

Chapter 1

The era of biological medicines

Since their first use in the 1980s, biological medicines (including biosimilar medicines) have grown to become an indispensable tool in modern medicine. Worldwide, millions of patients have already benefited from approved biological medicines, but what exactly are they, and how are they produced?^{1,2}

Biological medicines¹ have revolutionized the treatment of many disabling and life-threatening diseases

■ Biological medicines:

- include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapies, tissues, and recombinant therapeutic proteins
- are highly specific and targeted medicines
- help to treat or prevent many rare and severe diseases, including:



Cancers



Arthritis



Psoriasis



Inflammatory
digestive
disorders



Growth
disorders



Diabetes

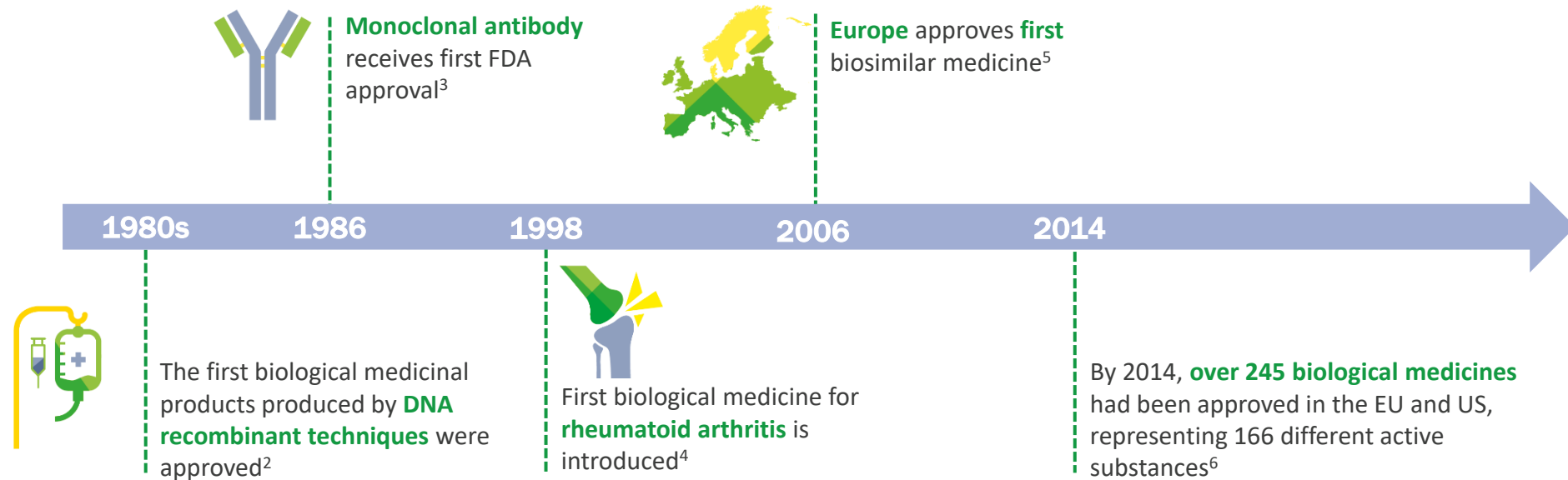


Nephrology

Biological medicines are developed based on a deep understanding of the disease biology

Biological medicines contain one or more active substances made by or derived from a biological source¹

- Since their first use in the 1980s, biological medicines have grown to become an indispensable tool in modern medicine²

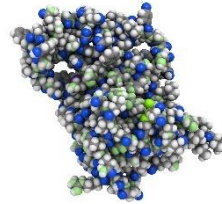


Biological medicines are an integral and indispensable part of modern medicine⁶

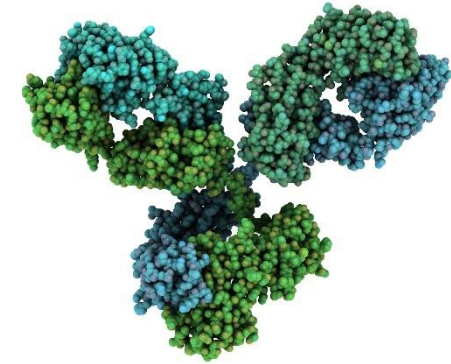
Biological medicines are predominantly larger and more complex than chemically synthesized medicines



Chemically synthesized medicine



Growth hormone



Antibody

Type of molecule	Small molecule	Protein (without sugars)	Glycoprotein (variable sugars)
Synthesis	Chemical	Bacterial	Mammalian
Uniformity	Single substance	Single main substance	Mixture of variants
Size	21 atoms (aspirin)	3000 atoms (HGH)	>20,000 atoms (mAb)

The complexity of biological medicines is such that they cannot usually be synthesized by conventional methods

Abbreviations: HGH, human growth hormone; mAb, monoclonal antibody.

