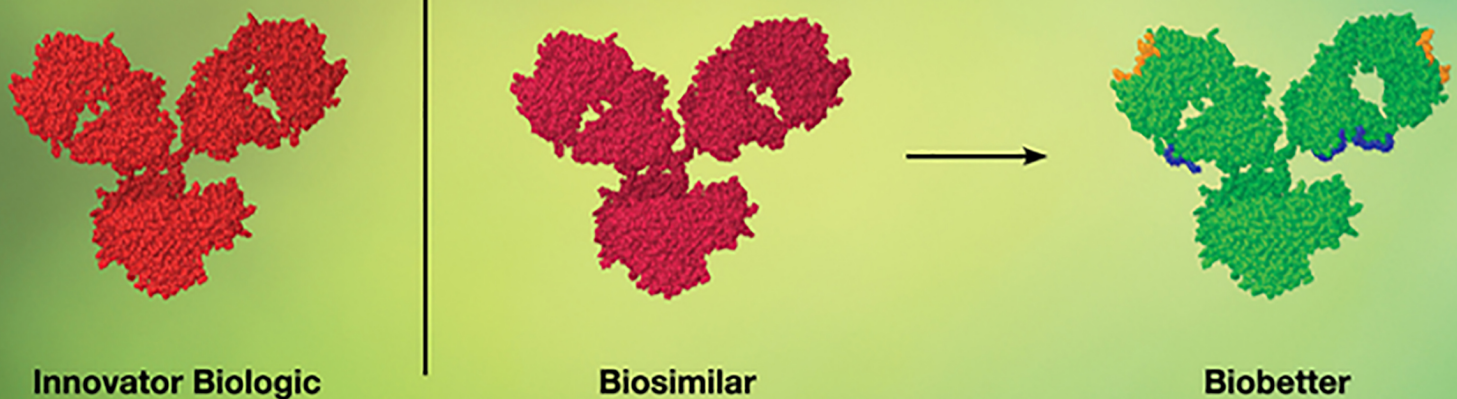
EDITED BY
IQBAL RAMZAN

BIOLOGICS, BIOSIMILARS, AND BIOBETTERS

AN INTRODUCTION FOR PHARMACISTS, PHYSICIANS, AND OTHER HEALTH PRACTITIONERS



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Biologics, Biosimilars, and Biobetters

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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
University at Buffalo, Buffalo NY USA

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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26 June 2020

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Innovator Biologics, Biosimilars, and Biobetters

Terminology, Nomenclature, and Definitions

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KEY POINTS

- Many different terms are used for innovator biologics, biosimilars, and biobetters internationally.
- Greater harmonization of terminology, definitions, and nomenclature across different regulatory jurisdictions and countries would assist health practitioners and patients in understanding the complex issues of biologic medicines.
- The salient language of innovator biologics, biosimilars, and biobetters are introduced in this chapter to set the context for the rest of the book, which deals with specific issues in greater detail pitched at pharmacists, doctors, and patients.

Abbreviations

Abbreviation	Full name
ABPI	Association of British Pharmaceutical Industry
AfPA	Alliance for Patient Access
BAP	Biosimilars Action Plan
BLA	Biologics License Application
BPC	Biologics Prescribers Collaborative
BPCI Act	Biologics Price Competition and Innovation Act
CAR-T	Chimeric Antigen Receptor Therapy
CHMP	Committee for Medicinal Products for Human Use (EMA)
CIOMS	Council of International Organizations of Medical Sciences
CQAs	Critical Quality Attributes
CVMP	Committee for Medicinal Products for Veterinary Use
Da	Dalton
DNA	Deoxyribonucleic Acid
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GABi/GaBI	Generics and Biosimilars Initiative
LDN	Limited Distribution Network
mAbs	monoclonal Antibodies
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NMS	Non-Medical Switching
NOBs	Non-Original Biologics
PBS	Pharmaceutical Benefits Scheme
P&T	Pharmacy & Therapeutics (Committee)
PTMs	Post-Translational Modifications
QbD	Quality by Design
QUM	Quality Use of Medicine
RMP	Risk Management Plan
RPS	Reference Product Sponsor
RWE	Real-World Evidence
SEBs	Subsequent-Entry Biologics
SMD	Small Molecule Drug
UMC	Uppsala Monitoring Centre
UNESCO	United Nations Educational, Scientific and Cultural Organization
USA	United States of America
USD	US Dollar
WHO	World Health Organisation

Biologics, Biosimilars, and Biobetters: An Introduction for Pharmacists, Physicians, and Other Health Practitioners,
First Edition. Edited by Iqbal Ramzan.

1.1 Place of Biologics in Modern Therapeutics

Biologic therapies have entirely revolutionized the treatment of many debilitating, life-changing chronic autoimmune diseases like rheumatic arthritis and plaque psoriasis as well as life-threatening cancers for which no viable treatment option has existed previously. They also play a critical therapeutic role in many endocrine disorders and neurodegenerative conditions. Biologics are the fastest growing sector of the drug market[1] and are also the most expensive therapies. As a result, "highly similar" versions of innovator biologics, biosimilars have been introduced to provide cost-effective biologic treatments.

