Preface

If you are humble, nothing will touch you, neither praise nor disgrace, because you know what you are.

Mother Teresa, Missionaries of Charity in Calcutta India, 1910–1997

Preparing the 2nd edition of my book was a humbling experience for me. My primary purpose for updating the 1st edition was to continue to provide relevant insight and practical suggestions for a risk-managed, common sense, scientific, practical business approach to managing the Chemistry, Manufacturing and Controls (CMC) regulatory compliance requirements and expectations for biopharmaceuticals as human medicinal products. But the scope of this approach was almost overwhelming as there was so much that could not be included in the updated edition. Also, the more I evaluated what to include in the updated edition, the more I realized how little I really understood about everything that is occurring in the field of biopharmaceuticals and other biologics. I trust that my choices will be of the most benefit.

The magazine, Popular Mechanics, www.popularmechanics.com, made a bold prediction in their January 2000 issue. Looking forward to 2050, it was stated, "We expect the first part of the 21st century to usher in a new golden age of pharmaceuticals. It will begin with the introduction of a powerful arsenal of weapons against the 200 or so diseases we call cancer." Well, we are not there yet by any means, but so much has changed since the 1st edition of this book was published in 2004. There are now additional manufacturing processes for producing commercial biopharmaceuticals—transgenic plant cell cultures and transgenic animals. In addition to commercial recombinant proteins and monoclonal antibodies, there are now commercial cell-based medicines (cellular therapy) and DNA-based medicines (gene therapy). Biosimilars are now on the marketplace in Europe and under review for commercial approval in the USA. Vaccine manufacturing has resurged due to the concerns of potentially pandemic mutated animal influenzas (e.g., swine flu, bird flu). Strategic international regulatory guidances have been adopted that are driving the entire pharmaceutical industry, including biopharmaceuticals, to a higher standard of performance, including Quality by Design (QbD), Quality Risk Management (QRM), and Pharmaceutical Quality Systems (PQS). The vast majority of the over 600 regulatory references listed in this book were either issued or updated since the release of the 1st edition.

All of these changes since 2004 led me to expand this updated edition to include not only biopharmaceuticals but also other biologics (e.g., live virus vaccines, human plasma-derived proteins, cell-based medicines, natural-sourced proteins) that have CMC regulatory compliance concerns and challenges in common with the genetically engineered biologics (i.e., the biopharmaceuticals).

A great deal of thanks goes to two regulatory authorities—the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA)—who provide through their respective websites an abundance of guidance to help our industry. Twenty years ago, I can remember how difficult and time-consuming it was to obtain copies of the necessary FDA guidance documents, let alone any international ones. Our industry owes much thanks to these regulatory agencies for their foresight and commitment to transparency and getting the information into the hands of those who need it. Through means of the Internet, anybody can now download these documents for review from anywhere and at any time. It is for this reason that I have provided website addresses for the regulations, guidance documents, and case examples that were used in the preparation of this book.

Thanks also go to the companies who stumbled in their CMC regulatory strategy, resulting in delay or rejection of their biopharmaceutical or biologic, so that we can learn from their mistakes. At times, an effective CMC regulatory compliance strategy can seem like a mystery. Sometimes this mystery is self-induced in our companies—(1) job security, especially for regulatory affairs personnel and project managers who master the CMC strategy or (2) the infamous proprietary defense—divulging this CMC regulatory strategy only to limited members within one's own company or group, that is, the initiated. Sometimes, the mystery is due to the staff not being aware that an effective CMC regulatory compliance strategy can be at hand. Through means of this 2nd edition, I want to reveal the "good news" that CMC regulatory compliance no longer has to be a mystery. Also, I want to reveal the "bad news" that there can be too much CMC regulatory compliance information available, "an information overload." At times, assistance is needed to work through all of the help and guidance publicly available, especially in evaluating as to whether it has any useful application to your company's product at its current stage of clinical development. This is where this book becomes invaluable (along with the help of a good consultant of course). To reinforce that no company's proprietary information is used in this book, I have provided Internet website locators for the public communication of the information being discussed.

