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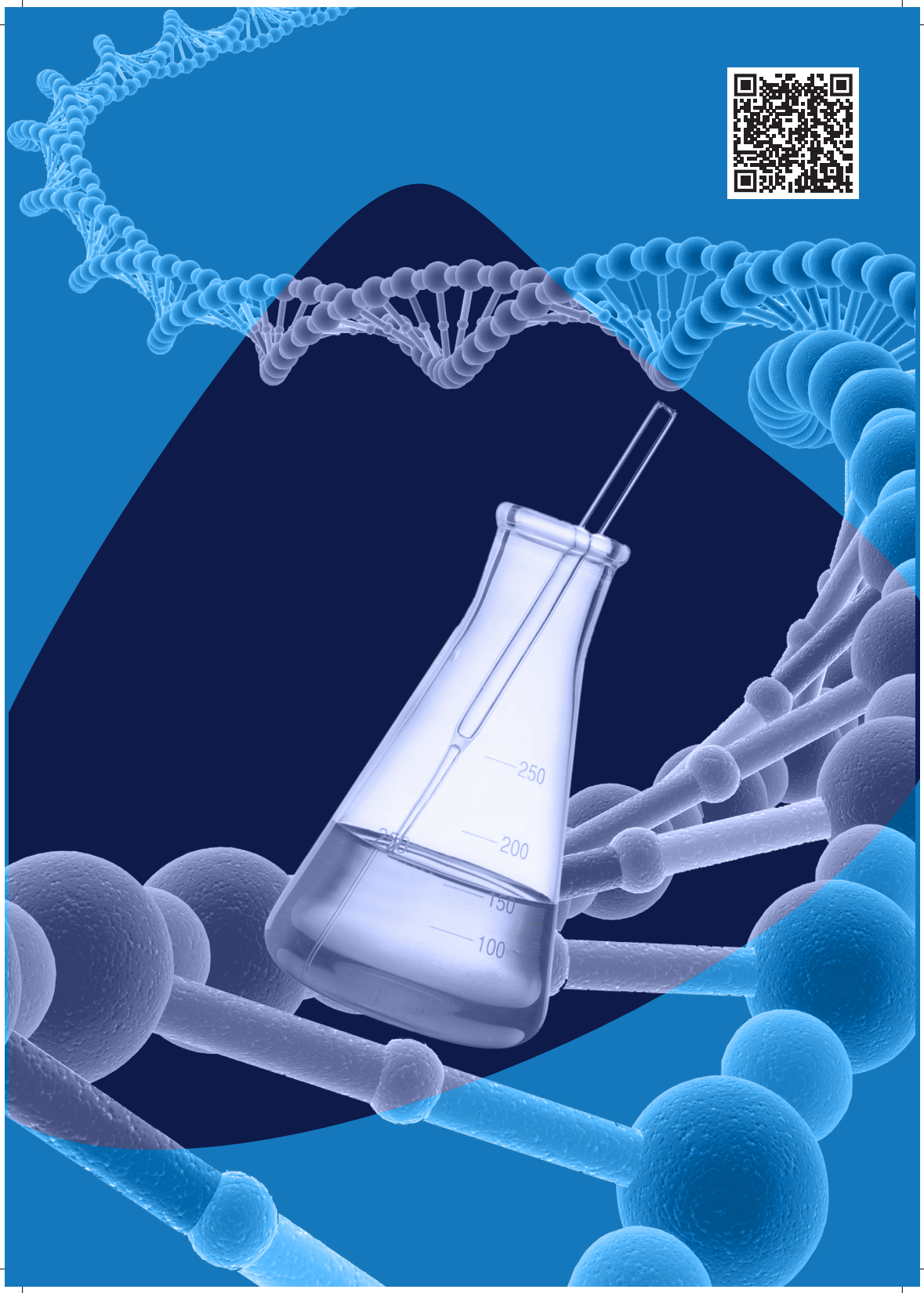
Turkish Biopharmaceuticals and Vaccines Platform

THE RISE OF BIOSIMILAR MEDICINES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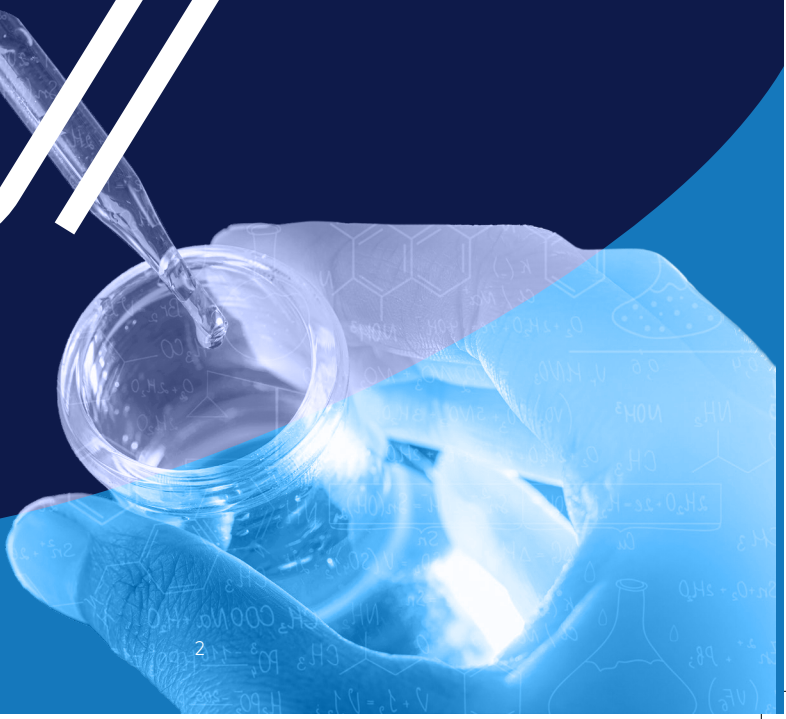
DEFINITION



