biosimilar medicines
better access. better health.

COMMUNICATIONS TOOLKIT

Biosimilar Medicines Group

November 2016

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Contents

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1. About us

The Biosimilar Medicines Group is a sector group of *Medicines for Europe* and represents the leading companies developing, manufacturing and marketing biosimilar medicines across Europe. Our member companies bring competition to the biologic medicines market, thereby increasing access to highly innovative medical treatments to patients, in Europe and around the world, and supporting the sustainability of the European healthcare systems. The vision of *Medicines for Europe* is to provide sustainable access to high quality medicines for all patients, based on 5 important pillars: patients, quality, value, sustainability and partnership.

The Biosimilar Medicines Group is open to all companies actively engaged in the biosimilar medicines sector in Europe.

2. Our Vision & Mission

VISION: To provide access to high quality biologic medicines to patients in Europe and worldwide.

MISSION: To inform the scientific, regulatory and general policy environment enabling broader patient access to modern therapies, ensuring the long-term sustainability of the biosimilar medicines industry through a high standard, safe and effective development process, a robust and predictable regulatory framework, continued investment and innovation in biosimilar medicines as well as the creation of competition in the biologic medicines sector.

3. Did you know

What are biologic medicines?

According to Part I of Annex I of Directive 2001/83/EC, a biological medicinal product is a product that contains a biological substance.

A biological substance is a substance that is produced by or extracted from a biological source and that needs a combination of physico-chemical-biological testing together with the production process and its control for its characterisation and the determination of its quality.

For example, recombinant proteins, monoclonal antibodies, medicinal products derived from human blood and human plasma, immunological medicinal products and advanced therapy medicinal products should be considered biological medicinal products.[1]

Europe has over 30 years of experience with biologic medicines[2].

[1] EMA website, accessed March 2016
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000125.jsp

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By 2014, over 245 biologic medicines had been authorised in the EU and US, representing 166 different active substances[3].

What are biosimilar medicines?

A biosimilar medicine is a biologic medicine that contains a version of the active substance of an already authorised biological medicinal product (reference medicine) and which is marketed following the expiry date of exclusivity rights on the reference medicine. The active substance is of biological origin i.e. it is made by or derived from a biological source, such as a bacterium or yeast.

To be authorised, a biosimilar medicine applicant needs to demonstrate that the same clinical benefits can be expected for the biosimilar and its reference medicine based on the fact that all key characteristics for quality, safety and efficacy profiles are the same.

The European Medicines Agency (EMA) assesses the scientific data available and issues an opinion on the suitability of a medicine for authorisation for use by patients in the EU.

The EU Commission decides, based on that opinion, whether or not to authorise a medicine.

Beyond the initial authorisation and as with all medicines, the EMA continues to monitor the safety of biosimilar medicines as long as they are in use.

These medicines help treat or prevent many diseases ranging from hormone deficiencies, anaemia associated with chronic kidney disease to other widespread and difficult-to-treat diseases such as cancers and auto-immune diseases, rheumatoid arthritis, multiple sclerosis and inflammatory bowel diseases. There is already over 30 years' experience with biologic medicines in Europe: the first approved substance for therapeutic use was biosynthetic "human" insulin, first marketed in 1982[2]. We now have 10 years of additional experience with biosimilar medicines. Since 2006, EU approved biosimilar medicines have already generated more than 400 million patient days of clinical experience worldwide.

Biosimilar medicines are therefore transforming healthcare in key therapeutic areas today, enhancing safe patient access and the sustainability of European healthcare systems, as demonstrated by the cumulated ***Real World Evidence*** (link to Glossary here).

Glossary

Biologic medicine: a biologic medicine is made up of proteins and is far more complex than well-known chemically synthesised medicines. It is made using living organisms.

Biosimilar medicine: a biosimilar medicine is a biologic medicine which is highly similar to the already approved reference product. These medicines treat diseases ranging from hormone deficiencies, anaemia associated with chronic kidney disease to other widespread and difficult-to-treat diseases such as cancers and auto-

[2] http://ec.europa.eu/health/human-use/50years/docs/50years_pharma_timeline_v3.pdf
[3] Biopharmaceutical benchmarks 2014, G. Walsh, Volume 32, Number 10 October 2014, Nature Biotechnology

immune diseases. Biosimilar medicines, like all biologic medicines, are made up of proteins and are far more complex than well-known chemically synthesised medicines and are made using living organisms.

Biosimilarity: property of a medicine to show similarity and lack of significant differences in terms of quality, efficacy and safety to a reference biologic medicine to which it has been compared.

Extrapolation of indications: Extrapolation is a concept allowing a regulatory authority to extend the available data supporting the safety and efficacy of a medicine from one medical condition, disease or disorder (an indication) to another medical condition, disease or disorder (another indication).

It is an established scientific and regulatory process which has been used repeatedly for all sorts of medicines and situations.

For examples, please refer to "Biosimilars: the science of extrapolation of indication", Weise M et al. Published in Blood 2014;124(22):3191-3196 - Full text available here (open access)

Interchangeability: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of, the prescriber. [4]

Real World Evidence:To demonstrate the clinical and economic value (effectiveness) of an intervention within the healthcare system (e.g. introduction of a new therapeutic option), the data associated with this intervention in the healthcare system can be collated and analysed to provide a unique insight. Such collated data set are called 'Real World Evidence' in reference to the fact that they correspond to actual and practical information as opposed to predicted, expected or forecasted value.

Reference medicinal product: A medicinal product which has been granted a marketing authorisation by a Member State or by the European Commission on the basis of submitted quality, pre-clinical and clinical data, to which the application for marketing authorisation for a generic or a biosimilar product refers. [5]

Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.[6]

Key facts

- Since 2006, biosimilar medicines have generated more than 400 million patient days of clinical experience.
- 70% to 80% of all healthcare costs in the EU - an estimated €700 billion - is currently spent on chronic diseases.
- Biosimilar medicines are approved by the same stringent regulatory bodies authorising all biologic medicines in Europe.

[4] EC Consensus paper What you need to know about biosimilar medicines http://ec.europa.eu/DocsRoom/documents/8242
[5] EC Consensus paper What you need to know about biosimilar medicines file:///C:/Users/jmarechal/Downloads/biosimilars_report_en%20(11).pdf
[6] EC Consensus paper What you need to know about biosimilar medicines file:///C:/Users/jmarechal/Downloads/biosimilars_report_en%20(11).pdf

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- The first worldwide biosimilar medicine is *somatropin* and it was approved in the EU in 2006.
- The entrance of biosimilar *filgrastim* increased patient access by 44% in the UK between 2006 and 2013.
- The first biosimilar monoclonal antibody medicine is *infliximab* and it was launched in the EU in 2014.
- Over 15 European countries have manufacturing sites for biosimilar medicines, or biosimilar candidates under development or under evaluation.
- The use of biosimilar medicines is expected to result in overall savings from 11.8 up to 33.4 billion euros for 8 EU countries between 2007 and 2020.
- 12 biologic medicines with global sales of 78 billion euros in 2014 alone will lose exclusivity by 2020 in Europe.
- EU approved biosimilar medicines are available for patients in over 60 countries around the world, and recognised as high quality, safe and effective medicines.
- The basic scientific principle of biosimilar medicines development is comparability.

