Shvetank Bhatt · Harish Dureja ·
Samir Gunvantbhai Patel ·
Archita Samir Patel · Kamal Dua *Editors*

Biosimilars for Cancer Treatment

A Promising Approach

Springer

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Editors
Shvetank Bhatt
School of Health Sciences and Technology
Dr. Vishwanath Karad MIT World Peace University
Pune, Maharashtra, India

Samir Gunvantbhai Patel
Ramanbhai Patel College of Pharmacy
Charotar University of Science and Technology
Changa, Gujarat, India

Kamal Dua
Discipline of Pharmacy
University of Technology
Sydney, NSW, Australia

Harish Dureja
Department of Pharmaceutical Sciences
Maharshi Dayanand University
Rohtak, Haryana, India

Archita Samir Patel
Ramanbhai Patel College of Pharmacy
Charotar University of Science and Technology
Changa, Gujarat, India

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Preface

Cancer is a leading cause of death worldwide, accounting for nearly ten million deaths in 2020, or nearly one in six deaths. Head and Neck, breast, liver, pancreatic, gastro-esophageal, bladder, lung, colorectal, blood, and prostate cancers are the most common cancers. Cancer occurs when cells of the body starts multiplying in uncontrollable manner. This is due to modification in apoptotic pathways and related mechanisms. The diseases normally start with small area and localized and in the later stages cells become metastasized in different locations in body.

A biosimilar drug is a very similar copy of an already approved biological drug. Biosimilars work the same way as biologics in our body. Now a day the high cost of various cancer therapies kept a significant burden on the health care system of the country and that's why the oncology research has been focused now more on the use of biosimilars as they are safer and cost-effective. The use of biosimilars might provide competitive, lower-cost alternatives to biologics used in cancer care.

Manufacturing of biosimilars are difficult as compared to synthesizing new chemical entities. Maintaining batch-to-batch consistency is very critical in the production of biosimilars. The most frequently used biosimilar drugs are Bevacizumab, Epoetin alfa, Filgrastim, Pegfilgrastim, Rituximab and Trastuzumab. Recently various biosimilar drugs are approved for the treatment of various solid tumors and blood cancers such as lung cancer, bladder cancer, melanoma, head and neck cancer and diffuse large B-cell lymphoma etc. In todays 'scenario biosimilars have an important role in the effective management of the different type of cancers i.e. colon cancer, lung cancer, gastric cancer, breast cancer, cervical cancer, liver cancer, ovarian cancer and blood cancer etc. These biosimilars can be used as monotherapy or in combination with other therapies like chemotherapy and targeted therapy.

We hope the book shall be a useful compilation for undergraduate, postgraduate, doctoral students, and researchers working in cancer and drug delivery research,

research and development, and national research institutes. We hope to receive feedback, suggestions, and inputs from researchers and students that will help improve the next edition of the book.

Pune, Maharashtra, India — Shvetank Bhatt
Rohtak, Haryana, India — Harish Dureja
Changa, Gujarat, India — Samir Gunvantbhai Patel
Changa, Gujarat, India — Archita Samir Patel
Sydney, NSW, Australia — Kamal Dua

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Pune, Maharashtra, India Shvetank Bhatt

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Editors and Contributors

About the Editors

Shvetank Bhatt is currently working as an Associate Professor in the School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, India. He has done M.Pharm. in Pharmacology from Manipal College of Pharmaceutical Sciences, MAHE, Manipal, Karnataka, India and Ph.D. in Neuropharmacology from Birla Institute of Technology and Science (BITS) Pilani, Pilani Campus, Rajasthan, India. His areas of specialization are CNS disorders, pain, inflammation and immuno oncology. He has published numerous papers. He is a life member of the Association of Pharmaceutical Teachers of India (APTI) and the Indian Pharmacological Society (IPS).

Harish Dureja is Head of the Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India, and Director of the Centre for IPR Studies and Professional Consultancy Cell at M.D. University, Rohtak, India. He earned his Master's in Pharmacy from Punjabi University, Patiala, India, and Ph.D. in Pharmaceutical Sciences from Maharshi Dayanand University, Rohtak, India. He has published numerous articles in journals of repute. Dr. Dureja is also actively engaged in committees of various central and state universities, namely the Committee for Control and Supervision of Experiments on Animals (CCSEA), Pharmacy Council of India (PCI), All India Council of Technical Education (AICTE), National Testing Agency (NTA) and National Assessment and Accreditation Council (NAAC), etc.

Samir Gunvantbhai Patel works as Dean, Faculty of Pharmacy, Professor, Pharmaceutical Chemistry and Analysis, at Ramanbhai Patel College of Pharmacy (RPCP), Gujarat, India. He has more than 18 years of academic experience. His major research areas are design, synthesis and biological evaluation of cyclic peptides and synthetic derivatives for treating breast cancer, colon cancer and cancer metastasis. He has published several research articles and a few book chapters.

Archita Samir Patel is an Assistant Professor, Pharmaceutical Chemistry and Analysis, Ramanbhai Patel College of Pharmacy (RPCP), Gujarat, India. She has more than 18 years of academic experience. Her major research areas are the analysis of small molecules, development and validation of stability indicating analytical methods for small molecules and herbal actives, impurity profiling of synthetic drug substances and developing analytical methods using a chemometrics approach. She has published several research articles and a few book chapters.