The first innovator biologic was introduced ~40 years ago, and the first biosimilar was introduced in the European Union (EU) and United States (USA) in 2006 and 2015, respectively. Currently, there are over 300 biologics registered worldwide and the EU has over 60 approved biosimilars. In the United States, biosimilars are an emerging market, with 19 approved biosimilars. Biosimilar market access comparison between the United States and EU has shown that market access in the United States is less favorable. This is due to many factors including lack of incentives to prescribe biosimilars in the United States and small price discounts of biosimilars compared to innovator biologics.[2]

In many countries, including Australia and emerging pharmaceutical markets like Brazil, biosimilar use is actively encouraged as governments attempt to contain the costs of expensive innovator biologics. Assuming discounts on off-patent innovator biologics and biosimilars of ~50%, it is predicted that by 2020 there will be annual savings of over €8–10 billion in the EU.[3]

Biologics are complex proteins or protein-like molecules produced using biotechnology techniques in living cells. Their structural, functional, and manufacturing processes lead to clinical concerns/controversy about their efficacy and safety, including the potential for treatment failure and severe immunogenicity reactions. Pharmacists, doctors, and other health professionals, therefore, need to be fully conversant with all aspects of their clinical utility.

1.2 Background to Terminology, Nomenclature, and Definitions

In the biologics field, there are international differences in the various terms, definitions, and abbreviations that are used. This arises due to country/continent differences, different regulatory and policy frameworks, and the specific requirements of the various regulatory agencies.

Definitions, nomenclature, and terminology on biologics will now be reviewed in detail so there is a common understanding among readers.

1.3 Innovator Biologics, Biosimilars, and Biobetters

1.3.1 What Is a Biologic Medicine?

Biologic medicines are active substances made by or derived from a biological source, rather than a chemical source, or synthesized chemically. Biologic medicines are also known as biopharmaceuticals or biotherapies and they are comprised of proteins such as vaccines, hormones, enzymes, blood products, allergenic extracts, monoclonal antibodies (mAbs), human cells and tissues, and gene therapies (Table 1.1). Typically, biologics are proteins or protein-containing fragments. The first biologic (recombinant human insulin) was approved in 1982.[4]

When a biological medicine is administered to a patient, the expectation is that it will function as the

Table 1.1 Broad categories of biologic medicines.

Biologic	Description
Hormone	A substance (peptide or steroid) produced by a tissue or organ to elicit a physiologic action
Vaccine	An agent containing an antigen (live, killed, or attenuated pathogenic agent) to stimulate the immune system
Interferons	Proteins produced by cells in response to bacterial or viral infections
Growth factors	A substance that promotes growth, especially cellular growth
Polypeptides	Peptides containing from 10 to 50 amino acids
Proteins	Naturally occurring or synthetic polypeptides generally of 10 kDa in size
Monoclonal antibodies (MAbs)	A single synthetic immunoglobulin produced by recombinant techniques directed against a single antigen or endogenous molecule
Interleukins	Group of cytokine proteins
Cellular and tissue biotherapies	Like CAR-T
Emerging biotherapies	Like antibody–drug conjugates or bispecific antibodies

natural endogenous protein, resolving clinical symptoms and either preventing or slowing the progression of the disease process. The mechanism(s) by which biologic medicines produce their clinical effects varies from product to product and across different clinical indications and diseases. Biologics may be tailor-made to target the desired receptor or cells in the body.

Terms like "de novo biologic drugs" or "bio-originators" have also been used in the biologics literature. The first (initial) biologic medicine belonging to a specific class or category to be approved and registered (and/or marketed) is known as an innovator biologic or the biologic reference product. The term originator biologic is also used.

Biotechnology techniques are increasingly associated with the production of most biologic medicines. Biotechnology is the application of bioengineering techniques to manipulate living organisms such as bacteria or yeasts or living cells, of bacterial, animal, or human origin to produce biologic compounds for medicinal or other purposes. Genetic engineering is used to produce the required molecules or proteins of interest. The cells have their genes altered or modified, using recombinant DNA techniques so that they produce a specific substance or perform a specific function, that is, the genes for a particular protein are introduced into the genes of a host cell, which then produces the specific protein of interest.

Each innovator biologic manufacturer has its unique cell line and manufacturing process. The production processes are precisely controlled to guarantee the quality and consistency of the final product. The production of biologic medicines is complex and requires a very high level of technical expertise and numerous (hundreds or thousands) of in-process tests during product development and manufacture.

1.3.2 What Is a Biosimilar?

Unlike small molecule drug (SMD) generics, which are identical to their innovator drug, it is not possible to produce an identical copy of an innovator biologic due to their large size, complex structure, and manufacture in a unique living cell line. Instead, a biologic deemed to be "highly similar" to the innovator biologic is known as a biosimilar.

A biosimilar is a non-innovator biologic or biotherapy that is "highly similar" to and has no clinically meaningful differences from an approved innovator (licensed or reference) product. Thus, a biosimilar is deemed as having no clinically meaningful differences to the innovator product in terms of purity, potency, and safety. Manufacturers are generally required to provide supporting evidence that standards for biosimilarity recommended by the World Health Organization (WHO) are met[5] when seeking marketing approval from the USFDA, EMA, or other regulatory agencies.

Regulatory approval of a biosimilar involves a similarity exercise. This may include head-to-head comparability studies, and it is based on a totality of evidence concept[6] that generates a hierarchy of data and evidence to support similarity with the originator product. To support biosimilarity, the product must be deemed "highly similar" to the reference product; demonstrated by extensively characterizing chemical identity (structure), purity, and bioactivity (function) of both the reference and the proposed biosimilar. Minor differences between the reference product and the proposed biosimilar product in clinically *inactive* components are acceptable. There are similarities at molecular and structural levels or critical quality attributes (CQAs) between the reference and biosimilar products are similar.[7]

CQAs are divided into four separate categories: content-related attributes such as protein content; structural attributes; isoform profile; and, impurities and biological activity.[8]

Development of biosimilars is therefore methodologically complex, and it has been remarked that biosimilar development is an "imitation game."[9] A biosimilarity index (based on reproducibility probability) has been proposed to assess biosimilarity.[10] In summary, biosimilars are approved by showing "near fingerprint identity," but the term "near" is not absolute. Highly similar implies (but does not prove) therapeutic equivalency.