Related links

1. EC Consensus Document: http://ec.europa.eu/DocsRoom/documents/8242
2. EMA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp
3. European Commission DG SANTE: http://ec.europa.eu/dgs/health_food-safety/
4. European Commission DG GROWTH: http://ec.europa.eu/growth/
5. US Food and Drug Administration: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/
6. WHO Expert Committee on Biological Standarization (ECBS): http://www.who.int/biologicals/WHO_ECBS/en/
7. IGBA website: www.igbamedicines.org
8. PLOS : https://www.plos.org/open-access
9. PubMed: http://www.ncbi.nlm.nih.gov/pubmed

4. Biosimilar medicines today

Biosimilar medicines were invented in Europe 20 years ago to address the pressing need for better access to biopharmaceuticals in Europe. For example, a recent study demonstrated the inequity in access to biologic medicines for treatment of **rheumatoid arthritis** because lower income countries in Europe cannot afford such therapies[7]. However even within high-income countries such as Germany and the UK, only 10-14% of patients with rheumatoid arthritis received treatment with biologic medicines[8]. Considerable benefit awaits those patients who will gain access to treatment with biologic medicines in both low and high income EU countries thanks to the arrival of biosimilar medicines competition.

Through sophisticated new technology, our industry was able to deliver a global first with the first biosimilar medicine approved in 2006. Since that time, our industry has continued to invest substantially in new innovation, bringing the total number of biosimilar medicines available today on the European market to 20[9].

Our experience to date shows that biosimilar medicines significantly increase patient access to high quality treatments. Not only can more patients become eligible for treatment, they can also be used earlier in the treatment course, therefore enabling patients to live with better life quality standards. This is what happened in 2006 with the introduction of **biosimilar *filgrastim***, which is used for **neutropenia** to support the immune system of patients under chemotherapy treatment. Between 2006 and 2013, biosimilar *filgrastim* ensured that 44% more patients obtained access to gold standard medicines in the EU-5 countries[10]. Also for other therapeutic areas such as EPO or growth hormone, access increased considerably upon biosimilar competition and some countries were able to address unmet clinical needs[11]. The same positive trend is expected with the recent entry of the first biosimilar monoclonal antibody *infliximab* in light of the high uptake levels in Europe. So what do biosimilar medicines deliver?

Biosimilar medicines improve access to indispensable pillars of modern therapies for millions of patients

With more than **10 years of positive patient treatment experience and 20 products successfully launched**, biosimilar medicines provide a huge opportunity to deliver significantly improved access to modern therapies for millions of European patients in both chronic and acute care in areas such as cancer, diabetes, rheumatoid arthritis or other immune-related diseases. We know that 70% to 80% of all healthcare costs in the EU – an estimated 700 billion EUR – are currently spent on chronic diseases. Biosimilar medicines answer one of Europe's major healthcare challenges: how to ensure that all European patients get equitable access to treatment?

[7] Putrik et al. Ann Rheum Dis 2014;73:198-206
[8] Rheumatoid Arthritis (RA) Market Forecast 2012
[9] European Commission – Community Register http://ec.europa.eu/health/documents/community-register/html/newproc.htm
[10] EU-5 countries: France, Germany, Italy, Spain and UK
[11] IMS Health (2015). *The impact of biosimilar competition.*

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The European biosimilar medicines industry is the global pioneer of this sector and has over 15 years of experience in developing and manufacturing to the highest quality standards. All biosimilar medicines available in Europe are developed, manufactured and approved according to stringent EU laws designed to set the highest global standards of safety, efficacy and quality. Biosimilar medicines are subject to the same rigorous pharmacovigilance requirements as all other biologic medicines in the EU. The Biosimilar Medicines Group of Medicines for Europe also engages in multilateral dialogues to promote the same high standards for the global development of biosimilar medicines in venues such as the WHO, or the EU-US TTIP regulatory cooperation negotiations.

Biosimilar medicines bring better value for healthcare spending

Biosimilar medicines not only deliver more access to medicines, they also improve health outcomes through appropriate earlier use of biologic medicines, while **enhancing competition** in the biopharmaceutical market. Biosimilar medicines also provide **better value for money** for healthcare budgets. The impact of biosimilar medicines on healthcare budget savings is real.

The Biosimilar medicines industry delivers sustainability for healthcare systems

Thanks to the considerable improvements in **patient access** to medicines and healthcare, the number of those aged 60+ is increasing twice as fast as before 2007. This growing ageing population, combined with rising treatment costs linked to the growth of chronic diseases and the introduction of complex therapies, is placing stress on the **sustainability of healthcare systems**. In this context, there is a need for viable innovation to offer better access to therapy and **better health outcomes**, and this is precisely what the European biosimilar medicines industry is delivering.

The Biosimilar medicines industry is a key partner for stakeholders

The Biosimilar Medicines Group engages actively with the European healthcare community, policy-makers, medical and professional societies, as well as with patient associations, to provide the necessary information, understanding and education on complex scientific concepts around biologic and biosimilar medicines. Our group also has extensive experience in engaging with national healthcare communities to build education and understanding about biosimilar medicines.

Through **Medicines for Europe** and its sector group the **Biosimilar Medicines Group**, pharmaceutical companies engage in partnership and multi-stakeholder approaches, aimed at fostering mutual understanding and consensus policy making, taking account of all partners' concerns and constraints, but also expertise and assets.

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5. Contact Us

If you want to learn more about biosimilar medicines, you can find us at www.medicinesforeurope.com and on Twitter @medicinesforEU.

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ANNEX

FACTSHEET

ABOUT MEDICINES FOR EUROPE

factsheet | About Medicines for Europe

About Medicines for Europe

Medicines for Europe (formerly EGA) represents the generic, biosimilar and value added medicines industries across Europe. Its vision is to provide sustainable access to high quality medicines for Europe, based on 5 important pillars: patients, quality, value, sustainability and partnership. Its members employ 190,000 direct employees at over 400 manufacturing and R&D sites in Europe, and invest up to 17% of turnover invested in R&D.

Medicines for Europe member companies across Europe are both increasing access to medicines and driving improved health outcomes. They play a key role in creating sustainable European healthcare systems by continuing to provide high quality, effective generic medicines, whilst also innovating to create new biosimilar medicines and bringing to market value added medicines, which deliver better health outcomes, greater efficiency and/or improved safety in the hospital setting for patients.

For more information please follow us at www.medicinesforeurope.com and on Twitter @medicinesforEU.

The Generic Medicines Group

The Generic Medicines Group is a sector group of **Medicines for Europe**, representing the generic medicines developers and manufacturers, which provide high-quality cost-competitive medicines to millions of patients in Europe and around the world. Generic medicines account today for 67% of all prescribed medicines but for only 29% of the pharmaceutical expenditure, or 2-4% of total healthcare costs, in Europe. The generic medicines industry has increased access to medicines by over 100% in 7 key therapeutic areas without increasing the overall treatment cost across Europe.

The Biosimilar Medicines Group

The Biosimilar Medicines Group is a sector group of **Medicines for Europe** representing the leading companies developing, manufacturing and/or marketing biosimilar medicines across Europe. With more than 10 years of positive patient treatment experience and 20 products successfully launched, biosimilar medicines provide today a huge opportunity to deliver significantly improved access to modern therapies for millions of European patients in both chronic and acute care. Our members bring competition to the biological medicines market, thereby increasing access to highly innovative treatments to patients, in Europe and around the world, and supporting the sustainability of the European healthcare systems.