Kamal Dua is an Associate Professor in the Discipline of Pharmacy at the Graduate School of Health, University of Technology Sydney (UTS), Australia. He has research experience of over 13 years in the field of drug delivery systems targeting inflammatory diseases. Dr. Dua is also a node leader of drug delivery research in the centre for inflammation at Centenary Institute/UTS, where the targets identified from the research projects are pursued to develop novel formulations as the first step towards translation into clinics. Dr. Dua's research in two complementary areas; drug delivery and immunology are evidenced by his extensive publication record in reputed journals. Dr. Dua's research interests focus on harnessing the pharmaceutical potential of modulating critical regulators such as Interleukins and microRNAs and developing new and effective drug delivery formulations for the management of chronic airway diseases. He has published numerous research articles in journals of repute and authored and co-authored a few books. He is also an active member of many national and international professional societies.

Contributors

Senthil Visaga Ambi Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Department of Bioengineering, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Kuttiappan Anitha Department of Pharmacology, School of Pharmacy and Technology Management (SPTM), SVKM's Narsee Monjee Institute of Management Studies (NMIMS) Deemed-to-University, Shirpur, India

Pavithra Vimala Arulrajan Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Dhara Bhatt Medisynth Chemicals Pvt. Ltd., Navi Mumbai, Maharashtra, India

Shvetank Bhatt Department of Pharmaceutical Sciences, School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, India

School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, India

Prarit Chandel Chitkara University, School of Pharmacy, Baddi, Himachal Pradesh, India

Pallavi M. Chaudhari Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, India

Santenna Chenchula Department of Pharmacology, AIIMS, Bhopal, Madhya Pradesh, India

Pranali Chimaniya School of Pharmaceutical Education and Research, Peoples University, Bhopal, Madhya Pradesh, India

Harita Desai Department of Pharmaceutics, Bombay College of Pharmacy, Santacruz East, Mumbai, India

Arghya Kusum Dhar School of Pharmacy, The Neotia University, Sarisa, West Bengal, India

Subas Chandra Dinda School of Pharmacy, The Neotia University, Sarisha, West Bengal, India

Dipali Dongare Department of Biotechnology, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Harish Dureja Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Arvind Ganpule Department of Urology, Muljibhai Patel Urological Hospital, Nadiad, Gujarat, India

Gayathri Gopal Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Department of Bioengineering, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Nisha Gulati Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Daksh Sanjay Gupta Vivekanand Education Society's College of Pharmacy, Mumbai, Maharashtra, India

Dhruv Sanjay Gupta Department of Pharmaceutics, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's Narsee Monjee Institute of Management Studies (NMIMS) Deemed-to-University, Mumbai, Maharashtra, India

Girdhari Lal Gupta Department of Pharmacology, School of Pharmacy and Technology Management (SPTM), SVKM's Narsee Monjee Institute of Management Studies (NMIMS) Deemed-to-University, Shirpur, India

Pawan K. Gupta Amity Institute of Pharmacy, Amity University, Gwalior, Madhya Pradesh, India

Ekta Gurnany Department of Pharmaceutics, B. Pharmacy College, Rampura, Godhra, Gujarat, India

Ananya Nithin Kanade Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Neha Kanojia Chitkara University, School of Pharmacy, Baddi, Himachal Pradesh, India

Sidhartha S. Kar Faculty of Pharmacy, C. V. Raman Global University, Bhubaneswar, Odisha, India

Payal Kesharwani Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, Uttar Pradesh, India

Anoop Kumar Delhi Pharmaceutical Sciences and Research University (DPSRU), New Delhi, India

Pallavi Manish Lavhale Ram-Eesh Institute of Vocational and Technical Education, Greater Noida, Uttar Pradesh, India

Saurabh Morparia Department of Pharmaceutical Analysis, Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, Maharashtra, India

Manikanta Murahari Department of Pharmacy, Koneru Lakshmaiah Education Foundation, Vaddeswaram, Andhra Pradesh, India

Gayathri Devi Muthukumarasamy Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Lokesh Nagar Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Manish Nandpal Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Aryaa Nigade School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, India

Shireen Nishad Department of Biotechnology, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Narhari N. Palei Amity Institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh, India

Sachchida Nand Pandey Department of Pathology, Muljibhai Patel Urological Hospital, Nadiad, Gujarat, India

Nikunj Parekh Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Alkeshkumar Patel Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Archita Samir Patel Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Meghana Patel Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Priyal Patel Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Samir Gunvantbhai Patel Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Yash Patel Ramanbhai Patel College of Pharmacy, Charusat, Changa, Gujarat, India

Gauri Pathak School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, India

Bhagwat Patil Department of Pharmaceutics, Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune, India

Ravindra Babu Pingili Department of Pharmacology, School of Pharmacy and Technology Management (SPTM), SVKM's Narsee Monjee Institute of Management Studies (NMIMS) Deemed-to-University, Shirpur, India

Shiv Kumar Prajapati Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh, India

Dishank Purandare School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, India

Neha Raghuvanshi Department of Pharmaceutics, Bombay College of Pharmacy, Santacruz East, Mumbai, India

Anika Rana Department of Biotechnology, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Karthika Rangasamy Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Annu Saini Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Khyati Saini School of Pharmaceutical & Populations Health Informatics, DIT University, Dehradun, India

Keerthana Saravanan Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Pranav Shah Maliba Pharmacy College, UkaTarsadia University, Surat, Gujarat, India

Suhashini Shamuganathan Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Kangan Sharma School of Pharmaceutical & Populations Health Informatics, DIT University, Dehradun, India

Saritha R. Shetty Department of Pharmaceutics, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM's Narsee Monjee Institute of Management Studies (NMIMS) Deemed-to-University, Mumbai, Maharashtra, India

