering what drives change in the industry, particularly factors that are likely to influence the techniques and technologies that will be adopted for antibody purification in the decades to come.

The second edition of the book shows that the future remains promising for antibody manufacturing and that the industry still relies on innovation to make progress and adapt to the shifting market environment. Neither the original edition of the book nor the much expanded second edition would have been possible without the many academic and industry colleagues who have contributed their expertise, opinions, and above all their passion for the improvement of antibody manufacturing, leading to technological advances and innovations that will help break through the current ceiling in antibody processing and provide less-expensive and higher quality biopharmaceutical products long into the future.

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