The Value Added Medicines Group

The Value Added Medicines Group, a sector group of **Medicines for Europe** aims to rethink, reinvent and optimise medicines based on known molecules by bringing untapped innovation to improve care delivery. The Value Added Medicines Group adopts a complementary perspective compared to the other **Medicines for Europe** sector groups by tackling the targeted portion of patient needs that remain unmet to this day, delivering additional improvements to the healthcare community as a whole. Medicines for Europe Membership

MEMBER COMPANIES

3M
Accord Healthcare
Alfred E. Tiefenbacher
Alkaloid
Apobiologix
Camargo
Cinfa Biotech
CinnaGen
Cinfa Biotech
Consilient Health
DSM
Egis Pharmaceuticals
Farmoz
Formycon
Fresenius Kabi
Gedeon Richter
Glenmark
INFARCO
Insud Pharma
JGL
KRKA
Lupin
Medichem
Medochemie
Mylan
OJER Pharma
Oncomed
Polpharma
Samsung Bioepis
Sandoz
Stada
Sun Pharma
Synthon
Teva
Theranexus
ZENTIVA

AFFILIATE MEMBER COMPANIES

Acino Pharma
Anapharm Europe
Billev Pharma
Billev Pharma East
Cipla
Disphar
Farmaprojects
JSC Farmak
Pharma Patent
PharOS

PARTNER MEMBERS

BioPharma Services Inc
Extedo
Pharma Medica Research Inc.
Sanaclis

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AMMU (Ukraine)
AESEG (Spain)
APOGEN (Portugal)
AssoGenerici (Italy)
BGMA (United Kingdom)
BOGIN (Netherlands)
GEMME (France)
IEIS (Turkey)
IGL (Denmark)
Medaxes (BE)
Medicines for Ireland
Pro Generika (Germany)
PZPPF (Poland)

NATIONAL ASSOCIATIONS AFFILIATE MEMBERS

APM GR (Romania)
BGPharma (Bulgaria)
CAFF (Czech Republic)
CEA - PIA (HR)
FGA (Finland)
FGL (Sweden)
GE (Hungary)
GENAS (SK)
Intergenerika (Switzerland)
MAGYOSZ (HU)
OEGV (Austria)
VGA (LT)

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FACTSHEET

THE BIOSIMILAR MEDICINES GROUP

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Factsheet | The Biosimilar Medicines Group

About the Biosimilar Medicines Group

The **Biosimilar Medicines Group**, a sector group of **Medicines for Europe**, represents the leading companies in the biosimilar medicines space. The Biosimilar Medicines Group members bring competition to the biologicals market, thereby increasing access to highly innovative medical treatments to patients, in Europe and around the world, and supporting the sustainability of the European healthcare systems.

Medicines for Europe represents the European generic, biosimilar and value added medicines industries, which provide high-quality cost-competitive medicines to millions of Europeans. The vision of **Medicines for Europe** is to provide sustainable access to high quality medicines for all European patients, based on 5 important pillars: **patients**, **quality**, **value**, **sustainability** and **partnership**.

The Biosimilar Medicines Group is open to **Medicines for Europe** and non-**Medicines for Europe** members.

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Biosimilar Medicines: Key Facts

BIOSIMILAR MEDICINES
A major opportunity for Europe

Since 2006, EU approved biosimilar medicines have generated **more than 400 million patient days of clinical experience worldwide**

The **first worldwide biosimilar medicine** (somatropin) was approved in the EU in 2006[1]

The entrance of biosimilar **filgrastim increased patient access by 44%** in the EU between 2006 and 2013[2]

Over 15 European countries have manufacturing sites for biosimilar medicines or biosimilar candidates under development/evaluation

EU approved biosimilar medicines are available for patients in **over 60 countries around the world**, and recognised as high quality, safe and effective medicines

The use of biosimilars is expected to generate overall **savings from €11.8 up to €33.4 billion** for 8 EU countries between 2007 - 2020[3]

12 biological medicines with global sales of **€ 78 billion in 2014** will lose exclusivity by 2020 **in Europe**[2]

The **first biosimilar monoclonal antibody** (infliximab) was approved in the EU in 2013[1]

Sources: [1]EMA European public assessment report; [2]IMS Midas 2015; [3] IGES Study, 2012.

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Biosimilar Medicines Group Membership

COMPANIES

Accord Healthcare
Apobiologix
Cinfa Biotech
CinnaGen
Egis
Formycon
Fresenius Kabi
Gedeon Richter
Mylan
Polpharma
Samsung Bioepis
Sandoz
Stada
Teva

NATIONAL ASSOCIATIONS

APOGEN (Portugal)
BOGIN (Netherlands)
British Biosimilars Association (a group of BGMA) (UK)
CAFF (Czech Republic)
FGA (Finland)
FGL (Sweden)
GEMME (France)
GENAS (Slovakia)
IEIS (Turkey)
IGL (Denmark)
Italian Biosimilars Group (a group of Assogenerici) (Italy)
Intergenerika (Switzerland)
MAGYOSZ (HU)
Medaxes (BE)
Medicines for Ireland
Probiosimilars (a group of ProGenerika) (Germany)
VGA (LT)

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FACTSHEET

ON BIOSIMILAR MEDICINES

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Factsheet | On Biosimilar Medicines

What is a Biosimilar Medicine?

A **Biosimilar Medicine** is a biologic medicine that is developed to be highly similar to an existing biologic medicine (the 'reference medicine'). The pharmaceutical company needs to show that the biosimilar medicine does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy.

Biosimilar Medicines: Key Facts

BIOSIMILAR MEDICINES
A major opportunity for Europe

- Since 2006, EU approved biosimilar medicines have generated **more than 400 million patient days of clinical experience worldwide**
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Sources: [1]EMA European public assessment report;
[2]IMS Midas 2015; [3] IGES Study, 2012.

Key Therapeutic Areas Covered by Current Biosimilar Medicines

Active substance (year of first approval)	Therapeutic area
Somatropin (2006)	Pituitary dwarfism | Prader-Wili syndrome | Turner syndrome
Epoetin (2007)	Anemia | Consequence of chronic kidney failure | Follow-up of cancer treatment
Filgrastim (2008)	Neutropenia | Follow-up of cancer treatment | Hematopoietic stem cell transplantation
Infliximab (2013)	Rheumatoid arthritis | Crohn's disease | Ulcerative colitis | Psoriasis | Psoriatic arthritis | Ankylosing spondylitis
Follitropin (2013)	Anovulation
Insulin Glargine (2014)	Diabetes mellitus
Etanercept (2016)	Rheumatoid arthritis | Psoriatic arthritis | Plaque psoriasis | Ankylosing spondylitis

Key Therapeutic Areas Covered by Future Biosimilar Medicines

Active substance	Therapeutic area
Adalimumab	Crohn's disease | Ulcerative colitis | Rheumatoid arthritis | Psoriatic arthritis | Plaque psoriasis | Ankylosing spondylitis
Bevacizumab	Colorectal cancer | Lung cancer
Cetuximab	Colorectal cancer | Head and neck cancer
Insulin Aspart	Diabetes mellitus
Insulin Lispro	Diabetes mellitus
PEG-filgrastim	Neutropenia | Follow-up of cancer treatment | Hematopoietic stem cell transplantation
Ranibizumab	Macular degeneration
Rituximab	B-cell non-Hodgkin's lymphoma
Trastuzumab	Breast cancer