The targeted quality profile of biosimilars is strictly defined by the originator's product characteristics.[11] Typically, over time, since the original biologic was introduced, many product enhancements and efficiencies would have been achieved. Moreover, cell lines change over time. An important question, therefore, has been posed: "Is a biologic produced 15 years ago, a biosimilar of itself today?"[12]. In fact, it is hard to envisage that an originator biologic manufactured today would be able to demonstrate similarity to its product manufactured 15 years previously. Therefore, a global reference comparator for each biologic for biosimilar development and testing has been proposed.[13] Mandatory deposit of the original biologic's cell line with the regulator at the time of its approval has been suggested as a remedy.[14] The paradox of sharing the same therapeutic (and adverse) action without full (absolute) chemical identity has also been raised and is the subject of lively debate.[15]

Other terms used in the literature for biosimilars include follow-on biologics, similar biotherapeutic products (SBPs) or subsequent-entry biologics (SEBs) as

used by the regulatory authority in Canada[16] or non-original biologics (NOBs). Bio-mimics is also used, but the production of exact molecular copies of biologics (bio-copies) is almost impossible and biosimilars are not replicas of innovator biologics and cannot be regarded as (or be confused with) SMD generics and are not bio-generics. Biosimilar definitions in major regulatory jurisdictions are summarized in Table 1.2.

Questions posed in the biosimilar literature include: are biosimilars identical twins or just siblings; when are biosimilars similar enough[17]; are biosimilars "bio-same or bio-different[18] how dissimilarly similar are biosimilars[19]; biosimilars – how similar or dissimilar are they[20,21]; how far does similarity go[22–25]; should the term semi-similars be used instead of biosimilars[26] or are they overpriced me-toos?"[27]. It has also been asked, "if biosimilars are patentable?"[28].

Some emotive language has also crept into the literature; some fear the adoption of biosimilars while others see it as an opportunity.[29]

The above discussion highlights that internationally accepted terminology is important for biosimilars. An excellent resource on the language of biosimilars is available for historical and contemporary context.[30]

Table 1.2 Definitions of biosimilars by major regulatory agencies.

Regulatory agency/ Country	Definition
European Medicines Agency, EMA	Biologic product is similar to another biologic already authorized for use
World Health Organization, WHO	Biotherapeutic product that is similar (quality, safety, and efficacy) to the licensed reference product
Food and Drug Administration, FDA (USA)	A biologic product that is highly similar to the reference product in safety, purity, and potency; minor differences in clinically inactive components are acceptable
Biologics and Genetic Therapies Directorate, BGTD (Canada)	A biologic entering the market after a version previously authorized; demonstrated similarity to reference
Pharmaceuticals and Medical Devices Agency, PMDA (Japan)	A biotechnological drug developed by a different company, comparable to an approved biotechnology product
Therapeutic Goods Administration, TGA (Australia)	A version of already registered biologic with demonstrated similarity in physicochemical, biologic, and immunologic characteristics (efficacy, safety) based on comparability exercise

1.3.3 What Is a Biobetter?

Biobetters are related to existing biologics by the target of action but have been intentionally improved in manufacturing attributes, disposition/pharmacokinetics, efficacy, safety, or enhanced stability.[31] Biobetters build on the success of an approved innovator biologic or biosimilar but possess a lower commercial risk for biotechnology companies than a novel class of biologic. Biobetters are also known as second-generation biologics.

Biobetters improve on the relevant property of biologics. Many innovator biologics or biosimilars have less than optimal pharmacokinetic properties (e.g. high clearances or short half-lives). Besides, almost all these proteins are dosed parenterally by injection rather than orally. Thus, modifications to improve their pharmacokinetic behavior have led to biobetters. Examples include pegylated longer half-life version of filgrastim or a more extended half-life version of epoetin α, using fusion proteins.

While biosimilars are comparable to the originator product in terms of quality, safety, and efficacy, biobetters incorporate intentional modifications to the innovator's molecular profile. This distinction between biosimilars and biobetters has essential implications from a regulatory perspective. Biosimilars follow class-specific regulatory guidance whereas biobetters are considered as new molecular entities and have registration requirements of a new drug.

Biobetters may have advantages due to their pharmacologic comparability to innovator biologics, which may accelerate their development. For instance, choice of their dose and biomarkers in both nonclinical and clinical studies is simpler, and prior knowledge from the innovator biologic may reduce the scale/duration of clinical trials and safety monitoring focused on known side effects of the target pathway.

1.4 Differences Between Biosimilars and Generic Medicines

Significant differences exist between biologic medicines including innovator biologics, biosimilars, and biobetters compared with chemically synthesized or isolated small molecule drugs (SMDs) and their generics. Biologics and biosimilars are in a different league to their chemical pre-predecessors in terms of molecular complexity and natural variability.

Table 1.3 Pivotal differences between biologics and small molecule drugs.

