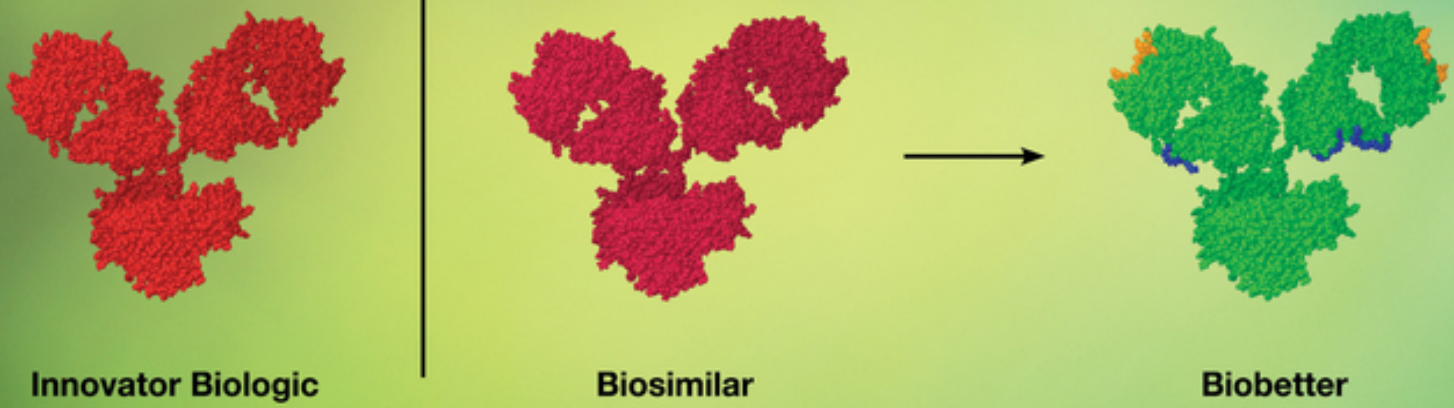
EDITED BY
IQBAL RAMZAN

BIOLOGICS, BIOSIMILARS, AND BIOBETTERS

AN INTRODUCTION FOR PHARMACISTS, PHYSICIANS, AND OTHER HEALTH PRACTITIONERS



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An Introduction for Pharmacists, Physicians, and Other Health Practitioners

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Foreword

Tracing back through history, one observes that the treatment of human disease, while always multimodal, has been strongly influenced, and even dominated, by select therapeutic strategies for discrete periods of time. Examples include the use of herbs to treat disease in prehistoric times (herbalism), bloodletting and humorism (starting around 500 years before the Christian era), germ theory, and chemotherapy (in the eighteenth and nineteenth centuries). Although the use of chemicals for medicine may be traced back to Paracelsus in the sixteenth century, pharmacotherapy with small molecule drugs (SMDs) did not dominate medicine until the twentieth century. At present, early in the twenty-first century, thousands of SMDs are in use as treatments for virtually all human diseases and conditions, including infectious disease, cardiovascular disease, mental health, pain, diabetes, and cancer.

The use of antibodies to treat disease may be traced to the 1890s, with the application of antisera to treat and prevent toxicity relating to diphtheria. Exogenous insulin was first used to treat diabetes in 1922, and human, recombinant insulin became available for therapeutic use in 1978. Building on these successes, and through advancements in the fields of protein chemistry, immunology, and molecular biology, we may now be entering a new phase where biological drugs, including peptides, proteins (e.g. antibodies), nucleic acid therapeutics (siRNA, antisense oligonucleotides, etc.), and cell therapies (T-cells, viruses, bacteriophages, etc.) emerge as dominant treatments for human disease.

At the time of writing this text in 2020, biologics account for more than 50% of new therapeutic entities under development at many major pharmaceutical companies, and monoclonal antibodies (mAbs) may be considered as the largest drug class (with ~75 mAbs approved for therapeutic use). Five of the current top 10 selling drugs are mAbs, including the top selling drug (adalimumab).

Relative to SMD, biologic drugs are often more selective in their actions, which translates to an improved ratio of beneficial effects relative to unwanted toxicity. However, biologics are much larger, and much more complex, than typical SMDs. An average mAb is associated with a molecular weight of ~150 000 Da, more than 30-times the average molecular weight of SMDs. Additionally, most biological drugs are not chemically synthesized, but are produced by biological systems (e.g. cells grown in bioreactors) that are subject to biological variability. Consequently, biological drugs may be most appropriately considered as complex distributions of molecular entities, rather than as unique chemical compositions. Variability exists within and between preparations of a biologic with regard to post-translational modifications (e.g. the extent and nature of glycosylation and sialylation), chemical modifications (e.g. deamidation and oxidation of labile functional groups), presence of aggregates, and the presence of host cell proteins (i.e. proteins relating to the cells used for production of the biologic). These and other product variables have been associated with significant effects on the pharmacokinetics, pharmacodynamics, and safety of the biologic product. As such, pharmacists, physicians, and other healthcare professionals have been faced with uncertainties regarding the safety and utility of preparations of biologics that are marketed as being “biosimilar” to an innovator biologic, or preparations that

are developed as being superior to an innovator product (i.e. “biobetter”).