Definitions

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BIOLOGICAL MEDICINAL PRODUCT

A medicinal product for human use whose active substance or substances are manufactured or purified from a biological source and whose quality, manufacturing process and controls are demonstrated by physicochemical and biological tests.[1]

BIOSIMILAR MEDICINAL PRODUCT (Biosimilar Medicine)

A medicinal product for human use that is highly similar to another already approved biological reference medicinal product.[1]

REFERENCE MEDICINAL PRODUCT (Reference Biotechnological Medicine)

A biological medicinal product that has been proven to have scientifically acceptable efficacy, quality and safety by the Agency (Turkish Medicines and Medical Devices Agency – TİTCK), and competent authorities that are founding or permanent members of the International Council for Harmonization (ICH), and has been licensed with a full dossier to be placed on the market for the first time in the world.[1]

RECOMBINANT DNA TECHNOLOGY

Recombinant DNA technology involves using enzymes and various laboratory techniques to manipulate and isolate DNA segments of interest. This method can be used to combine DNA from different species or to create genes with new functions. The resulting copies are often referred to as recombinant DNA.[2]

MONOCLONAL ANTIBODIES (MAB)

Immunoglobulins (Ig) with a defined specificity derived from a monoclonal cell line. Their biological activity is characterized by a specific binding characteristic to a ligand (commonly known as an antigen).[3]

EKSTRAPOLASYON / EXTRAPOLATION

Extrapolation is a scientific rationale that bridges all the data collected (ie, totality of the evidence) from one indication for the biosimilar product to all the indications originally approved for the originator.[4]

Definitions

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INTERCHANGEABILITY

The process of replacing a medicine with another medicine during an ongoing treatment. It is implemented in two ways: Switching or Auto Substitution.

- **Switching**
  Exchanging one medicine for another due to medical (lack of efficacy, side effects, etc.) or non-medical reasons (reimbursement, cost, etc.) at the treating physician's discretion

  There are two types of switch: Single switch or multiple switch.

  - **Single Switch**
    Practice of switching from one medicine to another during treatment (e.g. from a reference biotechnological medicine to a biosimilar medicine or vice versa)

  - **Multiple Switch**
    Practice of switching from one medicine to another during treatment and then back to the original medicine or to a third medicine (e.g. from a reference biotechnological medicine to a biosimilar medicine and then either back to the reference biotechnological medicine or to another biosimilar medicine)

- **Auto Substitution**
  Practice of replacing one product for another at the pharmacy-level without notifying or seeking the approval of the prescriber[4]

IMMUNOGENICITY

Immunogenicity is defined as the ability of cells/tissues to provoke an immune response and is caused by biomaterial that is perceived as a foreign object by the body's immune system. This reaction can lead to the production of neutralizing or non-neutralizing anti-drug antibodies (ADA's), which can neutralize the therapeutic effects of treatment and potentially cause adverse effects.[5]

HISTORY

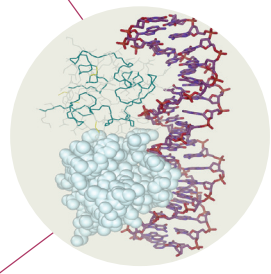
MILESTONES IN BIOTECHNOLOGY

CONVENTIONAL PERIOD
1919–1940

GREGOR MENDEL
Austrian biologist. Based on his studies of how traits are inherited across generations, he introduced the concept of the gene for the first time. **1865**

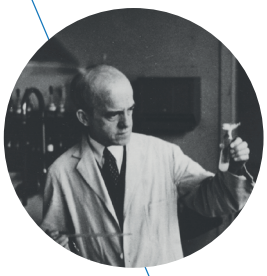
KARL EREKY
Hungarian agricultural engineer. The godfather of biotechnology. **1919**

ALEXANDER FLEMING
Scottish physician. Discoverer of penicillin. **1928**



The start of studies on **proteins** and **DNA,** the emergence of the term 'Molecular Biology'. **1938**

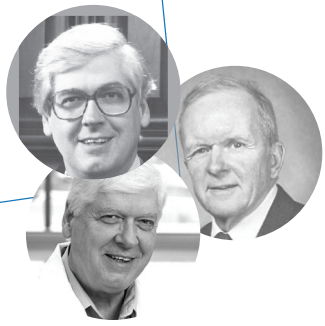
INTERIM PERIOD
1940–1975



OSWALD AVERY
American bacteriologist. Ascertained that DNA is the substance responsible for heredity. **1944**

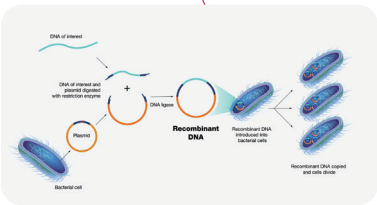
JAMES WATSON AND FRANCIS CRICK
The discovery of the double helix structure of DNA has been a milestone in the history of science. **1953**

MARSHALL NIRENBERG AND HEINRICH J. MATTHAEI
First codon decoded at the US National Institute of Health. **1961**



HAMILTON O. SMITH, THOMAS J. KELLY AND KENT W. WILCOX
Isolated and characterized the first type II restriction enzyme from *H. influenzae*. **1970**

MODERN PERIOD
1975 - TODAY



RECOMBINANT DNA TECHNOLOGY

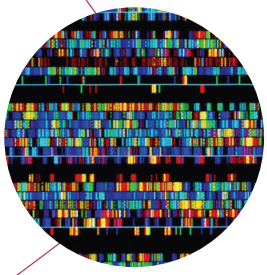
It was used for the synthesis of human growth hormone for the first time and DNA sequencing technologies were introduced. **1977**

DAVID GOEDDEL

The first recombinant DNA human insulin was prepared from insulin A and B chains expressed in Escherichia coli. **1978** Genentech and Lilly then introduced Humulin® R and N to the market. **1982**

ORTHOCLONE OKT3 (MUROMONAB-CD3)