Biologics	Small molecule drugs (SMDs)
Large/complex molecules or mixtures of these molecules	Well-defined chemical structures
Product is the process: >1000 process steps	Manufactured by chemical synthesis: specific agents are used in an ordered/sequential manner
Living processes that are very sensitive to minor changes in manufacturing: may alter the product and its function (efficacy, safety)	Well-defined chemical synthesis or isolation: subject to lower batch-to-batch variability
Product quality, purity, and function are ensured by "stable" or "consistent" manufacturing	Each individual component of the finished drug product is identified and quantified
Unwanted immune reactions are common	Unwanted immune reactions are rare

First and foremost, biologics are produced in living cells or organisms and are not chemically synthesized. Many of the other factors that hinder the full acceptance of biosimilars stem from these critical differences in the properties of biologics and SMDs. A summary of the pivotal differences between biologics and SMDs is provided in Table 1.3. Pharmacists and doctors need to keep these key differences in mind when having conversations about biosimilar medicines.

1.5 Interchangeability, Switchability, and Substitution

1.5.1 Interchangeability

Interchangeability is defined as the medical practice of changing one medicine for another to achieve the same clinical effect in a given clinical setting and patient, on the initiative of, or with the prescriber's agreement. An interchangeable product is a biosimilar that produces the same clinical outcome in any given patient. Demonstration of interchangeability presents many challenges.[32]

In the United States, registration of a biosimilar does not imply interchangeability and another class of biosimilars, "interchangeable biosimilars" have been introduced into the regulatory framework. To meet this interchangeability designation, a sponsor must demonstrate that the biosimilar produces the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of switching between the biosimilar and reference product is not greater than the risk of maintaining the patient on the reference product. No biosimilar has been granted interchangeability status so far.

1.5.2 Switchability

Switching, on the other hand, is a decision by the physician to exchange one medicine for another with the same therapeutic intent in a given patient. Alternation also refers to switching.[33] Another term in this context is non-medical switching (NMS) referring to when a patient whose current therapy is effective and well-tolerated is switched between therapies, such as an innovator biologic to its biosimilar for an economical, formulary, or other nonmedical reasons, i.e. for reasons other than the patient's health and safety.[34] Generally, NMS may be initiated by a hospital pharmacist, based on the local formulary, or the insurance company providing health insurance in consultation with the patient and the physician. The Biologics Prescribers Collaborative (BPC), representing specialist/general physician prescribers, and Alliance for Patient Access (AfPA) have developed NMS principles and guidelines.[35]

Shared decision-making between physicians, pharmacists, and patients is crucial for successful switching.[36] Patients' attitudes and level of satisfaction with switching to a biosimilar is related to being provided with necessary information about their health.[37] A comprehensive review concluded that evidence gaps around efficacy and safety of switching still exist.[38]

1.5.3 Substitution

Substitution refers to dispensing one medicine instead of another equivalent/interchangeable medicine by the pharmacist without consulting the prescriber.

In some jurisdictions/countries, interchangeability and switching are only permitted or recommended in some patients/conditions and at different treatment periods (for example, initiating therapy versus continuation of therapy).[39] Switch comes with challenges, so there needs to be clear local and national biosimilar substitution and switching policies and switch management strategies are important.[40] Pharmacists should play a pivotal role in patient empowerment as well as raising awareness of biosimilars among physicians and patients and reducing scepticism about the safety of biosimilars.

Key challenges for the integration of biosimilars into routine biologic therapy include questions around interchangeability, switching, and automatic substitution. Additional switch studies and drug registries may enhance our understanding of the safety and effectiveness of switching and a key hurdle to broader adoption of biosimilars is lack of interchangeability with reference biologics.[41]

Chapter 7 deals with interchangeability principles and evidence.

1.6 Other Clinical Considerations with Biosimilars

1.6.1 Indication Extrapolation

For innovator biologics, efficacy and safety must be demonstrated separately for each clinical indication. In contrast, biosimilar clinical trials are not required for all indications approved for the innovator biologic. Indication extrapolation is defined as approval of biosimilars for all indications of the innovator product even though the biosimilar may not have been studied in all indications.[42] The molecular similarity is the key guiding principle for extrapolation to multiple indications; it is an important concept in biosimilar development and is permitted by regulatory agencies, provided it is scientifically justified.[43]

1.6.2 Nocebo Effect

The nocebo effect is defined as a negative treatment effect that is induced by a patient's expectations that are unrelated to the pharmacologic actions of a medicine.[44] In any switching study, the subsequent biologic prescribed (like a biosimilar) is perceived to exert a lower therapeutic benefit due to this nocebo effect. The attitudes of doctors, patients, and payers are therefore crucial for the full acceptance of biosimilars because of the nocebo effect.[45]

1.6.3 Immunogenicity Reactions

An important consideration with all biologics is unwanted immunogenicity as biologics are often manufactured in living cells of nonhuman origin. Unwanted immunogenicity may lead to a reduction or loss of efficacy, altered pharmacokinetics, general immune and hypersensitivity reactions, and neutralization of the natural endogenous counterpart.[46] Immunogenicity of biosimilars would be expected to mirror those of the innovator biologic based on the similarity principle.[47]

1.6.4 Definition of Frequency of Adverse Effects

Pharmacists and doctors need to understand the accepted definitions of the frequency of adverse drug reactions. The Council for International Organizations of Medical Sciences (CIOMS), an international nongovernment organization established jointly by WHO and UNESCO in 1949, and its Uppsala Monitoring Centre, UMC, define[48] the frequency of adverse reactions as:

Very Common (≥1 in 10); **Common/Frequent** (≥1 in 100 and <1 in 10); **Uncommon/Infrequent** (≥1 in 1 000 and <1 in 100); Rare (≥1 in 10 000 & <1 in 1 000); and **Very Rare** (<1 in 10 000).