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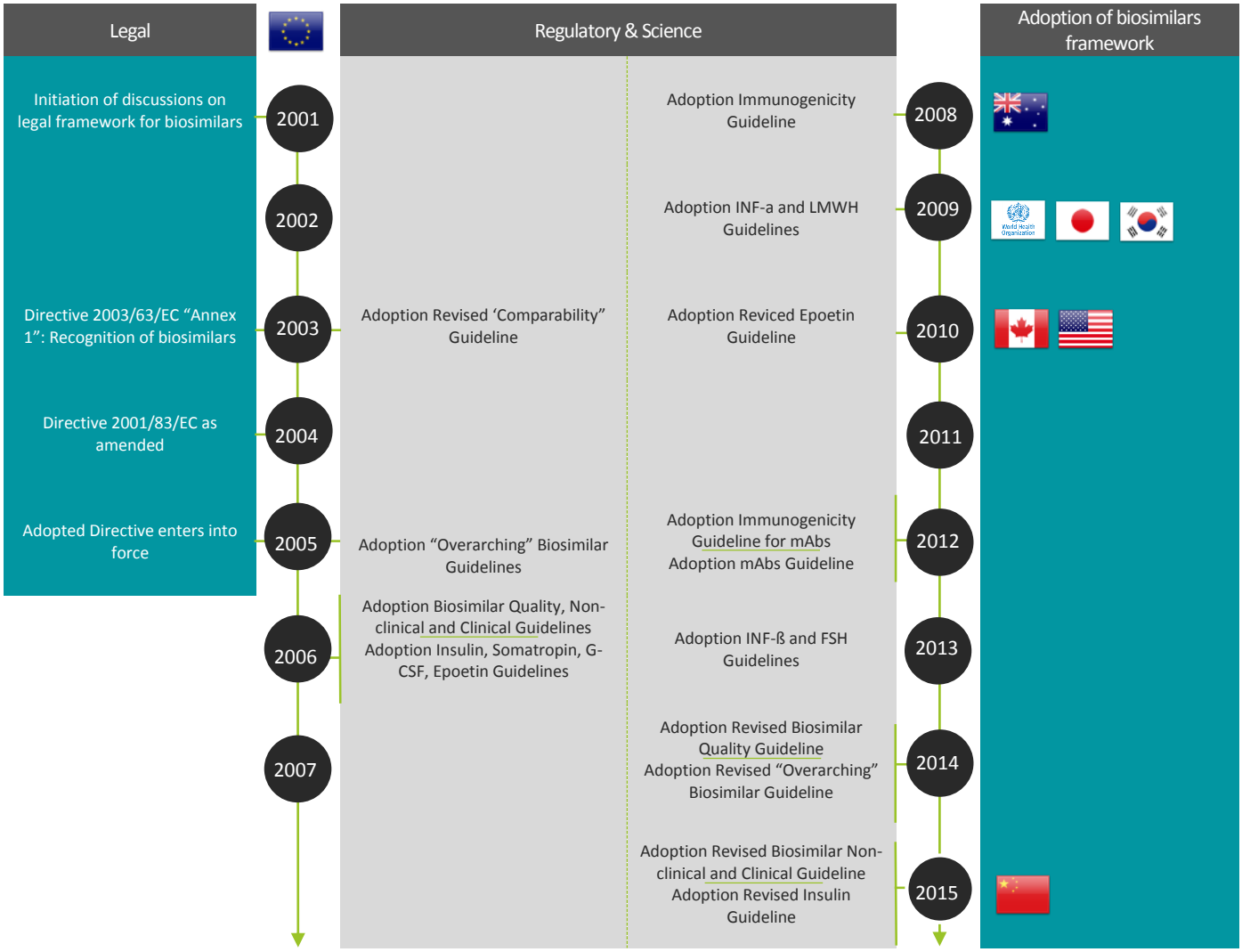
Biosimilar Medicines: EU legal, scientific & regulatory framework inspiring the world



About the Biosimilar Medicines Group

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Medicines for Europe represent the European generic, biosimilar and value added medicines industries, which provide access to high-quality cost-competitive medicines to millions of patients in Europe and worldwide. Medicines in Europe's vision is to provide sustainable access to high quality medicines for all patients, based on 5 important pillars: patients, quality, value, sustainability and partnership.

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INFOGRAPHIC

KEY FIGURES ON BIOSIMILAR MEDICINES

biosimilar medicines

KEY FIGURES ON BIOSIMILAR MEDICINES

LARGE CLINICAL EXPERIENCE

+700 MILLION

PATIENT DAYS

EU APPROVED BIOSIMILAR MEDICINES

2006

1st

1st WORLWIDE APPROVAL IN THE EU

BIOSIMILAR FILGRASTIM

+44% PATIENT ACCESS

IN THE EU (2006 - 2013)

AVAILABLE TO PATIENTS

IN **+60** COUNTRIES

AROUND THE WORLD

A GROWING OPPORTUNITY FOR HEALTHCARE BUDGETS

A **€78 BN** MARKET

WILL OPEN TO COMPETITION BY 2020

APPROVED

1st BIOSIMILAR MONOCLONAL ANTIBODY

EU - 2013

USE OF BIOSIMILARS

SAVINGS FROM

€11,8 UP TO **33,4** BN

FOR 8 EU COUNTRIES (2007-2020)

OVER **15** EUROPEAN COUNTRIES HAVE MANUFACTURING SITES FOR BIOSIMILAR MEDICINES OR BIOSIMILAR CANDIDATES UNDER DEVELOPMENT/EVALUATION

INFOGRAPHIC

FACTORS SUPPORTING A SUSTAINABLE EUROPEAN BIOSIMILAR MEDICINES MARKET (GFK REPORT)

PATIENTS
Improved access to medicines

PHYSICIANS
Opportunities to treat more patients with appropriate therapies

PAYERS
Cost savings and financial sustainability of healthcare systems

INDUSTRY
Reasonable return on investment with the continued attractiveness of R&D investment in new medicines development

Education and Understanding + **Experience and Use** + **Sustainable Pricing** + **Rational Decision Making** = **Clinical, Economic, & Patient Benefits**

1 EDUCATION & UNDERSTANDING

Multi-stakeholder understanding and acceptance of biosimilar medicines is critical for supporting long-term sustainability.

- Clear, non-promotional and unbiased information
- Focused on science
- Easily accessible & pro-actively communicated

2 EXPERIENCE AND USE

Accelerated experience and uptake of biosimilar medicines to establish confidence and trust is important for the short term benefit and long term sustainability of both biosimilar medicines markets and healthcare systems.

- Incentives & clinical guidelines
- Real World Evidence
- Multi-stakeholder approach

3 SUSTAINABLE PRICING

Avoid pricing policies that hinder competition and artificially force/mandate downward pricing which undermines the sustainability of markets.

- Tailored approach
- Encourage competition
- Incentivise R&D

4 RATIONAL DECISION MAKING

Pricing, procurement, positioning, and utilisation decision-making processes should be transparent and should not delay access to biosimilar medicines.

- Fair market
- More than only price
- Clinician involvement

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GfK

The EGA has become Medicines for Europe

Factors Supporting a Sustainable European Biosimilar Medicines Market

BIOSIMILARS MARKET MUST REMAIN SUSTAINABLE FOR ALL STAKEHOLDERS TO BENEFIT FROM THE OPPORTUNITIES

CONDITION: to be attractive and deliver continuous benefits to four key stakeholder groups in both the short and long term

1 EDUCATION & UNDERSTANDING

Clear, non-promotional and unbiased information

Regulators (e.g. EMA, European Commission, National Competent Authorities) and other stakeholders should provide clear, unbiased and non-promotional information to doctors, other healthcare professionals, payers and patients.

Focused on science

Education is required on the scientific concept of biosimilar medicines, their quality, safety and efficacy and the EMA approval process. In addition, the concept of “indication extrapolation”, an essential aspect of the biosimilar medicines regulatory pathway, should be clearly communicated and explained to all stakeholders in a context and language that provides complete understanding and support.

Easily accessible & pro-actively communicated

Physicians should be made aware of the easy access to unbiased and available information on biosimilar medicines (e.g. EMA Q&A on biosimilar medicines for the general public, the EMA European Public Assessment Reports (EPARs) or the EC Consensus Information document).

2 EXPERIENCE AND USE

Incentives & clinical guidelines

Policies should incentivise the early use of biosimilar medicines. Clinical guidelines are valuable to accelerate the uptake of biosimilar medicines. Procurement and utilisation should be transparent and multifaceted, not driven by the consideration of cost alone.

Real World Evidence

The confidence and trust of physicians (and other stakeholders) should be reinforced by supporting and incentivising appropriate early use, and encouraging them to collect and publish Real World Evidence (RWE).

Multi-stakeholder approach

Utilisation and procurement policies should evolve to include multi-stakeholder input and agreement.

3 SUSTAINABLE PRICING

Tailored approach

Biologic medicines are very complex to develop and manufacture. It is estimated that developing a biosimilar medicine takes 8 to 10 years and costs between €90 million and €180 million. In addition, post-marketing requirements are very costly.