Satish Shilpi School of Pharmaceutical & Populations Health Informatics, DIT University, Dehradun, India

Abhishek Singh Amity Institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh, India

Neeta Solanki Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, India

Ashwin Subramanian Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Vasanti Suvarna Department of Pharmaceutical Analysis, Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, Maharashtra, India

Komal Thapa Chitkara University, School of Pharmacy, Baddi, Himachal Pradesh, India

Vaishnavi Thorat School of Health Sciences and Technology, Dr. Vishwanath Karad MIT World Peace University, Pune, Maharashtra, India

Pratima Tripathi Department of Biotechnology, National Institute of Pharmaceutical Education and Research, Lucknow, Uttar Pradesh, India

Saraswathi Venkataraman Biopharmaceutical Research Lab, Anusandhan Kendra-1, School of Chemical and Biotechnology, SASTRA Deemed-to-be-University, Thanjavur, Tamil Nadu, India

Nitin Verma Chitkara University, School of Pharmacy, Baddi, Himachal Pradesh, India

Seema Yadav Amity Institute of Pharmacy, Amity University, Lucknow, Uttar Pradesh, India

Overview of Biosimilars

1

Dipali Dongare, Anika Rana, Shireen Nishad, and Pratima Tripathi

Abstract

Biotechnological drugs are increasingly crucial in modern medicine, which anticipated to occupy half the pharmaceutical market soon. Patent expirations have spurred the emergence of biosimilars, akin to follow on biologics aiming to replicate original biotech medicines. While a couple of biosimilars gained approval in the EU, others are in the pipeline. Despite their potential to reduce treatment costs, our understanding and long-term safety data for biosimilars, including immunogenicity, remain limited. Comparing biosimilars to classic chemical drug generics is vital, demanding focused discussions among physicians. Regulatory clarity, safety concerns, pharmacovigilance, automatic substitution policies, nomenclature, and labeling rules constitute crucial areas requiring attention as biosimilars evolve in the healthcare landscape.

Keywords

European Union · Tevagrastim · Biopharmaceuticals · Molecular generics

1.1 What Are Biosimilars?

A biosimilar is a biologic product that has been created to closely resemble the reference product, a biologic that has already received FDA approval. A biosimilar cannot differ from the reference product in any way that is clinically significant. If a biosimilar meets all the criteria for safety, potency, and purity for the intended use under the prescribed circumstances, it is deemed to be highly comparable to the

D. Dongare · A. Rana · S. Nishad · P. Tripathi (✉)
Department of Biotechnology, National Institute of Pharmaceutical Educationn and Research, Lucknow, Uttar Pradesh, India

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reference product. The safety, purity, and potency of a biosimilar are demonstrated through a battery of tests and studies conducted by the producer with the aim of contrasting the biosimilar with the reference product (Fig. 1.1).

A product must have the same mechanism of action (how it functions in the body), dosage form (such as liquid), mode of administration (such as injection or infusion), and strength as its reference product in order to be authorized as a biosimilar by the FDA. The clinically inactive parts of the medication may differ slightly between the reference product and the biosimilar, among other possible small variations. In contrast, the FDA assesses these variations to make sure they are reasonable and do not affect the biosimilar's efficacy in comparison to the reference product.

The inventor never discloses the proprietary manufacturing process of reference drug. So, while balancing innovation, competitiveness, and regulatory compliance, biosimilar manufacturers seek to produce biosimilars that are comparable to already available reference biologics using different methods and resources (Afzali et al. 2021). The FDA closely monitors the biosimilar's manufacturing process, just as it does with the reference product. Minor deviations are anticipated (Kurki et al. 2017). But according to FDA regulations, these variances must be closely regulated, tracked, and maintained within reasonable bounds (Food and Administration 2019).

The absence of clinically significant variations between the biosimilar and the reference product is another prerequisite for biosimilars. This implies that a patient will react to the biosimilar in the same way as they would to the original medication physically (Derbyshire 2017). In order to demonstrate this, the biosimilar's manufacturer, or sponsor, compares elements like immunogenicity—the body's reaction to the drug, pharmacokinetics—how the drug is metabolized, broken down, or eliminated by the body, and pharmacodynamics—the impact of the drug has on the body and the illness.

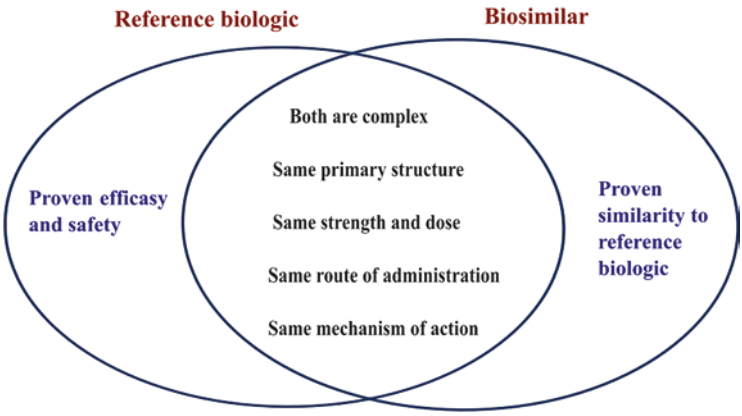

Fig. 1.1 Similarities and differences between reference biologic and biosimilar. Reference biologic undergoes extensive clinical trials to prove efficacy and safety, whereas biosimilar aims to prove similarities with reference biologic with no clinically meaningful differences

The EU established the biosimilars approval process in 2006, and these rules were updated in 2015. The recommendations have rapidly evolved for biosimilars, with the majority of nations adopting the overall framework of the US FDA, EMA, or WHO, while some nations developed their own guidelines based on these concepts (Aladul et al. 2018).