1.6.5 Pharmacovigilance of Biologics

Any drug may produce adverse reactions, with varying levels of severity and frequency. Not all adverse reactions are, however, identified before the approval of a new drug, some only being observed during post-marketing use when the drug is prescribed more widely to patients, as opposed to only clinical trial participants.

As part of the marketing authorization for biologics, the sponsor must submit a pharmacovigilance plan as part of a risk management plan (RMP) to the relevant authorities in accordance with EU regulations.[49] Applicants seeking biosimilar approval also need to submit an RMP, as required for innovator biologics. The purpose of an RMP is to document the risk management system necessary to identify, characterize, and minimize a drug's significant risks. The plan should incorporate identified and potential risks outlining a plan for pharmacovigilance activities, to characterize and quantify clinically relevant risks, and to identify new adverse reactions and outline risk minimization measures.[50]

1.7 Manufacture, Delivery, and Naming Considerations

1.7.1 Post-Translational Modifications (PTMs)

Biosimilars, like innovator biologics, raise challenges compared to SMDs, due to manufacturing complexity, presence of minor natural variations in the molecular structure (collectively known as microheterogeneity), and post-manufacturing (post-translational) modifications.[51,52] The production of innovator biologics and biosimilars comprises numerous steps and minuscule

differences in the product may result in different clinical outcomes. Consistent drug discovery and manufacturing paradigm are likely to minimize product variations. Besides, drift (unnoticed and unplanned deviations) and evolution (planned changes) may lead to divergence, which can also lead to product variability and different product attributes. Divergence means that the biosimilar and the currently marketed innovator differ from the originator product that was first approved and marketed and the innovator product that was used in the comparability exercise.[53] Biotechnology process and manufacturing innovations, needed for regulatory reasons, production scale-up, change in a facility or raw materials, and improving quality or consistency or optimizing production efficiency,[54] may lead to a higher quality biologic.

Identifying and controlling PTMs and demonstrating biosimilarity require specific and sensitive analytical techniques. Pharmacists need to be familiar with such techniques and issues; these are discussed in Chapter 6.

1.7.2 Quality by Design Paradigm

Quality by design (QbD) is an approach that aims to ensure the quality of medicines by employing statistical, analytical, and risk-management methodology in the design, development, and manufacturing of medicines. It focuses on the use of multivariate analysis, often in combination with the modern process and analytical chemistry methods, and knowledge-management tools to enhance the identification and understanding of critical attributes of materials and critical parameters of the manufacturing process. This enhanced understanding of product and process is used to build quality into manufacturing and provide the basis for continuous improvement of products and processes.[55]

One of the goals of QbD is to ensure that all sources of variability affecting a process are identified, explained, and managed by appropriate measures. This enables the finished medicine to meet its predefined characteristics consistently.

The concepts behind QbD were introduced into international pharmaceutical guidelines between 2009 and 2012. EMA accepts applications that include QbD concepts.

1.7.3 Delivery Devices for Biologics

Converting a promising innovator biologic or biosimilar molecule into a pharmaceutical product presents numerous new challenges. For example, biologic medicines are highly viscous and formulated at high concentrations, which makes them more prone to aggregation. In addition, they need to be handled, packaged, stored, and transported carefully.[56] These requirements are driving innovation in packaging and delivery device development as, increasingly, drug companies demand technologies that can protect and administer these high-value medicines safely and conveniently.[57]

Historically, all biologic drugs were freeze-dried and packaged in glass vials and administered, after reconstitution, using glass syringes. While most biologics are still packaged and delivered using glass, a growing number of biologics (including biosimilars) are packaged in plastic vials and administered using plastic syringes.

Devices for biosimilar administration are essential in quality use of medicine (QUM) considerations for biosimilars as for all biologics[58]; they may also have critical practical implications for patients. These devices, either prefilled syringes, pens, or pumps, are important for dosing accuracy and reproducibility as well as long-term patient compliance and adherence. From a patient perspective, one would envisage that the device via which a biosimilar is administered must at least be able to match the innovator biologic's device for convenience and comfort. Inferior usability may also reduce treatment adherence and product uptake by patients. The design and user experience of the delivery device may also serve as a critical market differentiator between the innovator biologic and the biosimilar.

1.7.4 Naming and Labeling of Biosimilars

A critical question that is still eliciting much debate internationally is the naming convention for biosimilars; in other words, what should be their nonproprietary (noncommercial) name?

SMD generic medicines have the same nonproprietary names as their innovator medicines as the active ingredients in generics are identical to that in the innovator drugs. In contrast, biosimilars are not identical to innovator biologics. Giving all biologics, including biosimilars, different (distinguishable) nonproprietary names are consistent with the concept that no two versions of a biologic including a biosimilar are identical.[59]

Views on the naming of biosimilars fall broadly in two groups. The first is that since a biosimilar is highly similar to its innovator biologic, it should have the same name as the innovator. The other view is that for safety reasons, it is critical to have a unique name for each

biologic, including a biosimilar so each biologic can be identified individually.[59]

Under the FDA's naming system, each biologic, innovator/reference product, and biosimilar receives a unique nonproprietary name; a "core" name followed by a unique (but meaningless) four-letter suffix. Thus, each biologic has a unique, distinguishable name in the United States.