The first MAB to be authorized. Used to prevent rejection in kidney transplant. **1986**



HUMAN GENOM MAP

Other developments gained speed with an article published in Science and Nature. **2001**

FIRSTS IN BIOSIMILAR MEDICINES

In the EU, the EMA published its first biosimilar medicines guidelines. **October 2005**

RECOMBINANT HUMAN GROWTH HORMONE - RHGH

The first biosimilar medicine authorized by the EMA in the EU. **2006**

Republic of Türkiye, Ministry of Health, Turkish Medicines and Medical Devices Agency published the Guidelines on Biosimilar Medicinal Products. **August 2008**

FILGRASTIM

The first biosimilar medicine authorized by TITCK in Türkiye. **August 2009**

ENOXAPARIN SODIUM

The first biosimilar medicine developed via the acquisition of biological material and manufactured in Türkiye. **2012**

FIRSTS IN BIOSIMILAR MEDICINES

INFLIXIMAB
The first biosimilar MAB authorized by the EMA in the EU. **2013**

INFLIXIMAB
The first biosimilar MAB authorized by TITCK in Türkiye. **2014**

The Food and Drug Administration

FILGRASTIM
The first biosimilar medicine authorized by the FDA in the US. **2015**

INFLIXIMAB
The first biosimilar MAB authorized by the FDA in the US. **2016**

FILGRASTIM
The first biosimilar medicine developed from the cell line and marketed in . **2016**

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BIOTECHNOLOGICAL MEDICINES

Changes in the global pharmaceutical market that happened over the last decade caused the market trends to shift from chemicals to biological molecules. Among the so-called **"Blockbuster"** molecules with high sales turnover all over the world, the number of chemical drugs is decreasing.

The shift towards biological/biotechnological medicines is opening new horizons in the treatment of refractory diseases (autoimmune diseases, cancers, hematological diseases, rare diseases, etc.).

Cancer,autoimmune diseases and diabetes therapies, where biotechnology is most focused, account for more than 60% of the biologics market.

Top 20 best-selling medicines in the world as of the end of 2021[6]

	Active Substance/ Medicine	Pharmaceutical class	Indication(s)
1	Comirnaty COVID-19 MRNA vaccine	**Biotechnological**	Minimizing COVID-19 infection risk
2	Adalimumab	**Biotechnological**	RA, AS, UC (*), Crohn's disease, Psoriasis
3	Spikevax COVID-19 vaccine	**Biotechnological**	Minimizing COVID-19 infection risk
4	Pembrolizumab	**Biotechnological**	Malign melanoma, various cancers
5	Apixaban	Chemical	Anticoagulant
6	Lenalidomide	Chemical	Multiple myeloma
7	Ibrutinib	Chemical	Lymphocytic leukemia, Lymphoma
8	Aflibercept	**Biotechnological**	Macular degeneration, Diabetic retinopathy
9	Ustekinumab	**Biotechnological**	UC, Crohn's disease, Plaque psoriasis,Psoriatic arthritis
10	Bictegravir, emtricitabine and tenofovir alafenamide	Chemical	HIV therapy
11	Rivaroxaban	**Biotechnological**	Deep vein thrombosis, Pulmonary embolism
12	Nivolumab	**Biotechnological**	Melanoma, various cancers
13	Dulaglutide	Chemical	Type 2 diabetes
14	Dupilumab	**Biotechnological**	Atopic dermatitis, Asthma, Chronic rhinosinusitis with nasal polyps
15	Daratumumab	**Biotechnological**	Multiple myeloma
16	Kasirivimab/imdevimab (REGEN-COV)	**Biotechnological**	Minimizing COVID-19 infection risk
17	Ivacaftor/tezacaftor/ elexacaftor	Chemical	Cystic fibrosis
18	Human papillomavirus 9-valent vaccine	**Biotechnological**	HPV-induced cancers
19	Remdesivir	Chemical	COVID-19 treatment requiring hospitalization
20	Palbociclib	Chemical	HR positive and HER2 negative breast cancer

*RA: Rheumatoid Arthritis, AS: Ankylosing Spondylitis, UC: Ulcerative Colitis
In 2021, 12 of the Top 20 best-selling drugs in the world had been biotechnological, while 8 were chemical.

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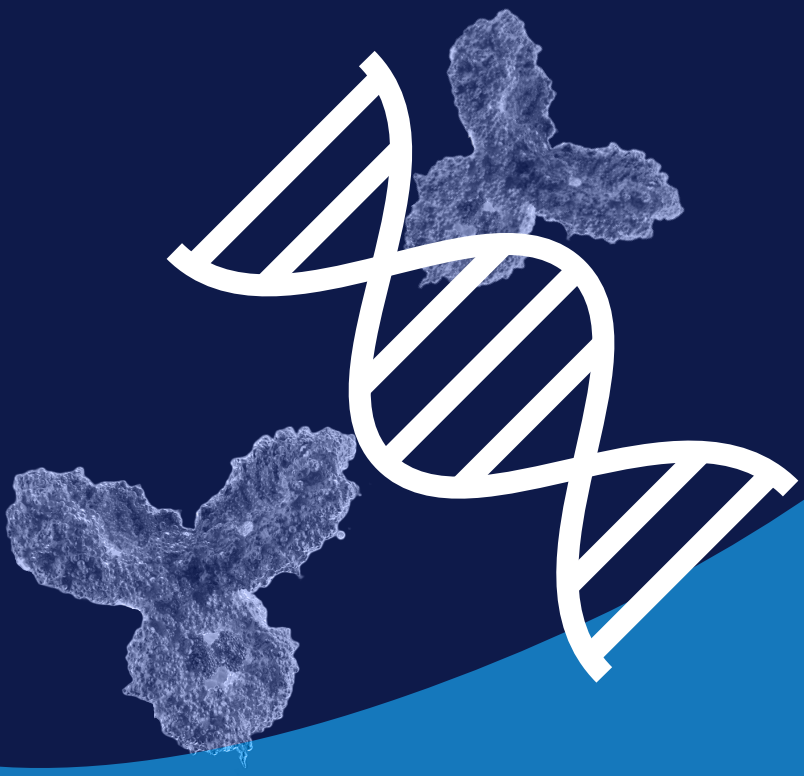