1.2 Biosimilar Development Process

Compared to the original reference biologic, biosimilar development process meets different development requirements. It gives stronger emphasis on analytical characterization and clinical equivalency with the reference biologic. The foundation for the developing of biosimilars is the thorough analytical characterization along with the development of processes necessary to create adequate biosimilarity to the original biologic, as the originator has previously proved the safety as well as effectiveness of the reference medication (de Mora et al. 2019). A biosimilar product may support significantly less extensive clinical testing with sufficient comparability testing, which means that the development expenses are considerably lower than those needed for an original medication (Glintborg et al. 2017) (Fig. 1.2). According to the US FDA guidelines, following are the steps for the approval of the biosimilars:

1. **Analytical characterization:** Analytical research shows the biological product's great similarity to the reference product despite very slight variations in its therapeutically inert constituents. Important factors for consideration in assessing analytical studies include stability, impurities, functional activities, physiochemical properties, and immunochemical properties (Rumore and Vogenberg 2016).
2. **Animal studies:** It includes an assessment of toxicity. Animal toxicity studies' scope and extent will be determined by the degree of known similarities or dif-

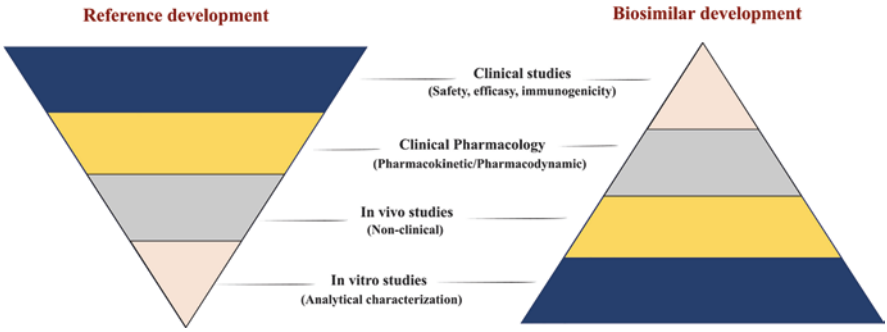

Fig. 1.2 Biosimilar development process. Biosimilars extensively focused on analytical characterization to closely resemble the reference drug without meaningful clinical difference than reference biologic

ferences between the reference product and the proposed biosimilar product, as well as by data submitted in the biosimilar application and made publicly available. In this, pharmacokinetic and pharmacodynamic studies are also done in animal models.

3. **Clinical studies:** To verify the safety, potency, and purity of the proposed biosimilar product in one or more of the indications for which the reference product is approved, a clinical study is conducted. In addition to evaluating the immunogenicity, pharmacokinetics as well as pharmacodynamics, this often involves a comparative clinical investigation. After clinical trials, FDA will approve the drug as biosimilar when all requirements have achieved.

1.3 Interchangeable Biosimilars

A biological drug that is extremely similar to another biological medication that has received prior approval is known as an interchangeable biosimilar. The reference product can be replaced with interchangeable biosimilars at the pharmacy without the help of prescribing physician. At the pharmacy level, the substitution known as an "auto-substitution" is used in clinical settings in the US, Canada, and Australia. Physician-directed substitution, or "switching," is a procedure that is carried out in certain EU member states as well as in Japan, India, and other countries.

"Interchangeability" is a term used in regulations, when further requirements for interchangeability are satisfied (Food U 2015). The US FDA grants a biosimilar the designation of interchangeable. Not every biosimilar can be used interchangeably. An interchangeable biosimilar must also fulfill additional requirements specified by the US Food and Drug Administration (FDA) based on an examination of the product known as the "switch trial design."

The FDA concludes that a reference biologic can be substituted with an interchangeable product when compared to reference drug, the biological drug "is biosimilar" and may be anticipated to result in the same clinical outcome as the reference product in any particular patient. According to the European Medicines Agency (EMA), decentralized agency of European Union (EU), the term "interchangeability" describes the ability to switch out a medication with another that is expected to provide the same therapeutic effect (McDonald 2015). According to the Health Canada, the drug regulatory agency of Canada, "interchangeability" commonly refers to a patient's ability to switch from one prescription medication to another that is equivalent, at the pharmacy's authority, without the prescriber's involvement.

1.4 How Are Biosimilars Different from Generic Medicines?

Pharmaceutical drugs that are meant to offer more affordable options to their respective reference products are known as biosimilars and generics. The two, however, differ greatly from one another, based on the complexity of their development, the

Table 1.1 Difference between reference biologic, biosimilar, and generic drug

Reference biologic	Biosimilar product	Generic drug
Generated in host cell lines with biological processes	Generated in host cell lines by a biological process	Produced by means of chemical synthesis
These are larger and complex molecules	These are larger and complex molecules	These are small and simple molecules
8–10 years required to market reference drug	7–8 years required to market the biosimilar product	2–3 years needed to market generic drug
Extensive clinical trials are required in case of reference drug	Biosimilar development involves at least one clinical trial	Generic drugs don't involve clinical trials
Analytical phase is less extensive in this case	Analytical phase is more extensive in biosimilar development	Analytical phase is less extensive and complex than in biosimilar
Periodic safety updates and pharmacovigilance updates are required	Periodic safety updates and pharmacovigilance updates are required	Requires brief period of time for generic drug approval
Reference biologic should provide evidence of "comparability"	Biosimilars need to show "similarity" with the reference biologic	Generics must demonstrate "bioequivalence" with reference drug

kind of medications they mimic, the time period they required to market the drug, etc. Following are some differentiative points which shows the distinctions between biosimilar and generic with the reference drug to which they mimic (Joshi et al. 2023a) (Table 1.1).