References: International Alliance of Patients' Organizations. [Briefing paper on Biological and Biosimilar Medicines 2013](#). Accessed February 2020.

Producing biological medicines tends to be more complex than producing chemically derived medicines^{1,2}

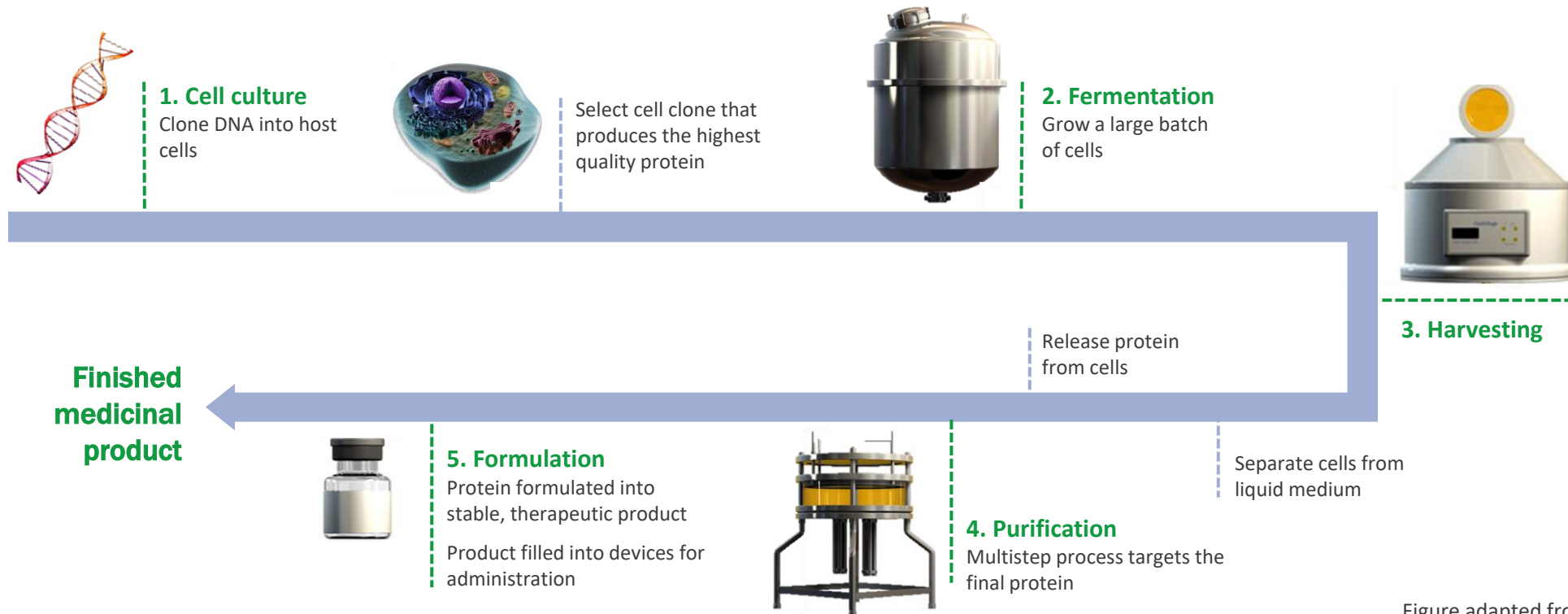


Figure adapted from Apobiologix³

The inherent variability of living organisms and the manufacturing process result in the biological medicine displaying a certain degree of variability ('microheterogeneity')¹

A biological medicine is a mixture of closely related variants of the same protein¹

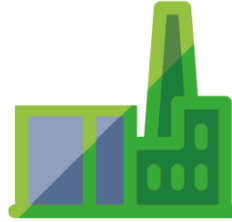
- The living organisms used to make biological medicines are **naturally variable**²
- An inherent degree of minor variability ('**microheterogeneity**') is thus normally present in biological medicines²
- Microheterogeneity is also present **within and/or between batches** of the same biological medicine²
- The degree of variability **must fall within a range** agreed upon by the health authority to ensure consistent safety and efficacy²
- **Strict controls** are always in place during manufacturing to ensure batch-to-batch consistency, and that the differences do not affect safety or efficacy¹

Strict controls ensure safe and efficacious biological medicines¹

Summary: The era of biological medicines



Biological medicines contain one or more active substances **made by or derived from a biological** source¹



The complexity of biological medicines is such that they **cannot usually be synthesized** by conventional methods²



The **variability** of the living organisms contributes to **microheterogeneity**³



Microheterogeneity is normal, and seen **within or between different batches** of the same biological product⁴



Strict controls during manufacturing **ensures safe and effective** biological medicines⁴



Biological medicines have grown to become an **indispensable tool** in modern medicine⁵

Chapter 2

Biological medicines — the major social and economic challenges

The global spend on pharmaceuticals continues to increase. The use of biological medicines offers new treatment choices to patients, but at a high financial cost. What are the challenges faced by payers and physicians in preserving access to biological medicines within a financially constrained healthcare system?