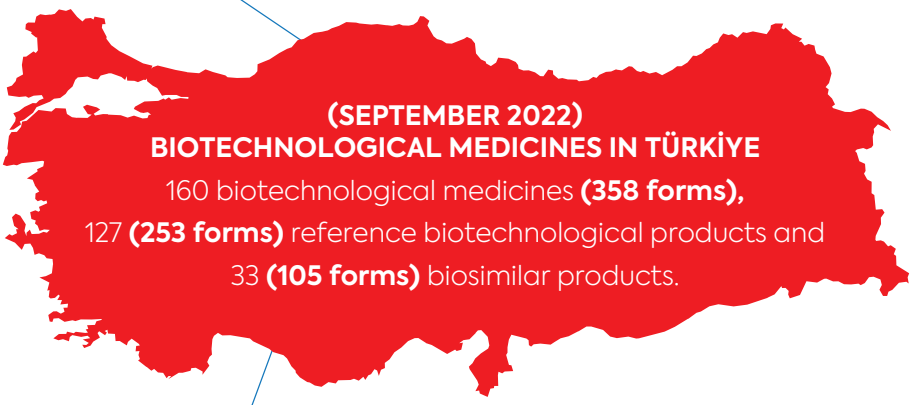
Looking at the major markets around the world, the first biosimilar medicine, **(SOMATROPIN),** was authorized in the European Union (EU) in 2006. In the US, the first biosimilar medicine was authorized by the FDA in 2015, nine years after the EU. After 16 years of treatment experience in the EU, the patient population treated with biosimilars will exceed 2 billion patients/day by the end of 2020.[7]

The situation in Türkiye can be outlined as follows. Currently, 160 biotechnological medicines (358 forms) licensed as reference biotechnological and biosimilar medicines in the **Turkish Pharmaceuticals Market.** Of these products, 127 (253 forms) are reference biotechnological products while 33 (105 forms) are biosimilar products.

The Turkish pharmaceuticals industry is manufacturing biotechnological pharmaceuticals at different stages such as cell line development, cell line acquisition, biological material and filling etc., and commercializing approximately 32 forms of pharmaceuticals under 8 brands. These products, which are carrying our industry to the next technological level, are manufactured in 6 production sites. As a result of the efforts realized with the investment incentive support of USD 1.1 billion provided to the sector to date, the pharmaceutical industry has increased the share of domestically manufactured pharmaceuticals in biotechnological medicines from 8% to **33%** in terms of units and from 1% to **9%** in terms of value in the last 7 years. The pharmaceutical sector, which continues around-the-clock investments in biotechnology with its own resources, is expected to increase its share in manufacturing to much higher levels with the new facilities that are about to start operations and those that are planned.

8 of biosimilar medicines are domestically manufactured while 25 are imported.[8]

The Rise of Biosimilar Medicines



Biosimilar medicines authorized in Türkiye

MANUFACTURED	8
Filling	**5**
ENOXAPARIN SODIUM	2
EPOETIN ALFA	1
INFLIXIMAB	1
TRASTUZUMAB	1
Biological Material	**1**
ENOXAPARIN SODIUM	1
Industrial Cell Line Development	**1**
FILGRASTIM	1
Industrial Cell Line Acquisition	**1**
INSULIN GLARGINE	1

IMPORTED	25
ABCIXIMAB	1
ADALIMUMAB	1
BEVACIZUMAB	3
EPOETIN ALFA	3
EPOETIN ZETA	1
ETANERCEPT	1
FILGRASTIM	5
INFLIXIMAB	1
INSULIN GLARGINE	1
RECOMBINANT FACTOR VII A	1
RITUXIMAB	3
SOMATROPIN	2
TRASTUZUMAB	2