1.5 A Biosimilar Has a Biologic (Natural) Source

Biologics, derived from natural resources like humans, animals, or microorganisms, are manufactured using advanced biotechnology methods such as recombinant DNA technology and controlled gene expression. These medications have significantly benefited patients dealing with a range of conditions, including rheumatologic diseases, inflammatory bowel disease, cancers, dermatological issues, and other connective tissue disorders. They offer the potential to halt disease progression, alleviate symptoms, and improve patients' overall quality of life (Ghosh et al. 2019). However, a major drawback of biologics has been their high cost, rendering them unaffordable and inaccessible, particularly in developing nations where healthcare coverage remains limited. Nonetheless, when the innovator company's patent protection expires, it creates opportunities for other companies to produce similar versions of these drugs at lower costs, known as biosimilars. Biosimilars are highly similar to FDA-approved reference biologics, exhibiting no clinically meaningful differences in safety and effectiveness (Laekeman 2013). However, due to the complex structure of biologics, slight alterations in sequences and posttranslational modifications mean that biosimilars are not exact replicas of their reference counterparts. Despite these nuances, biosimilars offer a promising avenue for making

crucial treatments more accessible while maintaining stringent standards for safety and efficacy.

There is widespread anticipation among healthcare professionals and experts that biosimilars will exert a positive influence on drug pricing, potentially reshaping the accessibility of crucial biologic medications. The optimistic outlook stems from the belief that the adoption of biosimilars could result in a reduction in the cost of biologics, thereby enhancing patients' access to these essential and life-saving treatments. A significant study conducted in the United States sheds light on this potential, estimating that over a decade, the utilization of biosimilars has the capacity to yield savings of approximately 54 billion US dollars (Niazi 2022). This compelling data underscores the substantial potential of biosimilars to contribute to more affordable healthcare by significantly reducing the overall treatment expenses associated with biologic therapies. As such, the collective impact of widespread biosimilar adoption could pave the way for enhanced accessibility to critical medications, potentially transforming the landscape of healthcare affordability and patient care.

1.6 A Biosimilar Needs Extra FDA Approval to Be Used Interchangeably

A biosimilar is not always interchangeable with its biologic brand name after receiving its initial FDA approval. Once biosimilars receive initial FDA approval, they can be used to treat diseases; but before they can be used interchangeably with brand-name biologics, they must first receive additional FDA approval (Joshi et al. 2023b). If a biosimilar is not authorized for usage in place of its brand-name biologic, a prescription must be issued from the prescriber for the biosimilar.

The FDA is the only regulatory body that can approve biosimilars that are equivalent to their original and has a statutory definition of interchangeability. The FDA released draft interchangeability guidelines in January 2017. According to these guidelines, a biosimilar must meet two requirements in order to be considered interchangeable: it must be "biosimilar to the reference product" and "can be expected to produce the same clinical result as the reference product in any given patient" (Tóthfalusi et al. 2014). Additionally, if a biological product is administered to a patient more than once, there is no greater risk of safety or diminished efficacy from using the biological product and the reference product alternated or switched between times (Declerck et al. 2017).

All biosimilar and interchangeable biosimilar products are authorized using a streamlined process that verifies biosimilarity by comparing the product to the reference product. Manufacturers must submit supplementary information detailing the potential uses of the interchangeable biosimilar with patients in the marketplace in order for it to be approved as an interchangeable biosimilar. Similar to generic drugs, individuals who get their prescriptions filled through their pharmacies have the option of switching between brand-name biologics and interchangeable biosimilars (Kim and Bindler 2016).

Clinical trial data has demonstrated that each biosimilar that has been licensed for usage is just as safe and effective as the biologic sold under its original brand name when treating a particular illness. The biosimilar manufacturer can decide to submit data to the FDA alone for this preliminary approval. However, the company has to provide the FDA with further data from clinical trials if it wants its biosimilar to be certified interchangeable, meaning that it can be automatically used in place of its brand-name medication (Wolff-Holz et al. 2019).

An interchangeable biosimilar is not necessarily safer or more effective than other biosimilars, even if the FDA can evaluate the safety of pharmacy-level substitution with the aid of this extra information.

For example: The first interchangeable biosimilar insulin that has been approved by the US FDA is Biocon-Viatris's biosimilar Insulin Glargine (Semglee®) (Joshi et al. 2023b). According to the INSTRIDE-3 Phase-3 Switch study, done in 2017, participants who switched between reference and biosimilar insulin glargine showed comparable safety, immunogenicity, and efficacy. This suggests that those on reference insulin glargine can safely switch to the biosimilar insulin glargine (Joshi et al. 2023b).