Chronic conditions are on the rise worldwide

2015 WHO global report¹

- 80% of chronic disease deaths today occur in low- and middle-income countries
- The threat is growing – the number of people, families and communities afflicted is increasing

With the global prevalence of age-related chronic diseases rising, **access to cost-effective medical treatment** will become increasingly important over the next decades worldwide



Health systems must adapt to meet the growing demand for the treatment of chronic conditions¹

In the US, **chronic conditions** account for:



90% of all healthcare costs²



and nearly **100% of Medicare*** spending³

Access to cost-effective treatment is paramount for the short, medium, and long-term sustainability of healthcare systems¹

Footnotes: *Medicare is a US federal health insurance program for elderly patients.

References: **1.** United Nations. World Aging Report. Available at: <http://bit.ly/1Y2LeF4>. Accessed March 2020; **2.** Centers for Disease Control and Prevention. Health and Economic Costs of Chronic Diseases. Available at: <https://www.cdc.gov/chronicdisease/about/costs/index.htm>. Accessed October 2020; **3.** Chronic Conditions Chartbook, 2017. Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Chartbook_Charts. Accessed October 2020.

The use of biological medicines continues to grow consistently each year



- In 2019, biologic spending was \$211 billion – **43% of total medicine spending in the U.S.**¹



- Biological medicines can cost up to **100,000 USD per year per patient**, negatively impacting on both patient choice and the healthcare system²



- By 2020, a number of diseases will have **new biological treatment options** available across developed markets¹



- The **constrained payer environment** is triggering a range of initiatives designed to limit growth in healthcare budgets

Payers seek to provide and preserve access to cutting-edge medicines, but also need to ensure the long-term financial sustainability of their healthcare systems³

The long-term potential of biological medicines is hampered by their high cost

Psoriasis

- Psoriasis affects approximately **7.4 million** Americans¹
- Access to biological medicines remains a challenge for many American patients due to factors such as **limited insurance coverage** and **prohibitive costs**²



A number of markets, including Western markets, restrict patient access to biological medicines due to their cost⁴

References: 1. Rachakonda TD, et al. *J Am Acad Dermatol* 2014;70:512–6; 2. Kamangar F, et al. *J Dermatolog Treat* 2013;24:13–24;

4. Putrik P, et al. *Ann Rheum Dis*. 2014;73:198–206.

1. 2015 WHO Global Report: Preventing chronic diseases: a vital investment

Access to biological medicines is not uniform across Europe

- Compared with Western Europe, Central and Eastern Europe have experienced reduced access to biological medicines^{1,2}

Percentage of patients with rheumatoid arthritis (RA) treated with a biological medicine:

Western Europe*

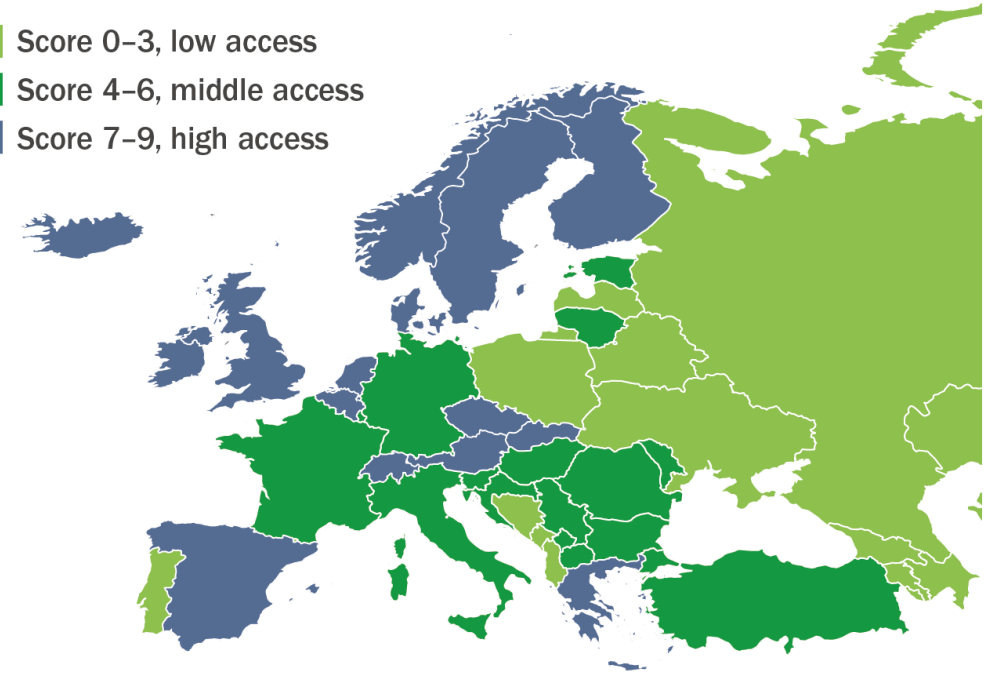
11–12%

Central & Eastern Europe**

1–5%

Level of access to biological treatments for RA across Europe³

- Score 0–3, low access
- Score 4–6, middle access
- Score 7–9, high access



This difference in access to biological medicines is largely due to general economic conditions²

Footnotes: *Based on values from 2009; **Based on values from 2011.