Europe, Australia, and Canada have adopted a different naming approach that incorporates distinguishable suffixes. These countries allow biologics including biosimilars to share nonproprietary names but have strengthened adverse event monitoring by either mandating inclusion of brand names or nonproprietary names as well as brand names in adverse event or pharmacovigilance reporting. In Australia, for example, the product's trade name, as well as the nonproprietary name, is a mandatory field when reporting an adverse event.[60]

The naming of biosimilars has implications far beyond the marketing and commercial sphere; it may directly affect patients' confidence in switching to biosimilars and traceability of each biosimilar product with respect to its efficacy and safety monitoring once on the market.

1.8 Listing of Approved Biologics

1.8.1 Purple Book in the United States

The *Purple Book* is a compendium of FDA-approved biological products and their biosimilar and interchangeable products. It resembles the *Orange Book*, which is a list of approved SMD generics. Information on each product listed in the *Purple Book* includes its BLA tracking number, product name, product proprietary name, date of licensure, date of first licensure, reference product exclusivity expiration date, indication as to whether the product is interchangeable (I) or biosimilar (B), and whether the product was withdrawn from the market.[61] Other countries have similar lists of approved innovator biologics and biosimilars.

1.8.2 European Generic Medicines Association (EGA) Biosimilars Handbook

This handbook provides information on the current state of biosimilar medicines in the EU. It describes the science and technology behind biosimilar medicines, how they are produced and regulated, and provides answers to many specific questions. These include the terminology used, the meaning of "quality, efficacy and safety" and "comparability," the purposes and methodologies of nonclinical and clinical tests and trials, the role of pharmacovigilance and risk management, and the significance of immunogenicity. Access to medicines, including substitution, interchangeability, and the importance of identification is also included.[62]

1.9 Biosimilar Initiatives and Organizations

Many initiatives and organizations with interest in broader adoption of biosimilars have come into being, driven by governments and/or private organizations and agencies including patient advocacy groups. A summary of these is provided as these initiatives and organizations affect the information flow and influence the uptake of innovator biologics and biosimilars. The intent here is not to discuss comprehensively every national or international initiative on the adoption of biosimilars but to present some prominent exemplars so that the reader is able to map to similar national and local initiative(s) in their own country. If such initiatives are not currently available in a country, then the reader may also be able to facilitate the creation of such an initiative tailored to the specific needs of their country.

1.9.1 Generics and Biosimilars Initiative (GaBi/GaBI)

Generics and Biosimilars Initiative (GaBi/GaBI) was founded in 2008. The mission of GaBI is to foster the efficient use of high quality and safe medicines at an affordable price, thus advancing and supporting the idea of accessible, affordable, and sustainable health care internationally.

GaBI aims to raise the scientific status of SMD generics and biosimilar medicines and to provide comprehensive high-quality, scientifically sound, reliable, well-documented, and up-to-date information about generics and biosimilar medicines in both print and electronic media in an open-access format. To this end, GaBI provides a service for healthcare providers to support them in making cost-effective choices when it comes to treatment option decisions. Physicians and pharmacists are the primary target of GaBI, followed by healthcare policymakers and drug regulators, third-party insurers, and pharmaceutical/biotech industry.[63] This initiative has GaBI Online and GaBI Journal as its principal resources.

1.9.2 Biologics Price Competition and Innovation Act in the United States

The US Congress passed the Biologics Price Competition and Innovation (BPCI) Act in 2009, authorizing the FDA to oversee an "abbreviated pathway" for approval of biologics that are "biosimilar" to already approved biologic products.[64] The BPCI Act (also known as the Affordable Care Act) aligns with the FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary testing.

Under the BPCI Act, a sponsor may seek approval of a "biosimilar" product. A biological product may be demonstrated to be "biosimilar" if data show that the product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency.

In order to meet the higher standard of interchangeability, a sponsor must demonstrate that the biosimilar product can be expected to produce the same clinical result as the reference product in any given patient and, for a biological product that is administered more than once, that the risk of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of maintaining the patient on the reference product. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health-care provider.

The BPCI Act intended to facilitate timely approval of and access to biosimilars to US citizens. Recent evidence appears to suggest that this goal has not been achieved and other essential steps are required.[2,65]

1.9.3 Biosimilars Action Plan (USFDA)

In July 2018, the USFDA published its Biosimilars Action Plan, BAP.[66] Key elements of the BAP include (i) improving the efficiency of the biosimilar and interchangeable product development and approval process; (ii) maximizing scientific and regulatory clarity for the biosimilar product development community; (iii) developing effective communication to improve understanding of biosimilars among patients, clinicians, and payers; and (iv) supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay biosimilar competition.

1.9.4 NHS England Commissioning Framework for Biological Medicines

NHS England released this framework in late 2017. This document supports NHS commissioners to act promptly to make the most of the opportunity presented by increased competition among biological medicines, including biosimilars. In particular, this framework sets out the importance of taking a collaborative approach to the commissioning of innovator biologics and biosimilars.[67] A companion commentary on preparing for the biologic switch is also available.[68]

1.9.5 PrescQIPP

PrescQIPP is a UK NHS funded not-for-profit organization that supports quality optimized prescribing for patients. It helps NHS organizations to improve medicines-related care to patients, through the provision of accessible and evidence-based resources.[69] PrescQIPP also provides a platform to share innovation, learning, and good practice. It operates for the benefit of NHS patients, commissioners, and organizations. PrescQIPP provides many resources on biologics and other high-cost medicines (for example, on biosimilars of infliximab, insulin, and etanercept, respectively).

