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Mohammed Shameem is an Executive Director and Head of the Sterile Product and Analytical Development, Biologics, Merck Research Laboratories, USA. He received his PhD from Kumamoto University, Japan in Pharmaceutical Sciences and postdoctoral training from National Institute of Health Sciences, Tokyo, University of Kentucky and University of Southern California. He has been actively involved over 18 years in innovation and developing sterile dosage forms and delivery systems for biologics and small molecules across a wide range of clinical modalities. He contributed to the successful development and registration of several marketed products (PegIntron[®], Sylatron[®], Temodar IV[®]) in the USA, EU and Japan and holds numerous patents and publications. He was a recipient of Schering Plough's 2004 President Award for development of pegylated interferon (Redipen) in a self-injection delivery system for hepatitis C treatment.

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Foreword

Monoclonal antibodies: development, delivery and applications

Lei Zheng & Mohammed Shameem

“In loving memory of my mother for all her sacrifices”

Mohammed Shameem

Monoclonal antibodies (mAbs) represent the fastest growing segment of the global pharmaceutical industry due to their impressive efficacy, safety and tolerability profiles. There are over 30 approved mAb products for treating cancers and immunological disorders, six of them among the top 10 selling drugs in 2013, and more than 300 are in clinical trials for standalone or combination therapies. Moreover, the identification of new classes of molecular targets such as the T-cell-regulating immune checkpoints (e.g., PD-1 and CTLA4), and subsequent development of molecules such as pembrolizumab and nivolumab, is revolutionizing therapeutic approaches to treat cancers, bringing renewed hope to patients, and unveiling the promise of future mAb-based therapies. mAbs have numerous advantages over small molecules because of their demonstrated target specificity, long half-lives and high probability of technical and regulatory success (2–5-fold that of small molecules). Furthermore, the advances in antibody engineering tools over the years and the application of innovative platform technologies have notably shortened the discovery and development cycles and dramatically reduced costs of production. These features have convinced most established pharmaceutical companies to include mAbs and related molecules in their pipeline as a ‘must have.’ Perhaps one of the most vibrant testimonies to mAbs contribution to modern pharmacopeia and commercial success is the large effort by many companies to develop biosimilars and biobetters to the first generation of molecules nearing end of patent protection. Recent

biosimilar guidelines in Europe and the USA have provided the regulatory framework to encourage research, development and registration of these drugs, bringing increased treatment options and accessibility to patients around the world. Despite the large number of approved mAb-based drugs and their structural similarity, technical challenges to develop these drugs in a speedy and predictable manner are still real. Minor amino acid sequence and/or structural differences may lead to unanticipated results impacting stability, behavior in solution, pharmaceutical properties and efficacy of a molecule.

This ebook, the first of its kind on mAbs, provides practical insights across discovery, development and clinical research. Established world experts from industry and academia have provided state-of-the-art overviews of key areas with important references. The chapters on developability assessment of drug candidates prior to entering the development phase, molecular engineering of mAb variants for improved functionality, drug targeting using antibody drug conjugates, formulation strategies to maximize product stability, diagnostics and clinical applications are well covered across the field in a thought provoking manner. The work presented in this book reflects on the necessary cross-functional collaboration required to develop a successful mAb-based product.

Advancements in recombinant antibody engineering have made a revolution in antibody discovery and selection. Early assessment of candidates for manufacturability through biophysical and biochemical characterization ensures the highest probability of success. They further drive the development of antibody-derived modalities, which have expanded the functionality of antibodies. For example, initially aiming at improving the binding affinity of antibodies, bispecific or multispecific antibodies have been developed to simultaneously bind two or more different antigens or different epitopes on the same antigen. As anticipated, synergistic effects of activating/inhibiting multiple pathways on the same targets have been observed with multispecific antibodies and further raised the enthusiasm in this technology advancement. Bispecific antibodies are also designed to target both cancer cells and immune cells, resulting in a synergy between direct tumor inhibition and antitumor immune response. Now, the development of bispecific and multispecific antibodies has become one of the most rapidly evolving fields. The formulation strategies to achieve the target product profile and to deliver a drug in a patient-friendly manner are directly linked to the commercial success of a product. Systematic study of basic formulation variables (excipients and/or conditions) and understanding intermolecular interactions (e.g., self-association) are key to solving the formulation issues. There has been a shift in emphasis to develop high protein concentration formulation and enabling technologies for subcutaneous administration, including

switching of commercial products (e.g., Herceptin[®], Rituxan[®]) from intravenous to subcutaneous administration in support of chronic administration in the home setting.

Another major advancement is in the technology for antibody–drug conjugates (ADCs). The effectiveness of chemotherapies is thwarted by the ineffective drug delivery to the cancer site and the systemic toxicities observed due to the nondiscriminatory nature of these therapies. ADCs help overcome both hurdles. The monoclonal antibody can be attached to radioactive particles, chemotherapy drugs or cell toxins. As an example, trastuzumab emtansine connects anti-HER2 antibody to maytansine (DM-1), an antimicrotubule agent. Trastuzumab emtansine was shown to have greater efficacy in Her2-positive breast cancer with reduced toxicities than the nonconjugated form of trastuzumab. The success of trastuzumab emtansine has paved the path for the development of many more ADCs; and now, hundreds of ADCs are under preclinical and clinical testing. Not only for therapeutic development, has linking antibodies to radioactive particles also renovated the technology of diagnostic imaging. ImmunoPET has taken advantage of the specificity of antibodies that traditional tracers of PET are lack of and thus has a great potential in advancing this commonly used diagnostic technology.

After witnessing the rapid development in the field of monoclonal antibodies, we have no doubt that our inventory of ‘magic bullets’ will be expanded at an accelerated rate. The progress in the clinical application will further increase the demand on more innovative technologies in the areas of antigen discovery, antibody selection, engineering, delivery, formulation and analytics. We would like to sincerely thank the authors for contributing cutting edge science and insight in this field. Together we can make a difference in patients’ lives. Let’s continue with our dedication and commitment for every drug we touch!

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