References: 1. Kobelt G, Kasteng F. Access to innovative treatments in rheumatoid arthritis in Europe. Available at: <http://bit.ly/Shamf8>. Accessed March 2020; 1. 2015 WHO Global Report: Preventing chronic diseases: a vital investment

2. Orlewska L, et al. *Med Sci Monit.* 2011;17:SR1-13; 3. Putrik P, et al. *Ann Rheum Dis.* 2014;73:198–206.

A lack of treatment choice has a detrimental impact on patient care¹

Rheumatoid Arthritis (RA)

- There are around 1.3 million Americans living with RA, many of whom require biological medicines²
- It is estimated that the US market for RA treatment will increase from 6.4 billion USD in 2013 to 9.3 billion USD by 2020³
- On average, patients with RA can expect to pay in excess of 3,000 USD annually in co-payments for biological medicines⁴



*"I use Enbrel. I couldn't walk without it, and when I lost my healthcare insurance it was \$1,800 per box. I sold my car to pay for the Enbrel"*⁵

Mika Collins, Michigan
Patient with RA

The availability of biosimilar medicines enhances competition, improves access to biological medicines, and contributes to the financial sustainability of healthcare systems⁵

References: 1. QuintilesIMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. 2016 ; 2. Best buy drugs. Consumer reports health. Using Biologics to Treat: Rheumatoid Arthritis. 2013. Available at: <http://bit.ly/2pZVXFT>. Accessed March 2020; 3. GBI Research. US Rheumatoid Arthritis Treatment Market Value to Reach \$9.3 Billion by 2020: Outlook and Implications. 2015. Available at: <http://bit.ly/2ryJBWJ>. Accessed March 2020; 4. Jennifer Freeman, MD. RA Costs: What are Payment Options for Treating Rheumatoid Arthritis? Available at: <https://www.rheumatoidarthritis.org/treatment/costs/paying-for-treatment/> Accessed October 2020. 5. Healthline: Rheumatoid arthritis patients bear heavy cost burden for biologic drugs. Available at: <http://bit.ly/2pQ63J9>. Accessed March 2020.

Biological medicines — the major social and economic challenges



Population ageing and the rising prevalence of **chronic conditions** is increasing the pressure on health systems^{1,2}



Global spend on pharmaceutical products continues to **increase**, and is expected to reach 1.4 trillion USD in the near future³



Biological medicines represent an **important but expensive** proportion of new drugs⁴



Payers seek to provide and preserve access to cutting-edge medicines, but also need to **ensure the long-term financial sustainability** of their healthcare system³



Access to biological medicines is not uniform, and is **often restricted** by their high cost^{4,5}



The **availability** of biosimilar medicines enhances competition, improves access to biological medicines, and contributes to the financial sustainability of healthcare systems⁶

References: 1. United Nations. World Aging Report. Available at: <http://bit.ly/1Y2LeF4>. Accessed March 2020; 2015 WHO Global Report: Preventing chronic diseases: a vital investment https://www.who.int/chp/chronic_disease_report/presentation/en/ Accessed October 2020; 2. CDC. Healthy Aging at a Glance 2011. Available at: <http://bit.ly/2ptzYJS>. Accessed March 2020; 3. IQVIA Global Medicine Spending and Usage Trends. Accessed October 2020; 4. QuintilesIMS Institute for Healthcare Informatics. Global Medicines Use in 2020: Outlook and Implications. 2015. Available at: <http://bit.ly/1H9Nze3>. Accessed March 2020; 5. Orlewska L, et al. *Med Sci Monit*. 2011;17:SR1-13; 6. EC. What you need to know about biosimilar medicinal products. Available at: <http://bit.ly/29AZtNM>. Accessed March 2020.

Chapter 3

Biosimilar medicines — rising to the cost challenge

Addressing the rising cost of biological medicines has become a priority for governments and healthcare systems around the globe.

Biosimilar medicines are providing more cost-effective biological treatments, but what are biosimilar medicines, and how do they meet this challenge?