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BIOSIMILAR MEDICINE DEVELOPMENT AND REGISTRATION

Biosimilar Medicine Development and Registration

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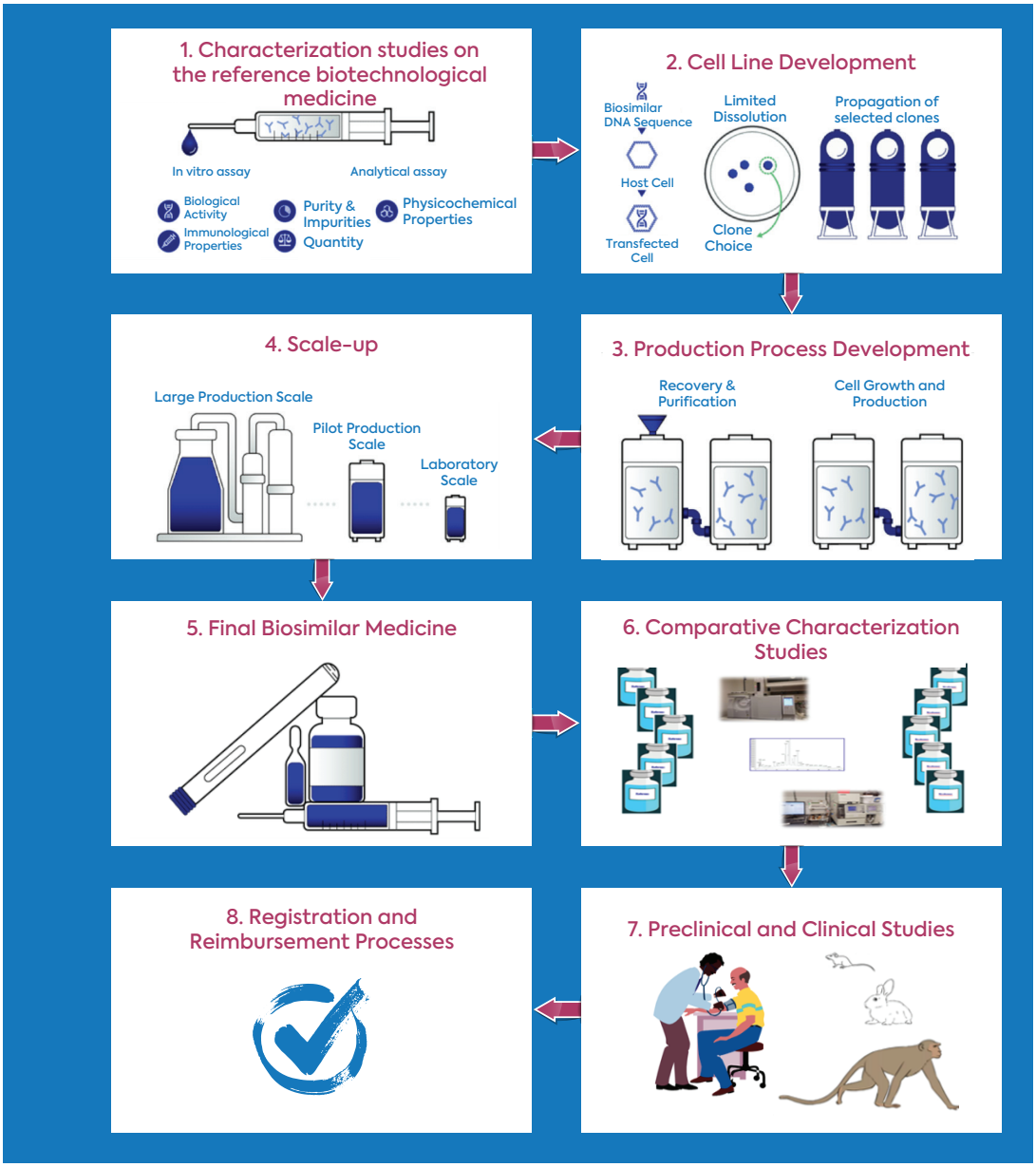
The development of biosimilar medicines is quite challenging and carries numerous risks. First and foremost, this multidisciplinary development process, that is carried out by a large group of people from different professions, entails comprehensive knowledge and experience as well as painstaking work.

The first step of the development process starts with the study, analysis and characterization of different batches of the reference biotechnological medicine. It then incorporates a very specific manufacturing process that involves many steps, from cell line establishment for the biosimilar medicine, cell growth, purification, formulation, stability to filling and labeling of the final product. The diagram on the next page outlines these production steps.[9]

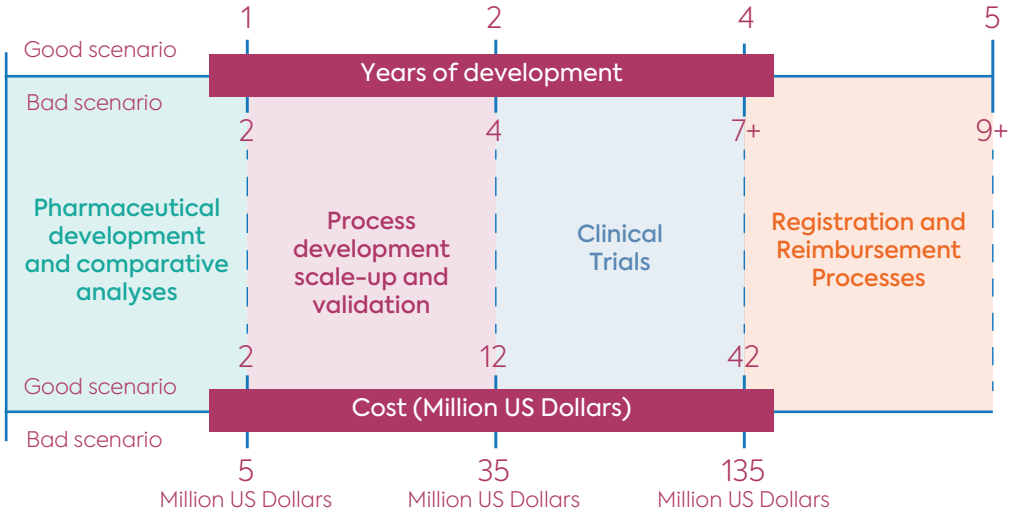
Biosimilar Medicine Development and Registration



Note: Adapted from Journal of Crohn's and Colitis, 2019, 259–266 with some additions. (See Reference 9)

The development of biosimilar medicines is fraught with challenges, both in terms of time and cost. This development can take up to 5 years under optimal conditions and even exceed 9 years under more challenging conditions. It costs about **42-135 million US dollars.**

Time and costs in biosimilar medicine development



Reference: Sanford C. Bernstein & Co., LLC, Research Division. New York

The regulatory approval and marketing authorization process of biosimilar medicinal products are carried out on a case-by-case basis and by the relevant health authority after evaluating the totality of evidence from the entire development program. This authority is TITCK (Turkish Medicines and Medical Devices Agency) in Türkiye while it is the EMA (European Medicines Agency) in the European Union, the FDA (Food and Drug Administration) in the United States, the TGA (Therapeutic Goods Administration) in Australia, and the MFDS in Korea (The Ministry of Food and Drug Safety).

This body of evidence features comprehensive comparative analytical, functional, non-clinical and clinical PK/PD, efficacy, safety and immunogenicity studies used by regulators when assessing whether a medicine can be considered a biosimilar.