Encourage competition

Maintaining and encouraging competition is the best way to ensure that all stakeholders receive the most value. Regulation between biosimilar medicines should create a level playing field for competition.

Incentivise R&D

Avoid pricing and procurement policies that drive prices to levels that threaten the financial viability of the biosimilar medicines industry and undermine continued investment by the pharmaceutical industry in future innovation (R&D). Thoughtful biosimilar medicines pricing will incentivise manufacturers to continue investing in new biosimilar medicines, thereby giving healthcare systems sustained savings and allowing more patient access to the best possible therapy options.

4 RATIONAL DECISION MAKING

Fair market

Procurement decision-making should not distort the market or lead to an arguably unfair position of dominance (e.g. originator long-term contracts/tenders prior to biosimilar approval). The timing and type of tenders must be aligned with the opportunity to deliver benefits to all stakeholders.

More than only price

Decision criteria should look at cost in the context of additional factors (e.g. outcomes and service provision) and balance procurement decisions to reflect factors other than price.

Clinician involvement

Procurement decision-making should include input from the clinical community and, particularly in the early phases, should provide clinicians with prescribing choice. Without general support from the clinical community any tender decision may be difficult or impossible to uphold.

READING LIST

BIOSIMILAR MEDICINES

biosimilar medicines
better access. better health.

Reading List| Biosimilar Medicines

Contents by topic

Contents by therapeutic area

biosimilar medicines
better access. better health.

By topic

1 - General information about biosimilar medicines

What I need to know about biosimilar medicines: Information for patients – Q&A

A consensus information document published by the European Commission, 2016
Full text available here (open access – Available in all EU languages).

Abstract
This leaflet has been written for patients who want information on biosimilar medicines. It aims to provide answers to some questions patients may have on biosimilar medicines. If you would like to read more about biosimilar medicines, there are references for further information at the end of this leaflet.

What you need to know about biosimilar medicinal products

A consensus information document published by the European Commission, 2013.
Full text available here (open access – Available in DE, EN, ES, FR, IT, PO, PT).

Abstract
This multi-stakeholder consensus document has been developed to provide comprehensive information on the concept of biosimilar medicinal products, including science, regulatory and economic aspects. All elements in this document are relevant to decision makers such as scientific societies, healthcare professionals and competent authorities, as well as to patients and their representative organisations. The document includes a Q&A for patients, physicians and payers.

Other relevant publications

- **Biosimilars: the challenges to bring a 'new' concept to market. A short review of the first decade of biosimilars**
  Cornes P. & Muenzberg M. Published in Pharma Horizon 2017;1(2):30-34.
  Full text available here
- **Biosimilars at the interface of science, medicine and economic**
  Gudat U. Published in Pharma Horizon 2017;1(2):35-38.
  Full text available here
- **Roundtable on biosimilars with European regulators and medical societies, Brussels, Belgium, 12 January 2016**
  Giezen T. et al. Published in Generics and Biosimilars Initiative (GaBI) Journal 2016;5(2):74-83.
  Full text available here (open access)
- **Biosimilar Medicines Handbook (new edition)**

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Medicines for Europe Biosimilar (2016)
Full text available here (open access)

- **Biosimilars: what it is not**
  de Mora, F. Published in British Journal of Clinical Pharmacology 2015: 80(5): 949-956.
  Full text available here (open access)

2 - Biological variability

Authorised manufacturing changes of therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents

Vezér B. et al. Published in Current Medical Research and Opinion 2016;32(5):829-834.
Full text available here

Abstract

Background: The quality of biologicals, including biosimilars, is subject to change as a result of manufacturing process modifications following initial authorization. It is important that such product changes have no adverse impact on product efficacy or safety, including immunogenicity.

Objectives: The aim of this study was to investigate the number and types of manufacturing changes of originator mAbs (the reference for the comparability exercise to confirm biosimilarity) according to European Public Assessment Report (EPAR) documentation and to ascertain the level of risk these changes might impart. The extensive body of evidence contained in the EPAR documents can help support the EMA during the EC marketing authorisation approval process for biosimilars, since it provides a broad base of scientific experience.

Research designs and methods: For EPAR-listed mAbs, details of all changes listed chronologically in the EPAR were evaluated and described. Based on these descriptions the manufacturing changes can be categorised by risk-status (low, moderate or high).

Results: Entries for 29 mAbs with publicly available EPAR reports were reviewed. These contained details of 404 manufacturing changes authorized by the European Medicines Agency (EMA): 22 were categorised as high-risk, 286 as moderate risk and 96 as low-risk manufacturing changes. A limitation of this analysis is that only summarises publicly available data from EPAR documents.

Conclusions: Manufacturing change data indicate that the EMA has significant experience of process changes for originator mAbs, and the impact they may have on the efficacy and safety of biologicals. This experience will be useful in biosimilar product development to ensure adherence to sound scientific principles. Compared with the established manufacturing process for a reference product, the production of biosimilars will usually be different. Consequently, in addition to a comprehensive comparative functional and physicochemical characterization analysis, clinical data is required to confirm mAb biosimilarity.

Acceptable changes in quality attributes of glycosylated biopharmaceuticals

Schiestl M. et al. Published in Nature Biotechnology 2011;29:310-312.

Full text available here

Abstract
No abstract available

Other relevant publications

- **Biosimilars in rheumatology: the wind of change**
  Schneider CK. Published in Annals of the Rheumatic Diseases 2013;72(3):315-318.
  Full text available here (open access)

- **Biosimilars to recombinant human FSH medicine: comparable efficacy and safety to the original biologic**
  de Mora F. & Fauser B. Reproductive Biomedicine Online 2017;35(1):81-86

  Full text available here (open access)

3 - Regulatory & scientific framework

Biosimilar regulation in the EU

Kurki P and Ekman N. Published in Expert Review of Clinical Pharmacology 2015;8(5):649-659.
Full text available here

Abstract
In the EU, the EMA has been working with biosimilars since 1998. This experience is crystallized in the extensive set of guidelines, which range from basic principles to details of clinical trials. While the guidance may appear complicated, it has enabled the development of biosimilars, of which 21 have managed to get marketing authorization. Currently marketed biosimilars in the EU have a good track record in safety and traceability. No biosimilars have been withdrawn from the market because of safety concerns. The most controversial issues with biosimilars are immunogenicity and extrapolation of therapeutic indications. The available data for these topics do not raise concerns among EU regulators. Interchangeability and substitution are regulated by individual EU member states.

Regulatory aspects of biosimilars. Myths and facts (in German)

Schneider CK. & Weise M. Published in Zeitschrift für Rheumatologie 2015;74(8):695-700.
Full text available here

Abstract
Background: Biosimilars are currently a hot topic and there are many unsolved questions, misunderstandings and sometimes considerable uncertainty, especially among clinicians and patients. Regulatory agencies, such as the

European Medicines Agency (EMA) issue guidelines for the development and approval of biosimilars, which are based on scientific principles.

Objective: This article addresses some of the frequently noted misunderstandings and misperceptions. For example, why biosimilars are (or can only be) "similar" but not "identical" compared to the original pharmaceutical product, and aspects, such as the pharmaceutical quality of biosimilars, immunogenicity and the approval process for biosimilars are highlighted.

Other relevant publications

- **The EU regulatory approach to generics and biosimilars is essentially similar.**
  van der Plas M et al. Published in Generics and Biosimilars Initiative (GaBI) Journal 2015;4(1):9-10.
  Full text available here (open access)
- **Safety assessment of biosimilars in Europe: a regulatory perspective.**
  Giezen T & Schneider CK. Published in Generics and Biosimilars Initiative (GaBI) Journal 2014;3(4):180-183.
  Full text available here (open access)
- **In support of the European Union biosimilar framework.**
  Schneider CK et al. Published in Nature Biotechnology 2012;30(8):748-749.
  Full text available here

4 - Information for patients

What you need to know about Biosimilar Medicines: Information for Patients – Q&A

European Medicines Agency & European Commission, 2016
Full text available here *(open access – Available in all EU languages).*

Abstract

The European Commission has published improved information for patients on biosimilar medicines. Biological medicines (including biosimilars) come from living organisms (cells) that have been modified using biotechnology. A biosimilar medicine is developed to be highly similar to an existing biological medicine. They have a great importance in the treatment of severe diseases such as cancers. Biosimilars have significant potential to create competition in the biological medicine market and provide patients with broader affordable access to state of the art medicines. The main goal of this document is to provide patients with information in language that is easy to understand, despite the complexity of the concept.