In the absence of competition, biological medicines place a huge financial burden on global healthcare systems

- By introducing competition, the savings generated could be used to treat patients in need in Europe and the USA, who are currently denied access to biological medicines

The addressable* biosimilar medicines market in the US and the five largest European markets, 2016–2020:

US biosimilar savings totalled 2,2 billion USD in 2019 and 4,5, billion over the past 10 years***



Potential combined savings of **France, Germany, Italy, Spain and the UK: 50 billion USD****



Availability of biosimilar medicines offers an economic benefit to healthcare systems, thereby in part addressing the issue of new, innovative, high-priced medicines¹

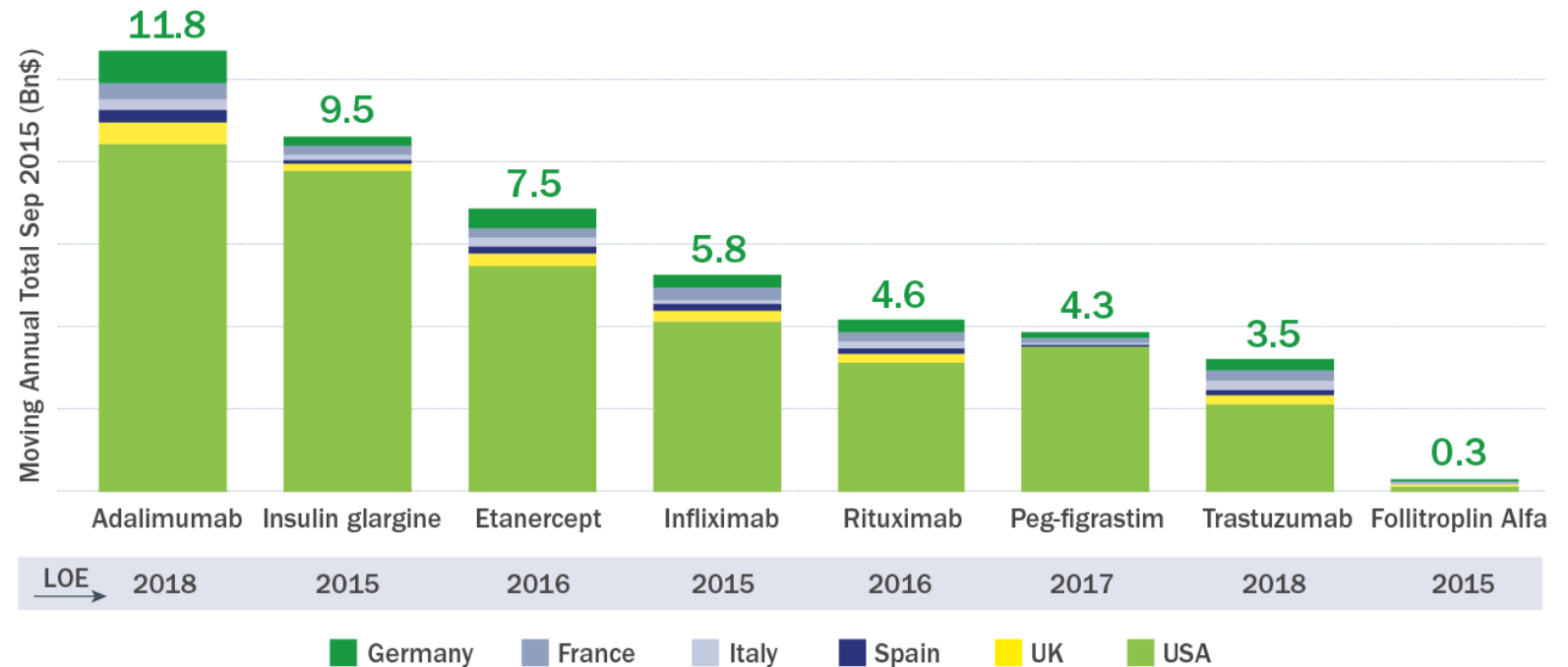
Footnotes: *Addressable market is calculated based on projected growth of originator market without biosimilar entry. Growth rate is based on historical growth and analogue analysis.

**Conversion rate: Conversion rate: 1 EUR = 1.091 USD.

References: QuintilesIMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. 2016. *** [IQVIA 2020 Report](#)

In many developed markets, eight prominent biological medicines came off patent between 2015 and 2020

- US and European* sales of key biological medicines have lost patent protection between 2015 and 2020:¹



The large number of biological medicines coming off patent presents a significant opportunity for the introduction of biosimilar medicines

Footnotes: *Values from five largest European markets. Conversion rate: 1 EUR = 1.091 USD.

Abbreviations: LOE, loss of exclusivity.

References: QuintilesIMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. 2016. Available at: <http://bit.ly/2es03mY>. Accessed July 2017.