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EXTRAPOLATION

Extrapolation is a scientific rationale that bridges the totality of the evidence from one indication for the biosimilar medicine to the approved indications of the reference product. In other words, it refers to the approval of a biosimilar medicine for a use that has not been directly investigated in a comparative clinical study of an approved indication of the reference biotechnological medicine.[4]
Although extrapolation practices vary from country to country and from authority to authority throughout the world, the generally accepted common opinion is that extrapolation is appropriate for products with multiple indications if the efficacy of the drug arises through the same mechanism of action, similar receptors and similar pathways.
For example, the EMA in the EU, the FDA in the United States and the MFDS in S. Korea have approved the biosimilar infliximab in all indications of the reference biotechnological medicine, despite having comparative clinical studies conducted on the reference biotechnological medicine only for the indications of Rheumatoid Arthritis and Ankylosing Spondylitis during development. In summary, the indications of Psoriasis, Crohn's disease and Ulcerative Colitis were extrapolated and approved.

Indications of Infliximab	Indications of Etanercept
Rheumatoid Arthritis	Rheumatoid Arthritis
Ankylosing Spondylitis	Ankylosing Spondylitis
Psoriatic Arthritis	Juvenile Idiopathic Arthritis
Psoriasis	Psoriatic Arthritis
Crohn's Disease	Plaque Psoriasis
Ulcerative Colitis	

In the ensuing years, the EMA approved a second infliximab biosimilar medicine, which had a comparative clinical study conducted only on the indication of ankylosing spondylitis during its clinical development program, for all indications of the reference biotechnological medicine.

Yet another example is etanercept. The biosimilar medicine, featuring only a rheumatoid arthritis study in its clinical development program, was approved by the EMA in all indications of the reference biotechnological medicine.

Although extrapolation reduces or eliminates the need for repeated clinical studies on the biosimilar medicine, it must be scientifically validated with appropriate data.

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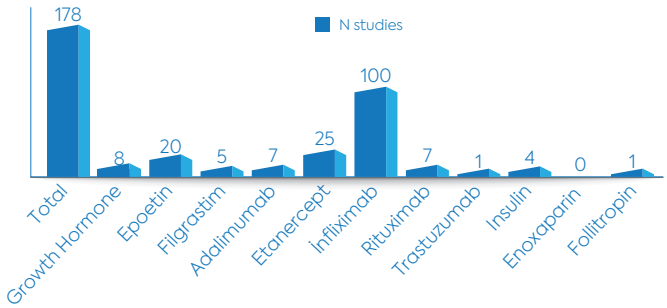
INTERCHANGEABILITY

Switching / Switching or Substitution

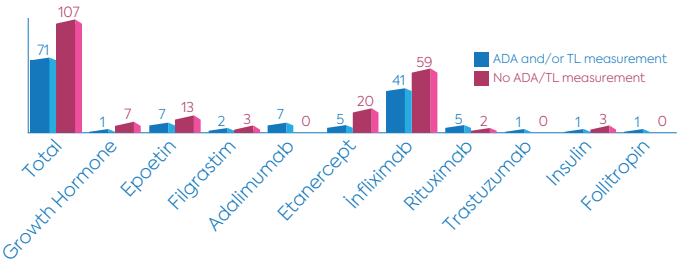
In Europe and Australia, interchangeability generally refers to the practice of exchanging one medicinal product for another generic/biosimilar medicinal product for the same therapeutic purpose in a given patient at the treating physician's discretion and is termed as switching. In the United States, the term "interchangeable biosimilar medicine" refers to a regulatory standard that, subject to state regulations, allows a pharmacist to substitute a reference medicine with an interchangeable biosimilar medicine without consulting the prescribing physician.10 In summary, the main heading of interchangeability features the subheadings of switching and substitution. Systematic switching refers to an exchange carried out at the prescriber's clinical discretion whereas substitution refers to an exchange carried out by the pharmacist without the prescriber's approval.

The results of 178 switching studies in over 20,000 patients were published in a review article by Barbier et al. None of these studies of switching between originator and biosimilar medicines showed a decrease in efficacy or an increase in side effects.



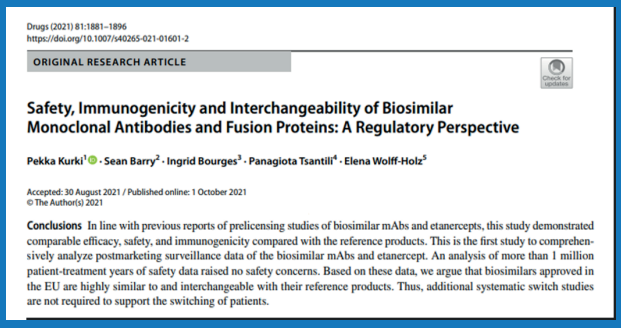
Note: Adapted from Clin Pharmacol Ther. 2020 Oct; 108(4): 734-755 (See Reference 11)

Number of studies on ADA (Anti Drug Antibodies) or TL (Through Level) measurements



Note: Adapted from Clin Pharmacol Ther. 2020 Oct; 108(4): 734-755 (See Reference 11)

Pekka Kurki et al. conducted a comprehensive study of post-marketing data on biosimilar MABs and etanercept authorized in the EU and found that all these biosimilars were fully compatible with pre-authorization data.



Drugs (2021) 81:1881–1896
https://doi.org/10.1007/s40265-021-01601-2

ORIGINAL RESEARCH ARTICLE

Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective

Pekka Kurki[1] · Sean Barry[2] · Ingrid Bourges[3] · Panagiota Tsantili[4] · Elena Wolff-Holz[5]

Accepted: 30 August 2021 / Published online: 1 October 2021
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Conclusions In line with previous reports of prelicensing studies of biosimilar mAbs and etanercepts, this study demonstrated comparable efficacy, safety, and immunogenicity compared with the reference products. This is the first study to comprehensively analyze postmarketing surveillance data of the biosimilar mAbs and etanercept. An analysis of more than 1 million patient-treatment years of safety data raised no safety concerns. Based on these data, we argue that biosimilars approved in the EU are highly similar to and interchangeable with their reference products. Thus, additional systematic switch studies are not required to support the switching of patients.

