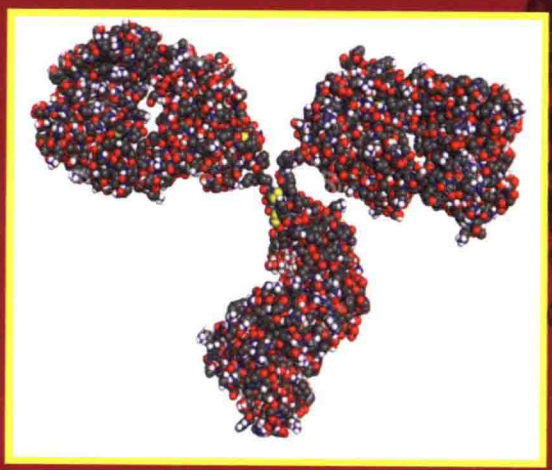
DRUGS AND THE PHARMACEUTICAL SCIENCES

Volume 216

BIOSIMILAR DRUG PRODUCT DEVELOPMENT



Laszlo Endrenyi
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CRC Press
Taylor & Francis Group

DRUGS AND THE PHARMACEUTICAL SCIENCES
Volume 216

BIOSIMILAR DRUG PRODUCT DEVELOPMENT

When a biological drug patent expires, alternative biosimilar products are developed. The development of biosimilar products is complicated and involves numerous considerations and steps. The assessment of biosimilarity and interchangeability is also complicated and difficult. **Biosimilar Drug Product Development** presents current issues for the development of biosimilars and gives detailed reviews of its various stages and contributing factors as well as relevant regulatory pathways and pre- and post-approval issues.

Features

- Covers practical issues commonly encountered in biosimilar drug product development
- Discusses current regulatory thinking concerning the approval pathway of biosimilar products and recent developments of statistical methods for the assessment of biosimilar products
- Reviews the analytical, animal and clinical development of biosimilars and discusses issues of structural and functional characterization, manufacturing process control, and immunogenicity
- Discusses post-approval pharmacovigilance, economic and legal considerations, and the extrapolation of indications
- Provides insightful discussion regarding interchangeability and substitution from statistical, regulatory and clinical perspectives

CRC Press
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6000 Broken Sound Parkway, NW
Suite 300, Boca Raton, FL 33487
711 Third Avenue
New York, NY 10017
2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

K25468
ISBN: 978-1-4987-1879-0
90000
9 781498 718790

Volume 216

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BIOSIMILAR DRUG PRODUCT DEVELOPMENT

CRC

Biosimilar Drug Product Development

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed by CPI on sustainably sourced paper
Version Date: 20160906

International Standard Book Number-13: 978-1-4987-1879-0 (Hardback)

Library of Congress Cataloging-in-Publication Data

Names: Endrenyi, Laszlo, editor. | Declerck, Paul (Professor in pharmaceutical sciences), editor. | Chow, Shein-Chung, 1955- editor.
Title: Biosimilar drug product development / [edited by] Endrenyi, Laszlo, Declerck, Dr. Paul, Chow, Shein-Chung.
Other titles: Drugs and the pharmaceutical sciences.
Description: Boca Raton : CRC Press, [2016] | Series: Drugs and the pharmaceutical sciences | Includes bibliographical references and index.
Identifiers: LCCN 2016038570| ISBN 9781498718790 (hardback : alk. paper) | ISBN 9781498718806 (e-book)
Subjects: | MESH: Biosimilar Pharmaceuticals | Drug Evaluation | Drug Approval
Classification: LCC RM301.25 | NLM QV 241 | DDC 615.1/9--dc23
LC record available at https://lccn.loc.gov/2016038570

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Biosimilar Drug Product Development

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Preface

More and more innovative biological products will lose their patents in the coming decade. Therefore, in order to reduce costs, attempts will continue to be made to establish an abbreviated regulatory pathway for the approval of biosimilar drug products of the innovator's biological products. However, owing to the complexity of the structures of biosimilar products and the nature of the manufacturing process, biological products differ from the traditional small-molecule (chemical) drug products. Many scientific challenges remain for establishing an abbreviated regulatory pathway for the approval of biosimilar products due to their unique characteristics.

This book is devoted entirely to the development of biosimilar drug products. It covers the scientific factors and/or practical issues that are commonly encountered at various stages of research and development of biosimilar products. It is our goal to provide a useful desk reference to scientists and researchers engaged in pharmaceutical/clinical research and the development of biosimilar drug products, those in the regulatory agencies who have to make decisions in the review and approval process of biological regulatory submissions. We hope that this book can serve as a bridge among the pharmaceutical/biotechnology industry, government regulatory agencies, and academia.