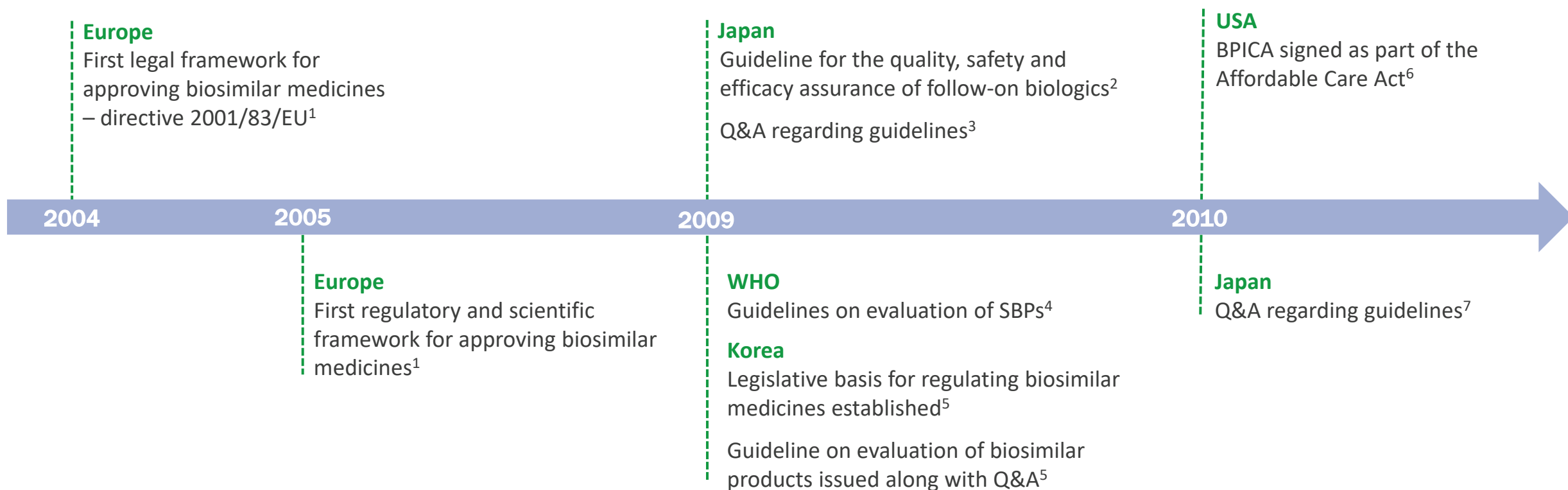
Europe was the first region in the world to develop a framework for biosimilar medicines

- A **biosimilar medicine** is a biological medicine that is developed to be **highly similar to an existing biological medicine** (the 'reference product')¹
- Biosimilar medicines can be marketed once all regulatory exclusivity and intellectual property right periods for the reference product have expired¹
- In 2004 and 2005, **Europe was the first region in the world** to develop a legal, regulatory, and scientific framework for approving biosimilar medicines²
- Within 10 years, the EU framework moved from a science-driven, conceptual approach to a science-driven, **knowledge-based approach**³
- Since 2006, EU-approved biosimilar medicines have already generated more than **2 billion** cumulated **patient treatment days of safe clinical experience**¹

Europe has pioneered the development, licensing, and marketing of biosimilar medicines²

References: 1. MIDAS MAT Q2 2020 data; rituximab and trastuzumab DDDs calculated via IQVIA Real World Data, Oncology Dynamics physician surveys on average cycles; pre-2009 analysis includes extrapolated treatment days for biosimilars launched between 2005 – 2008; country cohort includes 30 countries within Europe Economic Area; 2. EMA Biosimilar Guidelines. Available at <https://bit.ly/34iUkJY> : Accessed October 2020; 3. Weise M. Evolving landscape on data requirements to demonstrate biosimilarity – The EU perspective. Presented at 14th Biosimilar Medicines Group Conference, London 2016.

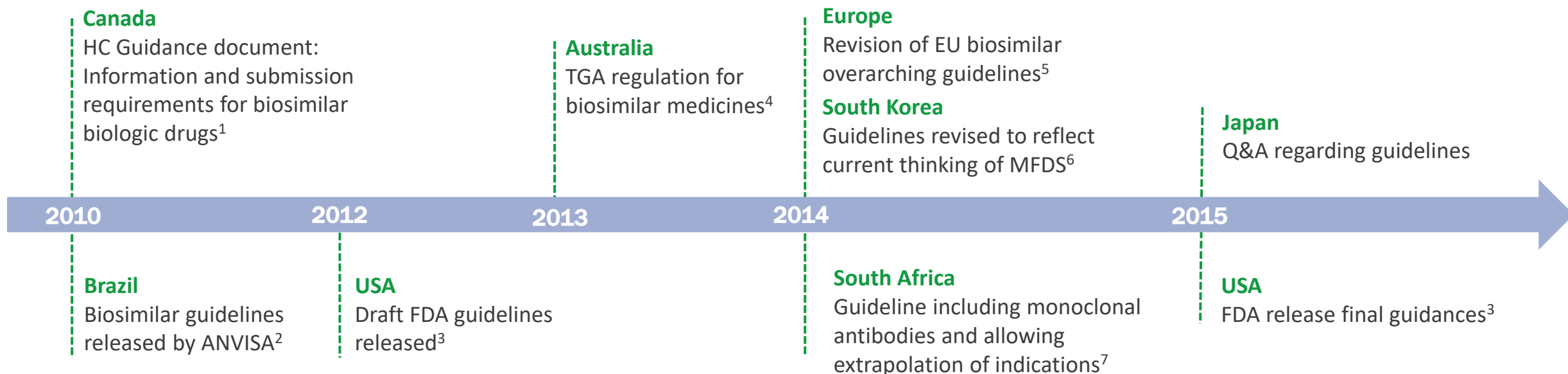
Scientific, regulatory, and legal frameworks have now been established around the world (1)