What you need to know about biosimilar medicinal products

A consensus information document published by the European Commission, 2013.
Full text available here (open access – Available in DE, EN, ES, FR, IT, PO, PT).

Abstract
This multi-stakeholder consensus document has been developed to provide comprehensive information on the concept of biosimilar medicinal products, including science, regulatory and economic aspects. All elements in this document are relevant to decision makers such as scientific societies, healthcare professionals and competent authorities, as well as to patients and their representative organisations. The document includes a Q&A for patients, physicians and payers.

5 - Information for prescribers

Physicians, Hippocrates and biosimilars: applying ancient principles in a modern society

Kurki P. Published in Generics and Biosimilars Initiative (GaBI) Journal 2016;5(4):149-150.
Full text available here (open access)

Abstract
Physicians are pondering the clinical use of biosimilars. A reliance on clinical trials is deeply rooted in the modern healthcare system, whereas comparability and totality of evidence remain unknown concepts. This editorial explores these ideas, with reference to a case study of Italian gastroenterologists.

Biosimilars: what clinicians should know

Weise M et al. Published in Blood 2012;120(26):5111-5117.
Full text available here (open access)

Abstract
Biosimilar medicinal products (biosimilars) have become a reality in the European Union and will soon be available in the United States. Despite an established legal pathway for biosimilars in the European Union since 2005 and increasing and detailed regulatory guidance on data requirements for their development and licensing, many clinicians, particularly oncologists, are reluctant to consider biosimilars as a treatment option for their patients. Major concerns voiced about biosimilars relate to their pharmaceutical quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product. In this article, the members and experts of the Working Party on Similar Biologic Medicinal Products of the European Medicines Agency (EMA) address these issues. A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients. This will become even more important with the advent of

biosimilar monoclonal antibodies. The issues also highlight the need for improved communication between physicians, learned societies, and regulators.

Biosimilars in the EU: Information guide for healthcare professionals

European Medicines Agency & European Commission, 2017
Full text available here (open access)

Abstract

Since the EU approved the first biosimilar medicine ('biosimilar') in 2006, the EU has pioneered the regulation of biosimilars. Over the past 10 years, the EU has approved the highest number of biosimilars worldwide, amassing considerable experience of their use and safety. The evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines. A biosimilar is a biological medicine highly similar to another biological medicine already approved in the EU (the so-called 'reference medicine'). Because biosimilars are made in living organisms there may be some minor differences from the reference medicine. These minor differences are not clinically meaningful, i.e. no differences are expected in safety and efficacy. Natural variability is inherent to all biological medicines and strict controls are always in place to ensure that it does not affect the way the medicine works or its safety. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU. The aim of biosimilar development is to demonstrate biosimilarity - high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile. By demonstrating biosimilarity, a biosimilar can rely on the safety and efficacy experience gained with the reference medicine. This avoids unnecessary repetition of clinical trials already carried out with the reference medicine. Demonstration of biosimilarity relies on comprehensive comparability studies with the reference medicine. (…)If a biosimilar is highly similar to a reference medicine, and has comparable safety and efficacy in one therapeutic indication, safety and efficacy data may be extrapolated to other indications already approved for the reference medicine. Extrapolation needs to be supported by all the scientific evidence generated in comparability studies (quality, non-clinical and clinical)(…). Biosimilar competition can offer advantages to EU healthcare systems, as it is expected to improve patients' access to safe and effective biological medicines with proven quality. EMA does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar. These fall within the remit of EU Member States.

Other relevant publications

- **Biosimilars for prescribers**
  Kurki P. Generics and Biosimilars Initiative (GaBI) Journal 2015;4(1):33-35.
  Full text available here (open access)

6 - Terminology

Terminology for biosimilars - a confusing minefield

Thorpe R. & Wadhwa M. Published in Generics and Biosimilars Initiative (GaBI) Journal 2012;1(3-4):132-134.
Full text available here (open access)

Abstract
Biosimilars are firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval. Unfortunately, inconsistency in nomenclature for biosimilars has caused confusion. This problem of terminology has been the subject of a recent publication. The confusion is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions in published reports. Several examples of this have occurred, some of which are discussed below. The definitions provided should be adopted for clarity in the future.

Biosimilars: why terminology matters

Weise M. et al. Published in Nature Biotechnology 2011;29(8):690-693.
Full text available here

Abstract
No abstract available

7 - Extrapolation of indications

Opportunities and challenges of extrapolation for biosimilars (in German)

Weise M & Wolff-Holz E. Published in Zeitschrifts für Gastroenterologie 2016;4:1211-1216.
Full text available here

Abstract
Although biosimilars approved in the European Union have proved to be safe and efficacious, their licensing requirements continue to be disputed by medical professionals. In particular, extrapolation to indications of the originator without one's own clinical data of the biosimilar is controversial. Conceptually, the development of biosimilars is derived from that of generics. However, due to their complexity and inherent variability, considerably more data are necessary for biosimilars to demonstrate comparability with the originator (the reference product) than for the usually low-molecular generics. Biosimilars increase competition and help contain healthcare, and they improve access for patients to valuable treatments with biologicals. However, biosimilar development is a laborious and lengthy process and requires major biotechnological know-how. The basis is comprehensive, structural, and functional characterization of the biosimilar and reference product as well as their comparison with suitable and sensitive methods. The clinical development programme is reduced and tailored to address remaining

uncertainties and to confirm comparable clinical performance. Extrapolation of data to other indications of the reference product is the greatest cost advantage of biosimilar development, but must always be scientifically justified and, if necessary, substantiated by further data. The scientific principles underlying the comparability exercise for a biosimilar are the same as those applied to a change in the manufacturing process of an already licensed biological. In both cases, different versions of a biological substance are compared and the clinical relevance of observed differences is assessed. Competent authorities do have decades of experience in evaluating changes in the manufacturing process, which they can now apply to biosimilars. For approval of a biosimilar and extrapolation of data, the totality of the evidence from the complete comparability exercise is considered, as has been the case for the first biosimilar infliximab.

Biosimilars: the science of extrapolation of indication

Weise M et al. Published in Blood 2014;124(22):3191-3196.
Full text available here (open access)

Abstract
Despite the establishment of a specific approval pathway, the issuance of detailed scientific guidelines for the development of similar biological medicinal products (so-called "biosimilars") and the approval of several biosimilars in the European Union, acceptance of biosimilars in the medical community continues to be low. This is especially true in therapeutic indications for which no specific clinical trials with the biosimilar have been performed and that have been licensed based on extrapolation of efficacy and safety data from other indications. This article addresses the concerns frequently raised in the medical community about the use of biosimilars in such extrapolated indications and explains the underlying scientific and regulatory decision making including some real-life examples from recently licensed biosimilars.

Other relevant publications

- **Biosimilars: Extrapolation for oncology**
  Curigliano et al. Critical Reviews in Oncology/Hematology 2016;104:131-137.
  Full text available here (open access)
- **Biosimilars: In support of extrapolation of indications**
  Ebbers, HC. Journal of Crohn's and Colitis 2014;8(5):431-435.
  Full text available here (open access)

8 - Immunogenicity

Multidisciplinary approach to evaluating immunogenicity of biosimilars: lessons learned and open questions based on 10 years' experience of the European Union regulatory pathway.

