Book Review: ADME and Translational Pharmacokinetics/Pharmacodynamics of Therapeutic Proteins

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For more than a decade, clinical pharmacology (CP), absorption-distribution metabolism, and excretion (ADME), and pharmacokinetics-pharmacodynamics (PKPD) properties of biologics have received particular attention from experts within the field through increasing numbers of publications and the occasional book dealing with general aspects of CP or PK science.1,2 While these publications have aided better understanding of this subject within the general PKPD population, a more thorough discussion of these aspects in the context of the underlying biochemical, biological, and technological processes that influence these properties for biologics has been lacking. This new book is the first to emerge with the ambitious objective of providing a “grand tour” of all things biologics ADME/PKPD/CP with an understandable focus on monoclonal antibodies (mAbs)—the dominant member of the biologics family.

At the outset, one is impressed with the scope of the book; it provides an outline of very diverse topics, starting with the basics of protein engineering and how these are used to design and manipulate the ADME properties of recombinant and synthetic proteins (Chapters 2 and 3). Chapters such as the one on immunogenicity (Chapter 11) provide a good background for the reason behind the differences in development strategy for biologics. The authors have to be congratulated for their endeavor to stitch these topics together in a single book—although the organization of the chapters with these specialized non-PK topics spread out among the more PK-focused ones left this reader slightly confused. In spite of the breadth of the science covered in the book, most of the chapters that deal with subjects not many PK practitioners will be familiar with are relatively short and crisp, dealing only with the core principles. This helps provide an overview of these topics without delving into depth and thus turn off a casual reader. Also, a wide variety of biologic modalities are covered in different chapters—antibody-drug-conjugates (ADC), bispecific antibodies, pH-dependent antibodies, blood–brain barrier-penetrating biologics—which will help break up the myth of a monolithic biologic modality. With such a wide range of topics, even an experienced scientific practitioner in this area is likely to find something new to engage them and expand their knowledge. But the cores of the book are the CP and PKPD aspects, which deal with principles of ADME and PKPD modeling for biologics and how they impact preclinical development, first-in-human dose selection, and clinical development. These are dealt with in great detail and are comprehensive.

Another welcome inclusion in this book is the development strategy for biologics (Chapters 22, 24, 25). These chapters outline typical differences in the clinical development strategy for biologics compared to typical small molecules. More information on preclinical development—especially focusing on PK and drug metabolism aspects—would also have been useful, especially since this is a stated aim in the foreword.

The main criticism from this reader was that the PKPD information, while being comprehensive, felt repetitive in some aspects, e.g., the ADME of biologics repeatedly appears in various chapters with different depths (6, 7, 10, 15…); target-mediated drug disposition alone is dealt with in two different chapters and is summarized in others as well. Furthermore, examples such as fixed vs. weight-based dosing (Chapter 9) and extension of target engagement to biomarkers and clinical response (Chapter 13) are general pharmacometric issues better addressed in a general book on pharmacometrics rather than in a book specifically dealing with biologics (the dosing question is also dealt with twice and could have been edited out in Chapter 25). Perhaps in a
future edition the editors would consider using the saved space from removing these redundancies to expand on some of the other emerging topics, such as the use of systems modeling in the design of mAb derivatives such as bispecifics and ADCs—an approach distinctly different from small molecules—or expand on some topics already presented such as tumor penetration of mAbs and preclinical development of biologics. More focus on non-mAb biologics—synthetic vs. natural peptides/proteins, etc.—would all be welcome additions to this tome.

In summary, this is an excellent and comprehensive book for beginners to the CP/PK area to acquaint themselves with the area of biologics (specifically mAb) CP/PKPD principles and for experienced CP/PK scientists for reference.

1. Dirks, N.L., & Melborn, B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin. Pharmacokinet. 49, 633–659 (2010).
2. Tabrizi, M.A., Bornstein, G.G. & Klakamp, S.L. Development of Antibody-Based Therapeutics: Translational Considerations (Springer, Berlin; 2012).

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