1.9.6 The Association of the British Pharmaceutical Industry

The UK government recognizes the Association of the British Pharmaceutical Industry (ABPI) as the industry body negotiating on behalf of the branded pharmaceutical industry for statutory consultation requirements including pricing schemes for medicines in the United Kingdom. The ABPI has partnerships with UK NHS on medicine-related projects including innovator biologics and biosimilars.[70]

1.9.7 NHS Scotland

Healthcare Improvement Scotland, as part of NHS Scotland, has led a biosimilar medicines national prescribing framework to support the safe, effective, and consistent use of biosimilar medicines in Scotland.[71]

1.9.8 National Institute for Health and Care Excellence

National Institute for Health and Care Excellence (NICE) in the United Kingdom supports the managed

introduction of biosimilar medicines as part of its key therapeutic topics and initiatives for medicines optimization. NICE has released a biosimilars position statement[72] and also has a position statement on the assessment of biosimilars.[73] NICE provides many other resources.

1.9.9 Australian Biosimilar Awareness Initiative

This initiative was announced in 2015 as part of the Australian Pharmaceutical Benefits Scheme (PBS) Access and Sustainability Package. The aim is to support awareness of, and confidence in, the use of biosimilar medicines for healthcare professionals and consumers.[74]

Several research activities like up-to-date literature review[75] form part of the initiative; these aim to separate the evidence from commentary better; gather data on current awareness and attitudes toward innovator biologics and biosimilars in Australia; and identify critical issues, like barriers to uptake and use of biosimilars.

1.9.10 NPS MedicineWise (Australia)

Several important initiatives are in place in Australia to ensure the health community embraces the full potential of innovator biologics and biosimilars. Within this context, and under the stewardship of NPS MedicineWise, The Biologic and Biosimilar Medicines 2020 Forum was held in 2016, to maximize the opportunities these medicines present to the Australian healthcare system.[76] The Australian National Medicines Policy provided a framework for the Forum to discuss the opportunities and challenges presented by the availability of both innovator biologic and biosimilar medicines. A broad range of perspectives from research, industry, government, medical, pharmacy, and consumer perspectives were considered. The expanding settings in which innovator biologics and biosimilars may be used was also taken into consideration including hospitals, specialist medical centers, primary care, community pharmacy, and nonclinical environments such as the home. The themes that emerged from the forum included: improving the evidence base; optimizing data capture; pharmacovigilance and naming conventions; and building stakeholder confidence and shared decision-making through high-quality information.

1.10 Common Terms Used in the Biologics Literature

This section intends to provide the reader with significant terms that are used in biologic medicine literature internationally.

1.10.1 Real-World Evidence

Real-world evidence (RWE) refers to data on the use of a drug product obtained outside of clinical trials.[77] In other words, the efficacy and safety data collected from medical records, pharmacovigilance records, personal devices, or electronic health applications after the medicine has been marketed, i.e. data and evidence about the drug product that is gathered during its widespread clinical use.

Depending on their design, RWE studies may follow patients for several years, or study treatments in patients not included in clinical trials (e.g. in children, elderly patients, or patients with concomitant diseases) or in clinical indications not studied during clinical trials. RWE studies may enhance the broader adoption of biosimilars.[78] Importantly, RWE studies must be carefully designed to yield credible, reproducible results using sound pharmacoepidemiological principles and practices.

1.10.2 Patent Dance

As mentioned, the BPCI Act in the United States provides for an elaborate process of information exchange, known as the "patent dance"[79] between a biosimilar applicant and an innovator/reference product sponsor (RPS) intended to resolve potential patent disputes in an orderly and expeditious fashion. This procedure (patent dance) has strict timing and sequencing requirements and involves several rounds of information exchange between the innovator/RPS and the biosimilar applicant.

1.10.3 Evergreening

Evergreening refers to the use of various strategies for patent extension, of innovator biologics as also occurs for SMD innovator drugs to delay the introduction of their SMD generics. Among other outcomes, evergreening may limit timely availability of biosimilars and affect their price.[80]

1.10.4 Limited Distribution Network

The limited distribution network, LDN, which restricts the distribution channel for a drug to one or a very small

number of distributors, can stifle competition for biosimilars and affect their price.[81]

1.10.5 Drug Tendering

The goal of pharmaceutical procurement is to purchase high-quality products with reliable supplier service and the lowest possible price. One method to contain spending is tendering, a formal procedure using competitive bidding for a particular contract; tendering is used when equivalents for a specific medicine are available, and is defined as "any formal and competitive procurement procedure through which offers are requested, received and evaluated for the procurement of goods, works or services, and as a consequence of which an award is made to the tenderer whose tender/offer is the most advantageous"[82]. Drug tendering may influence biosimilar uptake and price.[82]

1.10.6 Pharmacy and Therapeutics Committees

Pharmacy and Therapeutics (P&T) committees exist in most hospitals and pharmacists are key members of such committees offering objective, unbiased information and advice on all aspects of drug use. Considerations of quality, cost (reimbursement), access, and procurement and interchangeability of biosimilars with innovator biologics[83] will be even more important to P&T committees as new emerging and even more expensive biotherapies enter the market and hospitals and insurers and governments attempt to improve clinical care within enormous budgetary constraints.

1.10.7 Quality Use of Medicine

QUM involves improving medicine use, including prescription, non-prescription, and complementary medicines, and medical devices by health professionals and decision-makers as well as by consumers and the pharmaceutical industry.[84] QUM is also known as rational drug use, responsible drug use, or appropriate use of medicines and includes:

Selecting management options wisely; choosing suitable medicines if a medicine is considered necessary and ensuring that patients and carers have the knowledge and skills to use medicines safely and effectively. QUM concepts apply equally to decisions about medicine use by individuals as well as decisions that affect the health of the population.