This book follows the FDA's and EMA's proposed stepwise approach for evaluation and approval of the development of biosimilar products. The stepwise approach starts with analytical similarity assessment for functional and structural characterization of critical quality attributes that are relevant to clinical outcomes at various stages of the manufacturing process, *in vitro* studies for pharmacological activities, additional nonclinical studies if needed, and clinical studies for pharmacokinetic and immunogenicity assessment and efficacy confirmation. Thus, this book consists of 17 chapters. These chapters cover analytical similarity assessment (Chapters 2 through 4), manufacturing process control (Chapter 5), nonclinical studies (Chapter 6), design and analysis for assessing biosimilarity and drug interchangeability (Chapters 8, 10, and 11), pharmacovigilance (Chapter 13) and immunogenicity (Chapter 12), clinical development (Chapter 7), patent exclusivities (Chapter 14), extrapolation of indications for biosimilars (Chapter 9), and other issues (Chapters 15 through 17). The chapters intend to illuminate the many current issues and future directions of the development of biosimilars. They at times contain repetition of material, which may shed light on some topics from different directions.

From Taylor & Francis, we would like to thank Barbara Norwitz and Hilary Lafoe for giving us the opportunity to work on this book and to the support and production teams for their excellent assistance. We would like to thank colleagues and friends from academia, the pharmaceutical industry, and regulatory agencies for their support and discussions during the preparation of this book. We are, in particular, grateful to Dr. Agnes V. Klein and Dr. Jian Wang, Health Canada, not only for their own chapter contributions but also for helping to acquire and oversee other chapters.

Finally, the views expressed are those of the authors and not necessarily those of the University of Toronto, Toronto, Canada, the University of Leuven, Leuven, Belgium, and Duke University School of Medicine, Durham, North Carolina. We are solely responsible for the contents and any possible errors of this book. Any comments and suggestions will be much appreciated.

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1 Introduction
Scientific Factors in Biosimilar Product Development

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1.1 BACKGROUND

When an innovative drug product is going off patent, generic companies may file an abbreviated new drug application (ANDA) for the approval of the generic copies (with an identical active ingredient) of the innovative drug product under the Hatch–Waxman Act. For approval of generic drug products, the United States Food and Drug Administration (FDA) as well as other regulatory agencies require that evidence in average bioavailability be provided through the conduct of pharmacokinetic (PK) bioequivalence (in terms of rate and extent of drug absorption) studies. The assessment of bioequivalence as a surrogate endpoint for the evaluation of drug safety and efficacy is based on the *Fundamental Bioequivalence Assumption*. It states that if two drug products are shown to be bioequivalent in average bioavailability, it is assumed that they are therapeutically equivalent and can be used interchangeably.

Unlike drug products with identical active ingredients, the concept for the development of copies of biological products is different because they are made of living cells. The copies of biological products are referred to as biosimilars by the European Medicines Agency (EMA), similar biotherapeutic products (SBPs) by the World Health Organization (WHO), and subsequent-entry biologics (SEB) by Health Canada.

Biosimilars are fundamentally different from generic (chemical) drugs. Important differences include the size and complexity of the active substance and the nature of the manufacturing process. Because biosimilars are not exact copies of their originator products, different criteria for regulatory approval are required. This is partly a reflection of the complexities of manufacturing and the safety and efficacy controls of biosimilars when compared to their small-molecule generic counterparts (see, e.g., Chirino and Mire-Sluis, 2004; Crommelin et al., 2005; Roger and Mikhail, 2007; Schellekens, 2005). Since biological products are (recombinant) proteins produced by living cells, manufacturing processes for biological products are highly complex and require hundreds of specific isolation and purification steps. In practice, it is impossible to produce an identical copy of a biological product, as changes to the structure of the molecule can occur with changes in the production process. Since a protein can be modified during the process (e.g., different sugar chains may be added, the structure may have changed due to protein misfolding and so on), different manufacturing processes may lead to structural differences in the final product, which may result in differences in efficacy and safety, and may have an impact on the immune responses of patients. In some cases, these issues also occur during the postapproval changes of the innovator's biological products.

Since 2006, the EMA has provided several guidelines for the development of biosimilars. These have been followed by guidelines established by other regulatory agencies (Australia, Japan, South Korea, Canada) and the WHO. In 2015, the FDA published several guidances on the development of biosimilar products (FDA, 2015a–c). The guidance entitled *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* recommends a stepwise approach for obtaining the totality of the evidence for assessing biosimilarity between a proposed biosimilar product and its corresponding innovative biological drug product. The stepwise approach starts with analytical similarity assessment for functional and structural

characterization of critical quality attributes (CQAs) that are relevant to clinical outcomes at various stages of the manufacturing process; animal studies for toxicity; pharmacokinetics and pharmacodynamics for pharmacological activities; clinical studies for efficacy confirmation; immunogenicity for safety and tolerability; and pharmacovigilance for long-term safety. Accordingly, the purpose of this chapter is to outline scientific factors and practical issues that are commonly encountered in the development of biosimilar products.