Abbreviations: BPICA, Biologics Price Competition and Innovation Act; EMA, European Medicines Agency; MHLW, Ministry of Health, Labour and Welfare; SBP, similar biotherapeutic products; WHO, World Health Organisation.

References: 1. EMA. [Biosimilar](#). Accessed March 2020; 2. MHLW. [Guideline for the Quality, Safety, and Efficacy Assurance of Follow-on Biologics](#). Accessed March 2020; 3. Yasuhiro Kishioka, Ph D [PMDA-Regulatory Framework for Biotherapeutic Products including Similar Biotherapeutic Products](#) Accessed October 2020; 4. WHO. [Guidelines on evaluation of similar biotherapeutic products \(SBPs\)](#). Accessed March 2020; 5. Park Y, et al. Presented at Biosimilars Medicines Group conference, London 2016; 6. [Biologics Price Competition and Innovation Act \(BPICA\)](#). Accessed October 2020; 7. [Yasuhiro Kishioka, Ph D PMDA-Regulatory Framework for Biotherapeutic Products including Similar Biotherapeutic Products](#). Accessed October 2020;

Scientific, regulatory, and legal frameworks have now been established around the world (2)

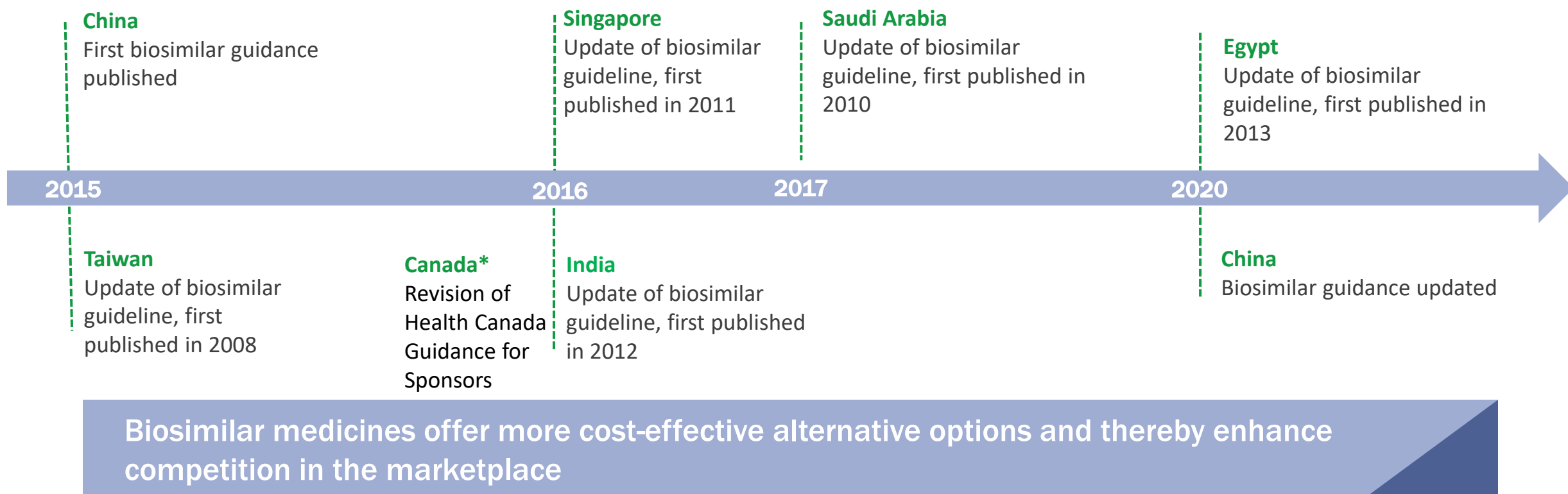


Biosimilar medicines offer more cost-effective alternative options and thereby enhance competition in the marketplace

Abbreviations: ANVISA, The Brazilian Health Regulatory Agency; EMA, European Medicines Agency; FDA, Food and Drug Administration; HC, Health Canada; JGA, Japan Generic Medicines Association MFDS, Ministry of Food and Drug Safety; MCCZA, Medicines Control Council of South Africa; TGA, Therapeutic Goods Administration.