Chamberlain PD. Published in Biosimilars 2014;4:23-43.
Full text available here (open access)

Abstract

Clinical evaluation of comparative immunogenicity represents an important component of the European Union regulatory review process for candidate biosimilar products. The clinical evaluation is part of a multidisciplinary review that cross-refers to product quality attributes as well as preclinical and ongoing risk management considerations. Results from the monitoring of anti-drug antibody formation in relevant populations treated for an adequate period of time are interpreted in relation to clinically relevant endpoints, including pharmacokinetics, pharmacodynamics, efficacy, and safety parameters. The European Union regulatory standard for designation of biosimilarity requires a suitable weight of evidence, determined on a product-specific basis, to demonstrate that the immunogenicity associated with the biosimilar product does not lead to a higher negative impact on clinically relevant outcomes compared with the reference product. The experience gained during the 10-year period following the implementation of the European Union biosimilars pathway indicates that a suitably cautious approach was applied, insofar as no immunogenicity-related issues have emerged for the approved applications of the different biosimilar products. In some cases, product quality-related issues were identified in the preauthorization setting as being potentially relevant for heightened risk of immunogenicity and were duly taken into account for the biosimilarity decision. Some unresolved issues remain, most notably concerning the limitation of non-interventional post-marketing surveillance measures to monitor the potential for changes in immunogenicity over the longer term, e.g. following introduction of changes in manufacture, formulation, or primary product container. Lack of standardization of bioanalytical methods precludes comparison of anti-drug antibody formation for different products that are evaluated in non-comparative clinical studies, and correlation with relevant clinical parameters is also lacking.

Other relevant publications

- **Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima**
  Ben-Horin S et al. Published in Gut 2016;65(7):1132-1138.
  Full text available here

9 - Traceability of biopharmaceuticals

Traceability of biopharmaceuticals in spontaneous reporting systems: a cross-sectional study in the FDA adverse reporting system (FAERS) and Eudravigilance databases.

Vermeer N et al. Published in Drug Safety 2013;36(8):617-625.
Full text available here

Abstract

Background: Adverse drug reactions (ADRs) of biopharmaceuticals can be batch or product specific, resulting from small differences in the manufacturing process. Detailed exposure information should be readily available in systems for post)marketing safety surveillance of biopharmaceuticals, including spontaneous reporting systems (SRSs), in which reports of ADRs are collected.

Objective: The aim of this study was to explore the current status of traceability of biopharmaceuticals in the US and the EU up to patient level in SRSs.

Design and setting: A cross-sectional study was conducted over the period 2004-2010, including ADR reports from two major SRSs: the FDA Adverse Event Reporting System (FAERS) in the US and EudraVigilance (EV) in the EU.

Main outcome measures: The availability of batch numbers was determined for biopharmaceuticals, and compared with small molecule drugs. For biopharmaceuticals for which a biosimilar has been approved for marketing in the EU, the identifiability of the product (i.e. the possibility of distinguishing the biosimilar from the reference biopharmaceutical) was determined.

Results: A total of 2,028,600 unique ADR reports were identified in the FAERS, reporting a total of 591,380 biopharmaceuticals (of which 487,065 were suspected). In EV there were 2,108,742 unique ADR reports, reporting a total of 439,971 biopharmaceuticals (356,293 suspected). Overall, for 24.0 % of the suspected biopharmaceuticals in the FAERS and 7.4 % of the suspected small molecule drugs ($p < 0.001$) batch numbers were available. A similar pattern was seen in EV: for 21.1 % of the suspected biopharmaceuticals batch numbers were available, compared with only 3.6 % of the small molecule drugs ($p < 0.001$). In both SRSs, consumers were most likely to report a batch number for suspected biologicals (36.3 % in the FAERS and 40.7 % in EV). A total of 13,790 biopharmaceuticals (9,759 suspected) for which a biosimilar has been approved in the EU were identified in EV. For 90.4 % of these biopharmaceuticals and 96.2 % of the suspected biopharmaceuticals the product was clearly identifiable.

Conclusion: This study underlines the need for improving traceability of biopharmaceuticals, in particular with respect to individual batches, allowing better identification and monitoring of postmarketing safety issues related to biopharmaceuticals.

10 - Physician-led switching

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Cohen HP. et al. Published in Drugs 2018; 78(4):463-478.
Full text available here

Abstract

Introduction: To evaluate the possibility that switching from reference biologic medicines to biosimilars could lead to altered clinical outcomes, including enhanced immunogenicity, compromised safety, or diminished efficacy for patients, a systematic literature review was conducted of all switching studies between related biologics (including biosimilars).

Methods: A systematic search was conducted using the Medline® and Embase® databases up to 30 June 2017 employing specific medical subject heading terms. Additionally, the snowball method and a hand search were also applied. Publications were considered if they contained efficacy or safety information related to a switch from a

reference medicine to a biosimilar. Non-English, non-human studies, editorials, notes, and short surveys were excluded.

Results: Primary data were available from 90 studies that enrolled 14,225 unique individuals. They included protein medicines used in supportive care as well as those used as therapeutic agents. The medicines contained seven different molecular entities that were used to treat 14 diseases. The great majority of the publications did not report differences in immunogenicity, safety, or efficacy. The nature and intensity of safety signals reported after switching from reference medicines to biosimilars were the same as those already known from continued use of the reference medicines alone. Three large multiple switch studies with different biosimilars did not show differences in efficacy or safety after multiple switches between reference medicine and biosimilar. Two publications reported a loss of efficacy or increased dropout rates.

Conclusions: While use of each biologic must be assessed individually, these results provide reassurance to healthcare professionals and the public that the risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine.

Interchangeability of biosimilars: A European perspective

Kurki P. et al. Published in Biodrugs 2017; 31(2):83-91.
Full text available here

Abstract

Many of the best-selling 'blockbuster' biological medicinal products are, or will soon be, facing competition from similar biological medicinal products (biosimilars) in the EU. Biosimilarity is based on the comparability concept, which has been used successfully for several decades to ensure close similarity of a biological product before and after a manufacturing change. Over the last 10 years, experience with biosimilars has shown that even complex biotechnology-derived proteins can be copied successfully. Most best-selling biologicals are used for chronic treatment. This has triggered intensive discussion on the interchangeability of a biosimilar with its reference product, with the main concern being immunogenicity. We explore the theoretical basis of the presumed risks of switching between a biosimilar and its reference product and the available data on switches. Our conclusion is that a switch between comparable versions of the same active substance approved in accordance with EU legislation is not expected to trigger or enhance immunogenicity. On the basis of current knowledge, it is unlikely and very difficult to substantiate that two products, comparable on a population level, would have different safety or efficacy in individual patients upon a switch. Our conclusion is that biosimilars licensed in the EU are interchangeable.

The safety of switching between therapeutic proteins.

Ebbers HC, Muenzberg M and Schellekens H. Published in Expert Opinion on Biological Therapy 2012:12(11):1473-1485.
Full text available here

Abstract

Introduction: The approval of several biosimilars in the past years has prompted discussion on potential safety risks associated with switching to and from these products. It has been suggested that switching may lead to safety concerns. However, data is limited on the clinical effects of switching.
Areas covered: In this review we provide an overview of data related to switching between human recombinant growth hormones, erythropoietins and granulocyte colony stimulating agents. We reviewed data from clinical trials, pharmacovigilance databases and an overview of the literature on the frequency of switching between these products. The review covers both switching between innovator products within the same product class and switching to and from biosimilars.
Expert opinion: Data on the frequency of switching in clinical practice is scarce, but it seems most frequent for erythropoietins. We have found no evidence from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns.