1.7 Are Biosimilars Safe?

A biosimilar must undergo clinical trial testing and FDA approval, just like other medications, before it may be used to treat a disease to ensure that it is safe to use in people. The biosimilar and its reference drug, first-developed biologic, are compared in clinical trials (Weise et al. 2012). The Food and Drug Administration (FDA) carefully examines the clinical trial data to ensure that the biosimilar medication is equally safe and effective as the biologic brand-name medication. A biosimilar medication will satisfy the stringent safety requirements if the FDA approves it. Testing is done during the biosimilar studies to ensure that it is identical to the reference under brand name in specific aspects (Kang et al. 2023). Testing must demonstrate that both medications:

- Come from the same source.
- Possess the same dose and potency.
- Can be given to patients via same route of administration.
- Offer comparable clinical advantages when treating a clinical condition.
- Possess the same adverse effects.

1.8 Why Are Biosimilars Being Developed?

The development of biosimilars serves a critical societal role by expanding patient access to transformative biological therapies that might otherwise be financially prohibitive. These drugs represent crucial treatments for various complex diseases like cancer, autoimmune disorders, and chronic illnesses,

significantly enhancing the standard of care (Ahmad et al. 2016). Biosimilars act as a gateway, mitigating the barriers caused by the high costs associated with original biologics, ensuring that patients receive timely and affordable treatment options. Encouraging the streamlined regulation and fostering competition among multiple developers is paramount. This approach not only prevents unnecessary hindrances in drug development but also maximizes the societal benefits of biosimilars by stimulating a more competitive landscape, leading to increased availability and affordability of these life-changing therapies (Weise et al. 2012). By optimizing regulatory pathways, biosimilars can effectively offer hope and improved quality of life for a broader spectrum of patients, aligning with the fundamental principle that healthcare access should not be hindered by financial constraints.

Biosimilars hold their utmost value, and they are accessible to every patient who necessitates these therapies, ensuring that no individual is deprived of potentially life-changing treatments due to financial constraints. The fundamental purpose of biosimilars lies in providing a cost-effective alternative to expensive biologics without compromising therapeutic efficacy or safety. However, for this value to be fully realized, it is essential to foster an environment of robust competition in the marketplace based on fair and accurate comparisons. Unfounded suggestions or misconceptions about differences in efficacy or safety between biosimilars and their reference biologics can distort this competition. Therefore, ensuring a clear understanding and trust among healthcare providers, regulators, and patients regarding the high similarity and equivalent clinical performance of biosimilars to their reference products is crucial (McCamish and Woollett 2012). This approach not only supports fair pricing but also guarantees that patients have access to these vital treatments, thus optimizing the value and impact of biosimilars in improving healthcare accessibility and outcomes for all who require them.

The distinction between biosimilars and generics is crucial, primarily due to the inherent complexities in manufacturing biologics versus chemical drugs. Biologics are intricate molecules produced from living organisms, making their manufacturing process more complex, delicate, and costly compared to small molecule generics (Ridgway et al. 2013). Consequently, the development and approval of biosimilars entail more extensive studies and stringent regulatory assessments to demonstrate their similarity and equivalence to the reference biologic. This rigorous regulatory oversight, driven by the unique manufacturing challenges of biosimilars, instils confidence in their quality and safety. Despite these differences, both biosimilars and generics share a common economic objective: driving down costs and enhancing patient accessibility to essential treatments. While the manufacturing challenges and regulatory scrutiny for biosimilars are distinct, the overarching goal remains the same—to offer more affordable alternatives to expensive biologics, thereby improving access to vital therapies for patients in need. This alignment in the economic rationale underscores the importance of both biosimilars and generics in contributing to healthcare cost reduction and broader patient accessibility to essential medications.

1.9 Biosimilar Drugs: Current Status

Biosimilars a new class of drugs, intended to any off patients, offer comparative safety and efficacy. Their active protein structure enables them to respond in various immunological conditions as well as acute and chronic conditions. The main reason of biosimilar development is their early expiry of patent protection for many biopharmaceuticals (Nowicki 2007). The year 2006 marked a significant milestone in the pharmaceutical realm with the approval of Omnitrope, a biosimilar iteration of Pfizer's Genotropin. Omnitrope, developed and brought to market by Sandoz, introduced a recombinant human growth hormone called somatropin. Subsequently, further expanding options in the European Union (EU), another biosimilar somatropin named Valtropin, crafted by Bio partners, received regulatory approval.

In Europe, two biosimilar versions of recombinant human erythropoietin have gained approval, collectively marketed under five different brand names. The first, HX575, available as Binocrit (Sandoz), Epoetin alfa HEXAL (Hexal), and Abseamed (Medice Arzneimittel), is a biosimilar of the reference product Eprex (epoetin alfa) and shares the international non-proprietary name (INN) epoetin alfa. The second approved biosimilar, SB309, marketed as Retacrit (Hospira) and Silapo (STADA), is also a biosimilar of Eprex (Schellekens 2004). However, it differs by utilizing the INN epoetin zeta instead of epoetin alfa. These approvals offer multiple alternatives with different brand names for the same biosimilar erythropoietin products in the European market (Kumar and Singh 2014).

In European market, three distinct biosimilar filgrastim products obtained approval, collectively offered under six different brand names, primarily for treating neutropenia. Ratiograstim, filgrastim ratiopharm (both from Ratiopharm), and biograstim (CT Arzneimittel) stem from the same manufacturer and exhibit similarity to the reference product Neupogen.

Additionally, Tevagrastim (Teva Generics), the second among the three approved biosimilar filgrastim products in Europe, shares similarity with Neupogen. More recently, another biosimilar filgrastim variant, EP2006, received approval. EP2006 is available under two distinct brand names—Zarzio by Sandoz and Filgrastim Hexal by Hexal (Roger 2010). Like the others, EP2006 also references Neupogen as its originator product. These approvals have expanded the range of available options, offering multiple brands for biosimilar filgrastim products in Europe, each designed to closely resemble and function similarly to the original Neupogen for treating neutropenia.