In line with previous reports on pre-authorization studies of biosimilar MABs and etanercept, this study demonstrated that efficacy, safety and immunogenicity are fully comparable when compared to reference biotechnological medicines.

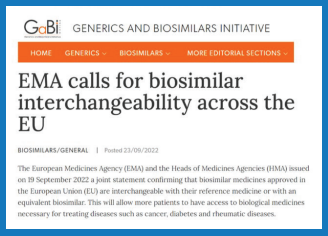
This is the first study to comprehensively analyze the post-marketing surveillance data for biosimilar MABs and etanercept. Analysis of more than 1 million patient-treatment-years of safety data revealed no safety concerns. Based on these data, the authors emphasized that biosimilar medicines authorized in the EU are highly similar and interchangeable with reference biotechnological medicines and that additional systematic switching studies are not required to support the switching of patients.[12]

In the wake of all these studies, evidence and many years of experience, the EMA announced a very important decision in September 2022. According to this decision, all biosimilar medicines authorized in the EU are interchangeable with their reference biotechnological medicines and also with another biosimilar medicines of the same reference product.[13,14]

EUROPEAN MEDICINES AGENCY

Biosimilars approved in the EU are interchangeable

EMA and the Heads of Medicines Agencies stated that a biosimilar medicine can be used instead of its reference product or an equivalent biosimilar



GaBi GENERICS AND BIOSIMILARS INITIATIVE

HOME GENERICS BIOSIMILARS MORE EDITORIAL SECTIONS

EMA calls for biosimilar interchangeability across the EU

BIOSIMILARS/GENERAL | Posted 23/09/2022

The European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) issued on 19 September 2022 a joint statement confirming that biosimilar medicines approved in the European Union (EU) are interchangeable with their reference medicine or with an equivalent biosimilar. This will allow more patients to have access to biological medicines necessary for treating diseases such as cancer, diabetes and rheumatic diseases.

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COUNTRY PRACTICES

COUNTRY PRACTICES

USA

As of August 2022, three of the biosimilar medicines licensed in the US (insulin glargine, adalimumab and ranibizumab) have been approved as "interchangeable" by the FDA.[15-16] Seven more medicines are expected to receive this approval in the near future.[15] In the US, the term "interchangeable biosimilar medicine" means that the medicine can be substituted by pharmacists without requiring the prescriber's approval. The relevant policies are created by the individual states. In the US, 46 of 50 states currently allow pharmacists to automatically substitute biosimilars that are approved as interchangeable by the FDA.[17]

AUSTRALIA

The Australian Government has adopted a pro-substitution approach to biosimilar medicines, denoted by an **'a'** superscript (a-flagged) in the Pharmaceutical Benefits Schedule (PBS). However, the prescribing physician can prevent brand substitution at the pharmacy level by checking the box "brand substitution is not allowed" on the prescription form. Medicines deemed substitutable at the pharmacy level by Australia's Pharmaceutical Benefits Advisory Committee (PBAC) contain a flag known as **'a-flagged'** in the official PBS. To date, 8 of the biosimilar medicines approved in Australia have been flagged as **"a-flagged"**.[18]

COUNTRY PRACTICES

CANADA

Canada, has initiated and maintains the **"Biosimilar Switching Policy"** in provinces such as British Columbia, Alberta, Quebec, Ontario, Northwest Territories, New Brunswick, Nova Scotia and Saskatchewan. According to these practices, which were first launched in the province of British Columbia in November 2019, switching to therapy with biosimilar medicines by pre-specified dates is mandatory for patients who have initiated treatment with a reference biotechnological drug, except in some special cases (such as pregnancy).[19]

ITALY

Supporting a greater uptake of biosimilar medicines, Italy introduced a new practice to be applicable in regional tenders with a Senate decision in early 2017. Accordingly, in the event that the patent of a reference biotechnological medicine, which has already been tendered and decided to be procured for 2-3 years, expires during the tender period and one or more biosimilar medicines are introduced to the market meanwhile, a new tender will be announced within 60 days, regardless of the remaining tender period, in order to ensure that biosimilar medicines can be incorporated in the tender as soon as possible. This practice encourages the use of biosimilar medicines in hospitals.[20]