Other relevant publications

- **Is there a reason for concern or is it just hype? A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars**
  András I. et al. Expert Opinion on Biological Therapy 2017
  Full text available here
- **Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial**
  Jørgensen K. et al. The Lancet 2017;389:2304-2316
  Full text available here
- **A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry**
  Glintborg B. et al. Annals of the Rheumatic Diseases 2017;
  Full text available here

11 – Policy & Access

Policies for biosimilar uptake in Europe: An overview

Moorkens E. et al. Published in PLoS One. 2017;12(12):e0190147.
Full text available here (open access)

Abstract
Background: Across European countries, differences exist in biosimilar policies, leading to variations in uptake of biosimilars and divergences in savings all over Europe.

Objectives: The aim of this article is to provide an overview of different initiatives and policies that may influence the uptake of biosimilars in different European countries. Recommendations will be formulated on how to create sustainable uptake.
Methods: An overview of policies on biosimilars was obtained via a questionnaire, supplemented with relevant articles. Topics were organized in five themes: availability, pricing, reimbursement, demand-side policies, and recommendations to enhance uptake.
Results: In all countries studied, biological medicines are available. Restrictions are mainly dependent on local organization of the healthcare system. Countries are willing to include biosimilars for reimbursement, but for commercial reasons they are not always marketed. In two thirds of countries, originator and biosimilar products may be subjected to internal reference pricing systems. Few countries have implemented specific incentives targeting physicians. Several countries are implementing pharmacist substitution; however, the scope and rules governing such substitution tend to vary between these countries. Reported educational policies tend to target primarily physicians, whereas fewer initiatives were reported for patients. Recommendations as proposed by the different country experts ranged from the need for information and communication on biosimilars to competitive pricing, more support for switching and guidance on substitution.
Conclusions: Most countries have put in place specific supply-side policies for promoting access to biosimilars. To supplement these measures, we propose that investments should be made to clearly communicate on biosimilars and educate stakeholders. Especially physicians need to be informed on the entry and use of biosimilars in order to create trust. When physicians are well-informed on the treatment options, further incentives should be offered to prescribe biosimilars. Gainsharing can be used as an incentive to prescribe, dispense or use biosimilars. This approach, in combination with binding quota, may support a sustainable biosimilar market.

Biosimilars: How can payers get long-term savings

Mestre-Ferrandiz J, Towse A & Berdud M. Published in PharmacoEconomics 2016;34:609-616.
Full text available here (open access)

Abstract

The term ‘biosimilar’ refers to an alternative similar version of an off-patent innovative originator biotechnology product (the ‘reference product’). Several biosimilars have been approved in Europe, and a number of top-selling biological medicines have lost, or will lose, patent protection over the next 5 years. We look at the experience in Europe so far. The USA has finally implemented a regulatory route for biosimilar approval. We recommend that European and US governments and payers take a strategic approach to get value for money from the use of biosimilars by (1) supporting and incentivising generation of high-quality comprehensive outcomes data on the effectiveness and safety of biosimilars and originator products; and (2) ensuring that incentives are in place for budget holders to benefit from price competition. This may create greater willingness on the part of budget holders and clinicians to use biosimilar and originator products with comparable outcomes interchangeably, and may drive down prices. Other options, such as direct price cuts for originator products or substitution rules without outcomes data, are likely to discourage biosimilar entry. With such approaches, governments may achieve a one-off cut in originator prices but may put at risk the creation of a more competitive market that would, in time, produce much greater savings. It was the creation of competitive markets for chemical generic drugs—notably, in

the USA, the UK and Germany—rather than price control, that enabled payers to achieve the high discounts now taken for granted.

Biosimilar infliximab in inflammatory bowel disease: Outcomes of a managed switching programme

Razanskaite V et al. Published in Journal of Crohn's and Colitis 2017:1-7.
Full text available here (open access)

Abstract

Background and aims: biosimilar infliximab CT-P13 offers the potential for large drug acquisition cost savings. However, there are limited published data regarding its efficacy, safety, and immunogenicity in inflammatory bowel disease [IBD], particularly in switching IBD patients from originator to biosimilar infliximab. We present the outcomes of a service evaluation of switching IBD patients established on originator infliximab to biosimilar, using a managed switching programme funded via a gain share agreement in a UK teaching hospital.

Methods: Evaluation outcomes included drug persistence, changes in drug acquisition costs, patient-reported side effects, adverse events, patient outcomes assessed using the IBD-control Patient-Reported Outcome Measures [PROM] questionnaire, serum drug and antibody levels, and routinely collected biochemical markers.

Results: A total of 143 patients with IBD [118 Crohn's disease, 23 ulcerative colitis, 2 IBD unclassified] were switched from originator infliximab to CT-P13. Patients reported a similar incidence of side effects before and after switch. No clinically significant differences were observed in mean C-reactive protein [CRP], albumin, haemoglobin levels, or platelet and white cell counts after the switch to CT-P13, whereas mean IBD-control-8 score improved from 10.4 to 11.2 [p = 0.041]. There was no significant difference in drug persistence between biosimilar and originator infliximab [p = 0.94] and no increase in immunogenicity was found. Drug acquisition costs decreased by £40,000-60,000 per month.

Conclusions: A managed switching programme from originator infliximab to biosimilar CT-P13 in IBD, using a gain-share agreement, delivers significant cost savings and investment in clinical services while maintaining similar patient-reported outcomes, biochemical response, drug persistence, and adverse event profile.

Other relevant publications

- **A review on biosimilar infliximab, CT-P13, in the treatment of inflammatory bowel disease.**
  Farkas K. and Molnár T. Immunotherapy. 2018; 10(2):107-117.
  Full text available here
- **Policy practices to maximise the social benefit from biosimilars**
  Inotai A. et al. Journal of Bioequivalence & Bioavailability 2017;9(4):467-472
  Full text available here (open access)
- **Impact of Infliximab and Etanercept Biosimilars on Biological Disease-Modifying Antirheumatic Drugs Utilisation and NHS Budget in the UK**
  Aladul MI et al. BioDrugs. 2017; 31(6):533-544.
  Full text available here

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By therapeutic area

A – Rheumatology

- **Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial**
  Jørgensen K. et al. The Lancet 2017;389:2304-2316.
  Full text available here
- **A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry**
  Glintborg B. et al. Annals of the Rheumatic Diseases 2017.
  Full text available here
- **Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician**
  Moots R. et al. Curr Rheumatol Rep. 2017; 19(6):37.
  Full text available here

B – Dermatology

- **Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician**
  Moots R. et al. Curr Rheumatol Rep. 2017; 19(6):37.
  Full text available here

C - Gastro-intestinal

- **Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial**
  Jørgensen K. et al. The Lancet 2017;389:2304-2316.
  Full text available here
- **A review on biosimilar infliximab, CT-P13, in the treatment of inflammatory bowel disease**
  Farkas K and Molnár T. Immunotherapy. 2018; 10(2):107-117.
  Full text available here
- **Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician**
  Moots R. et al. Curr Rheumatol Rep. 2017; 19(6):37.
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D – Oncology

- **Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim for the prevention of severe neutropenia, in patients with breast cancer receiving myelosuppressive chemotherapy**
  Krendyukov A et al. J Clin Oncol. 2017; 35(15_suppl):10116.
  Full text available here
- **Pooled analysis of two randomized, double-blind trials comparing proposed biosimilar LA-EP2006 with reference pegfilgrastim in breast cancer**
  K. Blackwell et al. Annals of Oncology 2017. Volume 28, Issue 9, 1 September 2017, Pages 2272–2277
  Full text available here (open access)
- **The safety of switching between therapeutic proteins**
  Ebbers HC. et al. Expert Opin Biol Ther. 2012; 12(11):1473–85.
  Full text available here

E - Endocrinology

- **The safety of switching between therapeutic proteins**
  Ebbers HC. et al. Expert Opin Biol Ther. 2012; 12(11):1473–85.
  Full text available here