In the United States, biopharmaceutical medications like insulin and growth hormone (e.g., Omnitrope) have gained approval through an expedited process. Yet, for the FDA to authorize more products, specific legislation aimed at facilitating the introduction of biosimilars will be necessary. A vast array of 100 biopharmaceuticals is presently in active clinical usage, with hundred more undergoing development (Crommelin et al. 2003). This extensive pipeline predominantly focuses on addressing criterial areas such as oncology, infectious disease, autoimmune disorders, and respiratory ailments. This robust development landscape indicated significant potential for the future emergence of biosimilar medicines (Table 1.2).

Table 1.2 Biosimilars approved in India

Product name	Active substance	Company	Launch year
Basalog	Insulin glargine	Biocon	2009
Biovac-B	Hepatitis-B vaccine	Wockhardt	2000
Cresp	Darbopoetin Alpha	Dr. Reddy's Laboratory	2010
FostiRel	Follitropin beta	Reliance life science	2010
Neukine	Filgrastim	Intas Biopharmaceuticals	2004
Wepox	Epoetin alpha	Wockhardt	2001
Wosulin	Human insulin	Wockhardt	2003

Of particular interest is the regulatory stance concerning biosimilars, especially those pivotal in saving lives, notably in oncology. There exists a keen interest in understanding whether the guidelines governing the development and approval processes for these life-saving biosimilars are notably more rigorous compared to the standards applied to current biosimilars utilized in supportive-care settings (Duerden 2007). The evaluation and potential differences in regulatory stringency can significantly impact the development, approval, and accessibility of biosimilars crucial for treating life-threatening conditions, warranting a careful examination of regulatory approaches in these specific contexts.

1.10 Pharmacovigilance and Biosimilars

Pharmacovigilance is defined by the World Health Organization (WHO) as the science and practices associated with the identification, assessment, understanding, and prevention of adverse drug reactions (ADRs) or any other drug-related issues (text IPCJBtc 2018). Any suspected reaction, suspected drug–drug or drug–food interaction, adverse drug reactions linked to drug withdrawal, medication errors or overdose, and lack of efficacy must be reported to regulatory bodies in accordance with acceptable pharmacovigilance practices. Pharmacovigilance also requires the aggregate reports including periodic safety update reports (PSURs) and risk management plans (RMPs). The PSUR is an essential instrument for identifying arising safety signals, evaluating changes in the benefit–risk profile, communicating risks to regulatory bodies, and identifying when risk management actions are required. It also serves as a tracking mechanism to evaluate how well these initiatives are working. The RMP records the risk management system deemed required to identify, characterize, and reduce a medicinal product's significant risks over the course of the product's life cycle, ensuring benefit–risk balance (Oza et al. 2019). Global regulatory bodies, such the US Food and Drug Administration and the European Medicines Agency, have established well-organized pharmacovigilance systems. In January 2018, Indian pharmacovigilance guidelines for marketing authorization holders (MAHs) was released by Indian Pharmacopoeia Commission (IPC) and Pharmacovigilance Programme of India (PvPI) (text IPCJBtc 2018; U.S. Department of Health and Human Services et al. 2005).

For any medicine that has been approved, systematic and continuous safety monitoring is required to identify and assess post-approval safety signals. These signals could be the result of inherent variations in immunogenicity among products or the identification of rare events that might be especially linked to a specific product (Seidl et al. 2012). In order to analyze and characterize a product's risk profile and to make well-informed decisions on risk minimization, the FDA guidelines on appropriate pharmacovigilance state that post-marketing safety data collecting and risk assessment based on observational data are essential (Casadevall et al. 2013).

Since biosimilar medications are manufactured by different companies than reference products and are not reference medicines in the conventional sense, pharmacovigilance is more crucial for them. A biosimilar medication may not show many side effects until it is taken more widely, for longer periods of time, and in a larger number of patients. Prescribers and manufacturers both need to be aware of the need for post-marketing surveillance and careful when managing patients who are using biosimilars (Kumar and Singh 2014).

1.11 Applications of Biosimilars

Biosimilars have gained prominence due to their potential to offer more affordable alternative to expensive drugs while providing efficacy and safety to the patient. Biosimilars also play an important role in various disease conditions such as in autoimmune disorders like Rheumatoid arthritis, Psoriasis, and Crohn's disease (Kaida-Yip et al. 2018). These drugs target the tumor necrosis factor-alpha (TNF-alpha) such as in adalimumab, infliximab provide cost-effective alternative to expensive biologics (Fig. 1.3).