HOLLAND

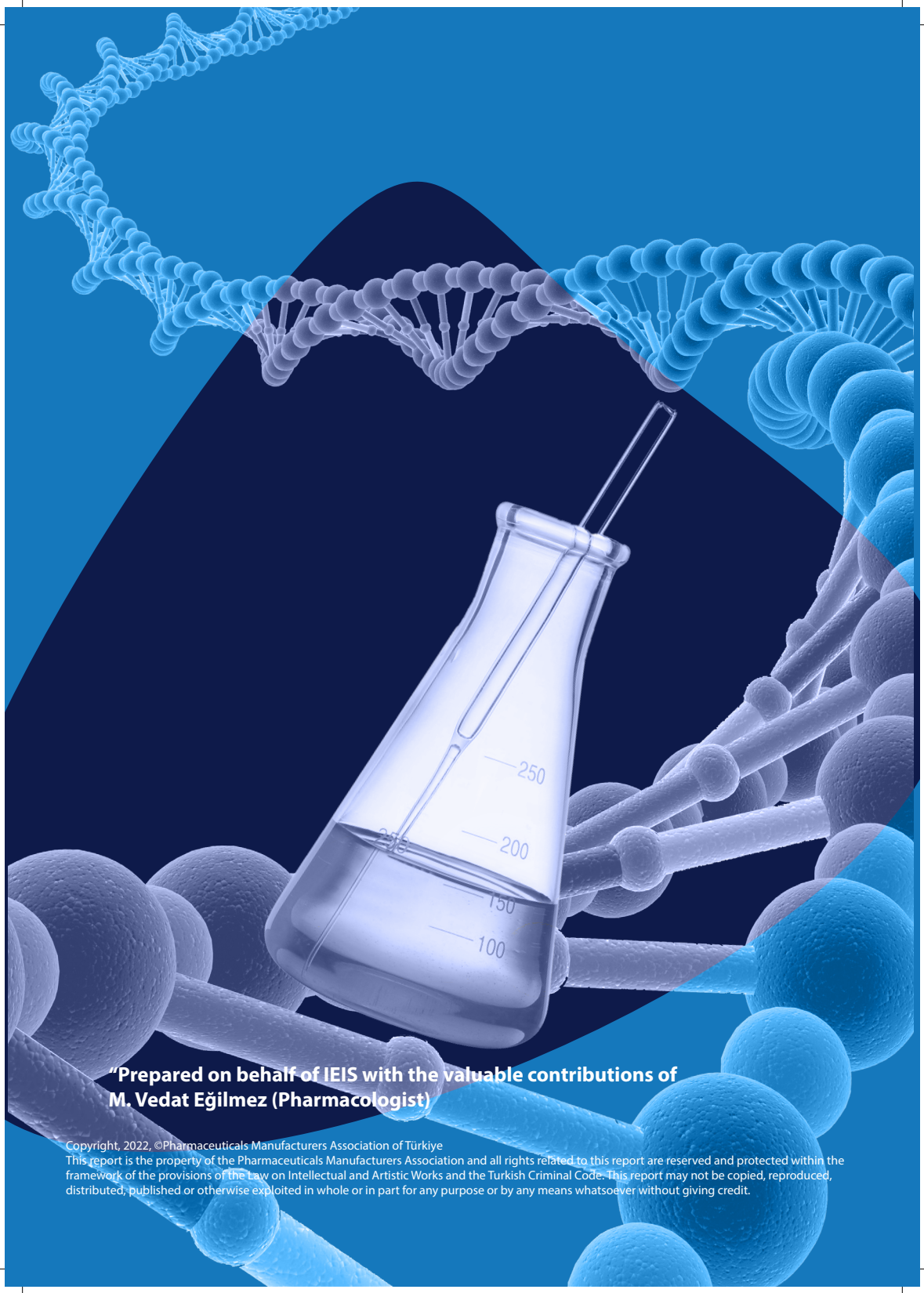
In 2015, the Dutch Medicines Committee recommended that the reference biotechnological medicine can be substituted by a biosimilar medicine, provided there is good clinical monitoring and the patient is informed, and that it is acceptable to initiate treatment with a biosimilar medicine, especially in new patients.[21]

References

1. TİTCK Biyobenzer Tıbbi Ürünler Hakkında Kılavuz. Eylül 2021.
2. National Human Genome Research

   Institute:https://www.genome.gov/genetics-glossary/Recombinant-DNA-Technology.
3. Guideline on development, production, characterisation and specification for monoclonal antibodies and related products. European Medicines Agency.21 July 2016.
4. John Rp Tesser, Daniel E Furst, Ira Jacobs; Biosimilars and the extrapolation of indications for inflammatory conditions. Biologics: Targets and Therapy 2017:11.
5. https://www.sciencedirect.com/topics/medicine-and-dentistry/immunogenicity.
6. Drug Discovery&Development;

   https://www.drugdiscoverytrends.com/50-of-2021s-best-selling-pharmaceuticals/.
7. https://www.medicinesforeurope.com/biosimilar-medicines/whats-new/?t=infographics&y= 2020
8. İEİS Türkiye Biyoteknolojik İlaç Pazarı Raporu. Ocak-Eylül 2022. www.ieis.org.tr.
9. Alessandro Armuzzia , Luisa Avedanob, Kay Grevesonc , Taegyun Kangd; Nurses are Critical in Aiding Patients Transitioning to Biosimilars in Inflammatory Bowel Disease: Education and Communication Strategies. Journal of Crohn's and Colitis, 2019, 259–266.
10. Duncan Longstaff; Switching from Biologic to Biosimilar: Australia's Unique Approach,SPRUSON&FERGUSON LAWYERS, May 28.2020.
11. Liese Barbier, Hans C. Ebbers, Paul Declerck, Steven Simoens, Arnold G. Vulto and Isabelle Huys; The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clin Pharmacol Ther. 2020 Oct; 108(4): 734–755.
12. Pekka Kurki, Sean Barry, Ingrid Bourges, Panagiota Tsantili and Elena Wolff-Holz; Safety, Immunogenicity and Interchangeability of Biosimilar Monoclonal Antibodies and Fusion Proteins: A Regulatory Perspective. Drugs (2021) 81:1881–1896.
13. https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar- medicines-eu_en.pdf.
14. https://www.gabionline.net/biosimilars/general/ema-calls-for-biosimilar-interchangeability-across-the-eu.
15. Tony Hagen; An Interchangeable Biosimilars vs Authorized Biologics Battle May Be Looming. The American Journal of Managed Care. October 27.2021.
16. https://www.gabionline.net/biosimilars/news/fda-approves-first-interchangeable-ranibizumab-biosimilar.
17. Biosimilars Interchangeability Laws by State. Cardinal Health. July 2021. https://www.cardinalhealth.com/content/dam/corp/web/documents/publication/Cardinal-Health-Biosimilar-Interchangeability-Laws-by-State.pdf.
18. Biosimilars in Australia-a-flagging and sustainability. Jan. 2021. https://www.gabionline.net/biosimilars/general/Biosimilars-in-Australia-a-flagging-and-sustainability.
19. www.gabionline.net/biosimilars/general/nova-scotia-canada-implements-biosimilar-switching-policy.
20. https://www.prnewswire.co.uk/news-releases/the-italian-finance-bill-for-2017-important-news-regarding-biosimilars-606496176.html - CISION PR Newswire.
21. The Dutch Medicines Board Opinion on Biosimilars: (www.biosimilars-nederland.nl/wp-content/uploads/2015/09/05-Franken-IBN-030915-franken2.pdf).



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