Throughout this book, I use the terms "biopharmaceutical" or "biotechnology-derived" or "rDNA-derived" or "recombinant" whenever I am discussing CMC issues specific for genetically engineered products. On the other hand, I use the terms "biologic" or "biological" whenever I am discussing CMC issues that apply to both natural-sourced and genetically engineered products.

In Chap. 1, the complexity of biologic regulation both within the United States and the European Union is unveiled. As shown in this chapter, the multiple pathways for regulatory approval can appear confusing for biologics and place pressure on the regulatory affairs group within a company, especially in explaining to those in their company why a biologic is treated under one pathway and not another. In Chap. 2, it is shown that in the eyes of both the FDA and the EMA, biologics are definitely different from chemical drugs. This is not a perception, but a reality, and it is reflected by the statements on their websites and in the wording of the regulatory guidances that they issue.

Also, as is shown in this chapter, the three major differences between biologics and chemical drugs are discussed: (1) use of living source materials to produce the biologic, (2) increased complexity of biologic manufacturing processes, and (3) increased complexity of the biologic molecules themselves. Finally, in this chapter, an explanation is presented of why biosimilar biological products are best viewed as similar biologics and not as true generics. In Chap. 3, the two forces that shape the corporate CMC regulatory compliance strategy for biologics—risk and resources—are examined. Also, in this chapter, the five core elements that comprise an effective corporate CMC regulatory compliance strategy for biologics—(1) embracing all CMC activities, (2) addressing unique requirements for specific biologic manufacturing processes, (3) addressing unique requirements for specific biologic products, (4) aligning the strategy to strategic ICH Q8/Q9/Q10/Q11 guidances, and (5) ensuring that the CMC activities meet the minimum requirements of cGMPs—are discussed in detail. Finally, the central role of a clinical phase-appropriate approach to the CMC regulatory compliance strategy for biologics is described. In Chap. 4, the primary adventitious agents of concern for biologics are examined in detail—prions, viruses, mycoplasmas, and bacteria/fungi microbes. The three major risk control procedures for these contaminating agents—barriers to entry, testing to confirm absence, and inactivation/removal—are discussed. In addition, lessons learned from previously reported infectious agent contaminations of biologics are presented. Finally, some CMC strategic tips are provided for minimizing the overall risk of adventitious agent contamination of biologics. In Chap. 5, the significant differences between source materials for chemical drugs and biologics are evaluated. Furthermore, the CMC regulatory compliance requirements for each type of biologic source material—cell banks, virus seed banks, and transgenic seed/animal banks—are thoroughly discussed in this chapter. Finally, four myths about biologic cell banks are debunked: (1) must have both a Master Cell Bank and a Working Cell Bank, (2) a phase 1 clinical stage Master Cell Bank is perfectly acceptable for commercial use, (3) multiple Master Cell Banks during clinical development are not a major risk, and (4) Working Cell Banks rarely cause problems. In Chap. 6, the CMC regulatory compliance impact on the manufacture of the biologic API due to the choice of the biologic source material, coupled with the design of the production/expression, harvest/isolation, and purification processes, is examined. The criticality of confirming genetic stability for manufacturing processes using source materials containing genetic expression systems is presented. In addition, the cGMP requirements for an adequate and appropriate control of the manufacture of the biologic API are discussed. Finally, the significant difference in process validation requirements between biologic processes and chemical drug processes is highlighted. In Chap. 7, the impact of the manufacture of the biologic final product, from the design of the formulation, coupled with the choice for an appropriate product-compatible container closure system, on CMC regulatory compliance is examined. In addition, the cGMP requirements for an adequate and appropriate control of the aseptic filling and sealing process in the manufacture of the biologic final product are discussed. The risk incurred when changing formulations along with the sensitivity of biologics to the