QUM concepts and principles as they apply to innovator biologics and biosimilars is the subject of a detailed discussion in Chapter 14.

1.10.8 European Public Assessment Report

EMA publishes detailed information on the medicines assessed by the Committee for Medicinal Products for Human Use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP) which are granted (or refused) central marketing authorization by the European Commission. The main vehicle for this information is known as a European Public Assessment Report (EPAR), which is a full scientific assessment report of medicines authorized in the EU.

An essential role of the EPAR is to reflect the scientific conclusions of the relevant EMA committee at the end of the assessment process, providing the grounds for the expert opinion on whether to approve an application.

EPARs are updated periodically to reflect the latest regulatory information on medicines. If the original terms and conditions of a marketing authorization are varied, the EPAR is updated to reflect such changes with an appropriate level of detail.

EPARs are a valuable source of information about innovator biologics and biosimilars.[85]

1.11 Abbreviations Associated with Biologic Medicines

Many abbreviations relating to innovator biologics, biosimilars, and biobetters are used in the literature by many and varied stakeholders. A summary of these frequently used abbreviations is presented in Table 1.4 to familiarize readers with these terms and abbreviations.

1.12 Concluding Remarks

The science behind innovator biologics, biosimilars, and biobetters are complex and the literature is changing rapidly. The scientific and clinical data are evolving at a much faster rate than the ability of pharmacists, doctors, other health practitioners and patients to keep pace with new information. Regulators, as well as policymakers, also find it challenging to keep pace with this change and evolution and to embed regulatory and policy frameworks in a timely and responsible manner. There will also continue to be greater

Table 1.4 Abbreviations used in biologic medicine literature.

Abbreviation	Full name
ADCs	Antibody–Drug Conjugates
ADR	Adverse Drug Reaction
ADE	Adverse Drug Event
AE	Adverse Event
ANDA	Abbreviated New Drug Application
ARTG	Australian Register of Therapeutic Goods
ATMP	Advanced Therapy Medicinal Products
BDMARDs	Biologic Disease-Modifying Anti-Rheumatic Drugs
BIA	Budget Impact Analysis
BLA	Biologics License Application
BPCI Act	Biologics Price Competition and Innovation Act
CAPs	Centrally Authorised Products (EU)
CAR-T	Chimeric Antigen Receptor Therapy
CDMO	Contract Development and Manufacturing Organisation
CEOR	ClinicoEconomics and Outcomes Research
CHMP	Committee for Medicinal Products for Human Use (EMA)
CIOMS	Council for International Organizations of Medical Sciences
CE	Comparability Exercise
CMA	Critical Material Attribute
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CTD	Common Technical Document
DCP	Decentralised Procedure
DDD	Defined Daily Dose
DDR	Dose-Dense Regimens
EC	European Commission
EMA (EMEA)	European Medicines Agency
EPARs	European Public Assessment Reports
EPO	Erythropoietin (epoetin)
EU	European Union
Eudra	European Drug Regulatory Authorities
FDA	Food and Drug Administration
FD&C	Food, Drug, and Cosmetic
FTC	Federal Trade Commission (in the United States)
GCP	Good Clinical Practice
GH	Growth Hormone
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HCPCS	Healthcare Common Procedure Coding System
HPLC	High-Performance Liquid Chromatography
IBD	Inflammatory Bowel Disease
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
IP	Intellectual Property
LDN	Limited Distribution Network
LMWH	Low Molecular Weight Heparins
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MCOs	Managed Care Organisations
MR	Mutual Recognition
NHS	National Health Service
NDA	New Drug Application
NMS	Non-Medical Switching
NICE	National Institute for Clinical Excellence (UK)
mAb	Monoclonal Antibody
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PFS	Pre-Filled Syringe
PHS	Public Health Service
PMS	Post-Marketing Surveillance
PPRS	Pharmaceutical Price Regulation Scheme (UK)
QbD	Quality by Design
RCT	Randomised Clinical Trial
REMS	Risk Evaluation and Mitigation Strategies
RMOCs	Regional Medicines Optimisation Committees (UK)
RMPs	Risk Management Plans
RMR	Reaction Monitoring Report
RPG	Reference Price Group
RWD	Real-World Data
SB	Synthetic Biology
SEBs	Subsequent-Entry Biologics
SBPs	Similar Biotherapeutic products
SMDs	Small molecule Drugs

Table 1.4 (Continued)

Abbreviation	Full name
SmPAR	Summary of Pharmacovigilance Assessment Report
SmPc	Summary of Product Characteristics
SPBs	Similar Protein Biotherapies
TGA	Therapeutic Goods Administration
TPP	Target Product Profile
TPQP	Target Product Quality Profile
WHO-UMC	World Health Organization-Uppsala Monitoring Centre

economic pressures from governments and payers of all political persuasions for affordable biologics like biosimilars to realize the full benefits of innovator biologic medicines. It is therefore imperative that pharmacists keep abreast of such rapid changes in the information as they will be expected to lead discussions with doctors and patients on these important therapeutic agents.

The subsequent chapters of this book are pitched explicitly to pharmacists and doctors and deal in greater detail with the various scientific, clinical, economic, QUM, and pharmacovigilance aspects of innovator biologics, biosimilars, and biobetters. The material provided in this and subsequent chapters should facilitate discussions by pharmacists with doctors and patients on these expensive and highly effective medicines so that the full therapeutic potential of all biologic medicines is realized in a timely manner.

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