This text is extremely timely in that it addresses many fundamental scientific, clinical, and regulatory issues relating to innovator biologics, biosimilars, and biobetters, through a thoughtful and detailed collection of 16 chapters. The text, which has been expertly compiled and edited by Dr. Iqbal Ramzan, provides discussion of the major classes of biological drugs, clear presentation of the terminology and nomenclature of the field, review of approved biosimilar and biobetter drugs, biophysical concepts and key biophysical analytical tests, pharmacokinetics, pharmacogenomics, pharmacovigilance, and pharmacoeconomics. The work provides a practical and clinical perspective to the use of biologics and biobetters, including consideration of controversial topics such as the interchangeability of innovator and biosimilar products. This book will serve as an excellent primer for all pharmacists and clinicians as we move forward into what may become a new era of medicine, an era dominated by the use of biological drugs.

Joseph P. Balthasar
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Preface

This is a comprehensive primer, study guide, and primary reference text for pharmacists, doctors, and other health practitioners that presents the relevant science, clinical, policy, and regulatory frameworks for biologic medicines. The contents are pitched at a level that is easily understandable and can be immediately applied in everyday practice.

Innovator biologics, their interchangeable equivalents, biosimilars and their more efficacious, successors, biobetters are taking up a larger share of the therapeutics drug market compared to small molecule drugs. They are potent, highly complex in their therapeutic and clinical utility and far more expensive. Pharmacists are the primary healthcare professionals who will be expected to provide advice on these drugs as governments and other third-party payers attempt to contain their costs by introducing interchangeable biologic medicine products.

This book explores the current and emerging scientific and clinical practices. It compares different policy and regulatory approaches across countries. There is a focus on what pharmacists need to discuss with doctors and patients about the regulatory approval principles of biosimilars and evidence for interchangeability. Pharmacists and other clinicians require an understanding of the suite of biophysical tests needed to establish similarity, the likely efficacy, safety, and clinical risk(s) of switching not only from an innovator biologic to a biosimilar or a biobetter but also from any biologic medicine to another. Sound clinical and policy decisions will require health professionals to assimilate new types of information to ensure patients

achieve optimal outcomes. This book will help them navigate this complex territory.

The book also provides recommendations for pharmacy educators and accreditors of pharmacy degree programs on the knowledge areas and competency standards to be met by pharmacy students and pharmacists on the entire burgeoning area of biologic medicines. Pragmatic regulatory approaches to dealing with these drugs in the context of rapidly evolving scientific and clinical data and evidence are also provided. A checklist is provided for pharmacists to facilitate conversations with doctors and patients to ensure quality use of medicine for biologic medicines to deliver patient-centered health outcomes.

Like many current health professionals, I had limited or no exposure to biologic medicines when I trained as a pharmacist. However, while serving as Dean of Pharmacy, at University of Sydney, for over 12 years, I had a bird's-eye view of the profession and of many future directions in healthcare. It was clear that pharmacists would be expected to take on a greater educative role with biologic medicines and I did not necessarily believe that they were sufficiently confident or knew enough about all aspects of biologic medicines. I therefore approached Jonathan Rose at Wiley and put forward a book proposal on biologic medicines. With his support, the proposal was approved after several iterations and I managed to assemble a very talented group of scientists and health professionals who were willing to share this journey with me.

Whether you are a pharmacist, a pharmacy student looking forward to entering professional practice, or a family doctor or specialist prescriber, I hope this book will empower you to understand the complexities of biologic medicines so that you can have an evidence-based and objective conversation with your patients. There is much

hype and many anecdotes, and it is critical to separate these from the facts and data that support use of these important new medicines.

Editing this book (and writing two chapters) has been a very challenging task, probably because I underestimated the enormity of the challenge. The sheer breath of the scientific and clinical literature on biologic medicines is breathtaking. In addition, the literature and the evidence base are evolving so rapidly. If I had correctly gauged how much effort it would have taken me, I probably would not have embarked on this assignment. I am very pleased with the outcome largely due to the very able group of chapter contributors who have worked tirelessly with me to get the book pitched at the right level for pharmacists, doctors, and patients.

I want to thank all the contributing authors for their dedication to this book and to working with me to translate all aspects of the complex science to a level that is easily understood by busy time-poor pharmacists and doctors. My sincere thanks also go to the team at Wiley led by Jonathan Rose who has been very supportive from the beginning and Aruna Pragasam for assisting on the book submission.

I would also like to thank my wife, Dr. Lynn Weekes, who has been tremendously encouraging and supportive through this challenging project even though she herself wrote her own book during much of this time. Kimberlee and Justen, your encouragement to finish the project is also appreciated.

I dedicate this book to my late mum (Amma) who gave me such a strong work ethic and taught me perseverance.

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