materials of the container closure (e.g., plastic, rubber polymer, metal, surfactant, adhesive, glass) is also highlighted. Discussion of the regulatory concerns around chemical modification (pegylation, conjugation) of the biologic API prior to formulation is also presented. In Chap. 8, the difference in how the safety risk of process-related impurities is assessed between chemical drugs (which have a regulatory road map) and biologics (where a case-by-case basis is applied) will be examined. It will be shown that compared to chemical drugs, biologics have a more complex process-related impurity safety profile, especially due to the living system-related impurities. Finally, in this chapter, the importance of applying a Quality Risk Management (QRM) approach in order to effectively control process-related impurities in a biologic is stressed. Examples from cell culture processes, transgenic animal/plant processes, virus processes (both viral vaccines and gene therapy vectors), and cell-based medicinal processes are provided. The challenge for biosimilar manufacturers in comparing their impurity profiles to that of the hidden innovator's biologic is also discussed. In Chap. 9, the need to carry out extensive physicochemical characterization of protein and monoclonal antibody molecular structure, employing multiple, complementary, as well as orthogonal, state-of-the-art analytical methods, is stressed. The three major pathways for molecular structural changes that can occur will be examined: primary amino acid sequence changes (e.g., truncation, deamidation, oxidation), posttranslational modifications (e.g., glycosylation), and higher-order structural changes (e.g., secondary folding, aggregation). In addition, in this chapter, it will be shown that a clinical phase-appropriate approach can be applied to this physicochemical structural characterization. Finally, the challenge of molecular structure characterization of gene therapy vectors and whole-cell nonprotein biologics will also be discussed. In Chap. 10, it will be shown that because of the molecular structural complexity of a biologic, including its many possible structural variants, functional activity assays are required that can discern which structures have what amount of potency. In this chapter, the three types of functional activity assays for measuring potency will be examined: bioassay, surrogate (analytical), and assay matrix. In addition, it will be shown that the development, optimization, and validation of these potency assays can be implemented by a clinical phase-appropriate approach. Finally, it will be stressed that most manufacturers underestimate the amount of resources and time needed to properly implement these functional activity assays. In Chap. 11, the central role that QC release and stability testing of the biologic API and final product play in the overall control strategy is addressed. Differences between testing requirements for biologics versus chemical drugs will be highlighted. Also, in this chapter, setting scientifically sound and appropriate specifications using a clinical phase-appropriate approach will be examined, including how to justify limits or ranges for four different types of specifications in the market application dossier. Finally, in this chapter, the proper design of a biologic stability program, and the correct interpretation of the stability data, in order to correctly assign the shelf life for a biologic is discussed. In Chap. 12, the challenge of how to demonstrate that a manufacturing process change does not impact the safety (immunogenicity) and/or the efficacy (potency) of the

biologic will be examined. The three major factors that drive the design of a comparability study will be stressed: (1) risk-based (major, moderate, and minor changes), (2) sequential (analytical, nonclinical, and clinical), and clinical phase-appropriate (early-stage clinical vs. later-stage clinical development). The difference between a comparability study and a comparability protocol will be discussed. Finally, in this chapter, demonstrating biologic comparability after a process change both within a manufacturer's operation (i.e., comparability pre-change vs. post-change product) and between two different manufacturers (i.e., biosimilarity) will be compared. In Chap. 13, the critical importance of communicating with the regulatory authorities on the CMC regulatory compliance strategy will be stressed. In addition, the critical importance of listening and following their guidance will be examined. Finally, in this chapter, an encouragement is given to senior management to take advantage of CMC-focused meetings available with the regulatory authorities.

Learning never ceases in the area of biologic CMC regulatory compliance strategy. After 35 years in the biologic industry, I would have thought by now that there would be "nothing new under the sun" to learn. But I am constantly amazed at the energy and creativity by my industry continually developing new manufacturing process technologies and new product types, which demand challenging CMC strategies to effectively manage and ensure their regulatory compliance. It is my sincere desire that this book will be of help to those who work in biopharmaceutical and biologic companies today and for many years to come. I encourage the users of this book to seek to learn more on their own about CMC regulatory compliance strategy for biopharmaceuticals and other biologics.

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