Biosimilars in oncology also offers a potential therapeutic role in disease condition. Biosimilar version of drugs such as trastuzumab, bevacizumab, and rituximab have been developed that offer similar safety and efficacy at potentially reduced costs (Ecker et al. 2015). In disease like diabetics, bone disorders, and kidney

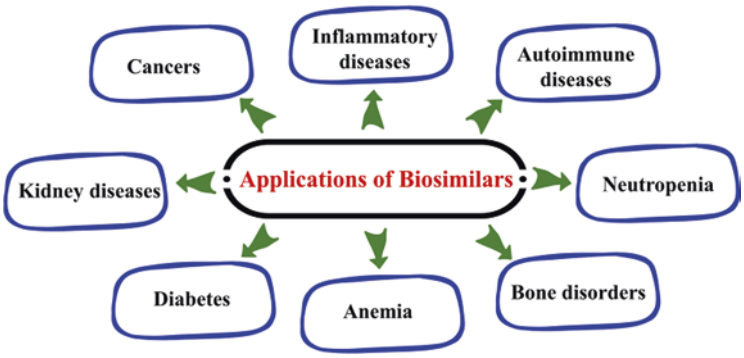

Fig. 1.3 Various Applications of Biosimilars. Various applications in different diseased conditions where biosimilars have been used efficiently

diseases, they offer similar version of therapeutics, aiming to provide affordable options for the patient requiring insulin therapy and erythropoietin stimulating agents are effective versions of biosimilars used as alternative therapy in chronic kidney diseases (Schellekens and Ryff 2002). Although still several emerging biosimilars for multiple sclerosis and certain rare disorders are being researched to expand the lifespan of the patients, they are also used in treating various hematological conditions, such as Filgrastim which is used to boost white blood cell count and epoetin, used to stimulate red blood cell production, these have been developed to potentially increase the accessibility of therapeutic approach to the patients with conditions like anemia and neutropenia (Rathore 2011).

Overall, in each of this diseased area, biosimilars hold a promise of cost-effective and safety profile of the patient. However, it is crucial to note that adaptation and acceptance of various biosimilars in different fields are important in understanding the effects of the bio-phytochemicals in diseased conditions.

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Immunobiology of Cancer

2

Nitin Verma, Komal Thapa, Neha Kanojia, and Prarit Chandel

Abstract

One of the results of three decades of very fast research into the mechanisms of cancer pathogenesis has been the advent of mechanism-based targeted medicines for the treatment of human tumours. The complex and dynamic interaction between cancerous cells and the immune system is reflected in the immunobiology of cancer. Over the past 15 years, there has been a renewed focus on cancer immunosurveillance, which has expanded to include cancer immunoediting. The latter contends that the immune system both shapes tumour immunogenicity and shields the host from the emergence of primary nonviral malignancies. It is backed by compelling correlative data from research on human cancer as well as robust experimental data from mice tumour models. Three stages make up the process of cancer immunoediting: equilibrium, escape, and elimination (also known as cancer immunosurveillance). We provide a summary of the evidence for each of the three cancer immunoediting steps below. The main ideas of immunobiology in cancer are briefly reviewed in this chapter, along with the most recent developments in using the immune system to treat cancer. We also explore the function of inflammation and its dual effects on tumour growth: acute inflammation may aid in immune responses against cancer, but chronic inflammation may promote carcinogenesis.

Keywords

Cytokines · Cytotoxicity · Immunobiology · Inflammation · Vaccines

N. Verma (✉) · K. Thapa · N. Kanojia · P. Chandel
Chitkara University, School of Pharmacy, Barotiwala, Himachal Pradesh, India
e-mail: nitin.verma@chitkarauniversity.edu.in

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2.1 Introduction

Coley showed that using bacterial products might cause some tumours that were inoperable to recede. For many years, it has been understood that the immune system is crucial to the development of cancer, chronic inflammation, and inflammation (Oiseth and Aziz 2017). As a result, scientists kept trying to connect those processes in order to comprehend the significance of Virchow's discoveries. The initial immune-related treatments were nonspecific immunotherapies that did not target a particular cancer cell culture and instead attempted to stimulate the immune system. Understanding the nature of this connection could throw light on the mechanisms of carcinogenesis, tumour growth, and metastatic dissemination. It may also present chances to devise treatment plans that improve prognosis, diagnosis, and the overall cancer treatment experience (Decker and Safdar 2009; Decker et al. 2017). The goal of further research was to pinpoint the antigens on cancer cells and create monoclonal antibodies (MABs) that specifically target those antigens (Gross 1943). This has led to a new direction in research: identifying the pathways and signalling molecules involved in immune suppression processes, which may be targets for anticancer treatments.

2.2 The Hallmarks of Cancer

The acquired abilities to maintain proliferative signalling, elude growth suppressors, fend off cell death, permit replicative immortality, induce/access vasculature, trigger invasion and metastasis, reprogram cellular metabolism, and elude immune destruction are currently included in the eight hallmarks (Smith Jr. and Stehlin Jr. 1965). Eleven years later, it is clear that deregulating cellular metabolism and preventing immune destruction, like the original six, can be regarded as core hallmarks of cancer. These two concepts were separated as "emerging hallmarks" in the most recent iteration of this notion. While a series of oncogenic events characterize the progression of cancer, the characteristics listed below only apply to aggressive cancer that has reached its full potential and not to its precursors. The fact that several noncancerous cell types can be found within malignancies and may contribute to the cancerous phenotype suggests that not all malignant cells share the characteristics of the disease. Another concern is whether they apply to all cancer cells. In fact, the idea of a cancer stem cell (CSC) is in direct opposition to the idea of a "cancer cell" (Chow et al. 2012; Halliday et al. 1995). The latter idea, which postulates a qualitative, deterministic, and irreversible change from CSC-tumour propagating cell (TPC) to derived cells, has come under scrutiny and is now refuted in the context of human colon carcinoma and a mammary cancer cell line. Without getting into this discussion, it follows logically that only a small percentage of cancerous cells will exhibit all the characteristics required to cause the cancer, given that the majority of cancerous cells are derived cells (Fife and Bluestone 2008; Brunet et al. 1987). This would particularly apply to the immortality attribute. All of the hallmarks cannot be attributed to all cancer cells, even if the ill-defined and contentious concept of a