Section 1.2 describes fundamental differences and assumptions between conventional drug products and follow-on biologics. Section 1.3 presents scientific factors and practical issues that are commonly encountered in the development of biosimilar products. The aim and scope of the book are provided in Section 1.4.

1.2 FUNDAMENTAL DIFFERENCES FROM GENERICS AND ASSUMPTIONS FOR BIOSIMILARS

1.2.1 Fundamental Differences from Generics

In comparison with conventional drug products, the concept for the development of follow-on biologics is very different. Webber (2007) defines follow-on (protein) biologics as products that are intended to be sufficiently similar to an approved product to permit the applicant to rely on existing scientific knowledge about the safety and efficacy of the approved reference product. Under this definition, follow-on products are intended not only to be similar to the reference product, but also to be therapeutically equivalent with the reference product. As a number of biological products patents have expired and many more are due to expire in the next few years, the subsequent follow-on products have generated considerable interest within the pharmaceutical/biotechnological industry as biosimilar manufacturers strive to obtain part of an already large and rapidly growing market. The potential opportunity for price reductions versus the innovator biologic products remains to be determined, as the advantage of a cheaper price may be outweighed by the potential increased risk of side-effects from biosimilar molecules that are not exact copies of their innovators. In this chapter, we focus on issues surrounding biosimilars, including manufacturing, quality control, clinical efficacy, side-effects (safety), and immunogenicity. In addition, we attempt to address the challenges in imposing regulations that deal with these issues.

1.2.2 Fundamental Assumptions

As indicated by Chow and Liu (2008), bioequivalence studies are performed under the so-called Fundamental Bioequivalence Assumption, which constitutes the legal basis for the regulatory approval of generic drug products. As noted earlier, the Fundamental Bioequivalence Assumption states:

> If two drug products are shown to be bioequivalent, it is assumed that they will reach the same therapeutic effect or they are therapeutically equivalent and hence can be used interchangeably.

Note that this statement can be interpreted to mean that the confidence interval for the ratio of geometric means is between 80% and 125%. An alternative would be to show that the tolerance intervals (or a distribution-free model) overlap sufficiently.

To protect the exclusivity of a brand-name drug product, the sponsors of the innovator drug products will make every attempt to prevent generic drug products from being approved by regulatory agencies such as the FDA. One strategy used in the United States is to challenge the Fundamental Bioequivalence Assumption by filing a *citizen petition* with scientific/clinical justification. Upon receipt of a citizen petition, the FDA has the legal obligation to respond within 180 days. It should be noted, however, that the FDA will not suspend the review/approval process of a generic submission of a given brand-name drug even if a citizen petition is under review within the FDA.

In spite of the Fundamental Bioequivalence Assumption, one of the controversial issues that has arisen is that bioequivalence may not necessarily imply therapeutic equivalence and therapeutic equivalence does not guarantee bioequivalence either. One criticism lodged in the assessment of average bioequivalence for generic approval is that it is based on legal/political considerations rather than scientific arguments. In the past several decades, many sponsors/researchers have attempted to challenge this assumption but without success.

In practice, verification of the Fundamental Bioequivalence Assumption is often difficult, if not impossible, without conducting clinical trials. Notably, the Fundamental Bioequivalence Assumption applies to drug products with identical active ingredient(s). Whether the Fundamental Bioequivalence Assumption is applicable to drug products with similar but different active ingredient(s), as in the case of biosimilars, becomes an interesting but controversial question.

Similar to the Fundamental Bioequivalence Assumption described above, it has been suggested that a Fundamental Biosimilarity Assumption be developed. The following statement could be considered:

> When a follow-on biological product is claimed to be biosimilar to an innovator product in some well-defined study endpoints, it is assumed that they will reach similar therapeutic effect or they are therapeutically equivalent.

Some well-defined study endpoints are those from different functional areas such as certain physicochemical characteristics, biological activities, pharmacokinetics/pharmacodynamics (PK/PD), and immunogenicity.

1.3 SCIENTIFIC FACTORS AND PRACTICAL ISSUES

1.3.1 Criteria for Biosimilarity

For the comparison between drug products, some criteria for the assessment of bioequivalence, similarity (e.g., comparison of dissolution profiles), and consistency (e.g., comparisons between manufacturing processes) are available in either regulatory guidelines/guidances and/or the literature. These criteria, however, can be classified as (1) absolute change versus relative change, (2) aggregated versus disaggregated, or (3) moment-based versus probability-based. In this section, we briefly review different categories of criteria.