

Preface

In recent years, biotechnologically-derived drugs (biotech drugs) including proteins, peptides, monoclonal antibodies and antibody fragments, as well as anti-sense oligonucleotides and DNA preparations for gene therapy, have been a major focus of research and development (R&D) efforts in the pharmaceutical industry, and biotech drugs constitute already a sizable fraction of the medications used in clinical practice.

Pharmacokinetic (PK) and pharmacodynamic (PD) concepts impact every stage of the drug development process starting from lead optimization to the design of Phase III pivotal trials. PK and PK/PD evaluations are widely considered cornerstones in the development of new drug products and are usually deeply embedded in the discovery and development plan. The widespread application of PK/PD concepts in all phases of drug development has repeatedly been promoted by industry, academia, and regulatory authorities, most recently through FDA's Critical Path to New Medical Products initiative and the concept of integrated model-based drug development.

An understanding of PK and PD and the related dose-concentration-effect relationship is crucial to any drug – including biotech products – since it lays the foundation for dosing regimen design and rational clinical application. While general PK and PD principles are just as applicable to biotech agents as they are to traditional small molecule drugs, PK and PK/PD analyses of biotech agents frequently pose extra challenges related to factors such as their similarity to endogenous molecules and/or nutrients and their immunogenicity.

This textbook provides a comprehensive overview on the PK and PD of biotech-derived drug products, highlights the specific requirements and challenges related to PK and PK/PD evaluations of these compounds and provides examples of their application in preclinical and clinical drug development. The impetus for this project originated from the notion that at the time of its initiation there was no comprehensive publication on the market that specifically addressed this topic.

Following a short introduction, the book is structured into three sections: The 'Basics' section discusses individually the pharmacokinetics of peptides, monoclonal antibodies, antisense oligonucleotides and gene delivery vectors. The subsequent 'Challenges and Opportunities' section includes more detailed considerations on selected topics, including technical challenges such as bioanalytical

methodologies, noncompartmental data analysis and exposure-response assessments. It furthermore discusses biopharmaceutical challenges as exemplified by the delivery of oligonucleotides and of peptides and proteins to the lung, and provides insights into the opportunities provided by chemical modification of biotech drugs and the regulatory challenges related to follow-on biologics. The third and final section provides examples for the 'Integration of Pharmacokinetic and Pharmacodynamic Concepts into the Biotech Drug Development Plan', including the preclinical and early clinical development of tasidotin, and the clinical development programs for cetuximab and pegfilgrastim.

The book addresses an audience with basic knowledge in clinical pharmacology, PK and PD, and clinical drug development. It is intended as a resource for graduate students, postdocs, and junior scientists, but also for those more experienced pharmaceutical scientists that have no experience in the PK and PD evaluation of biotech drugs and wish to gain knowledge in this area.

I would like to express my gratitude to all contributors of this project for providing their unique array of expertise to this book project which allowed us to compile a wide variety of viewpoints relevant to the PK and PK/PD evaluation of biotech drugs and derived products. In addition, I would like to thank Dr. Romy Kirsten and Dr. Andrea Pillmann at Wiley-VCH for their assistance in producing this book and Ms. Faith Barcroft for her invaluable text editing.

Finally I would like to dedicate this book to my family for their patience, encouragement and support during this project.

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