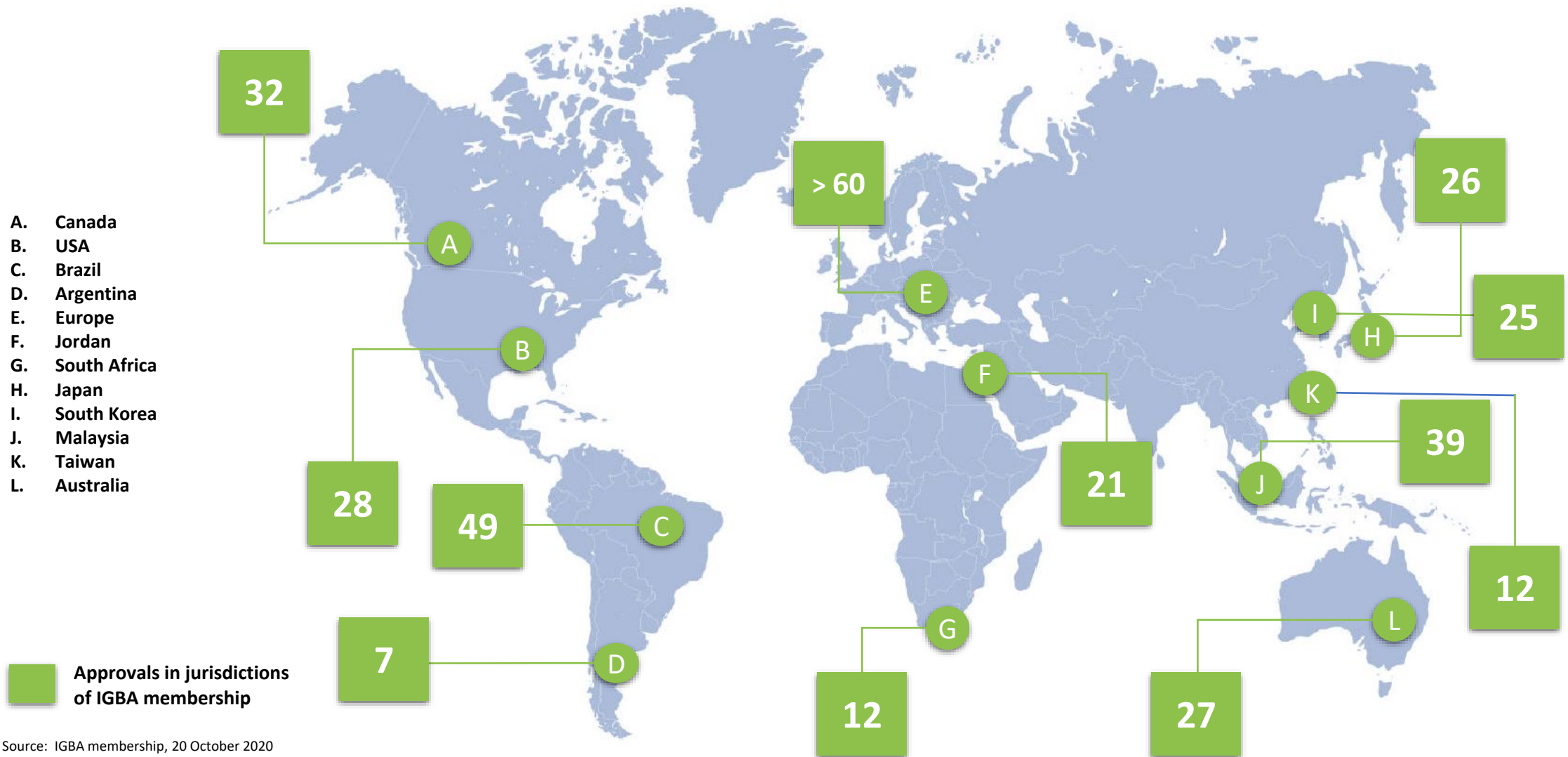
References: 1. Health Canada. Information and Submission Requirements for Biosimilar Biologic Drugs. Available at: <http://bit.ly/2tJYGZJ>. Accessed March 2020; 2. ANVISA. Resolution - RDC Nº 55. Available at: <http://bit.ly/2uPanhJ>. Accessed March 2020; 3. FDA. Biosimilars; 4. TGA. Regulation of biosimilar medicines. Available at: <http://bit.ly/2pquwpe>. Accessed March 2020; 5. EMA. Biosimilar. Available at: <http://bit.ly/1trteeH>. Accessed March 2020; 6. Park Y, *et al.* Presented at Biosimilars Medicines Group conference, London 2016; 7. MCCZA. Biosimilar medicines quality, non-clinical and clinical requirements;

Scientific, regulatory, and legal frameworks have now been established around the world (3)



* [Revision of Health Canada Guidance for Sponsors](#)

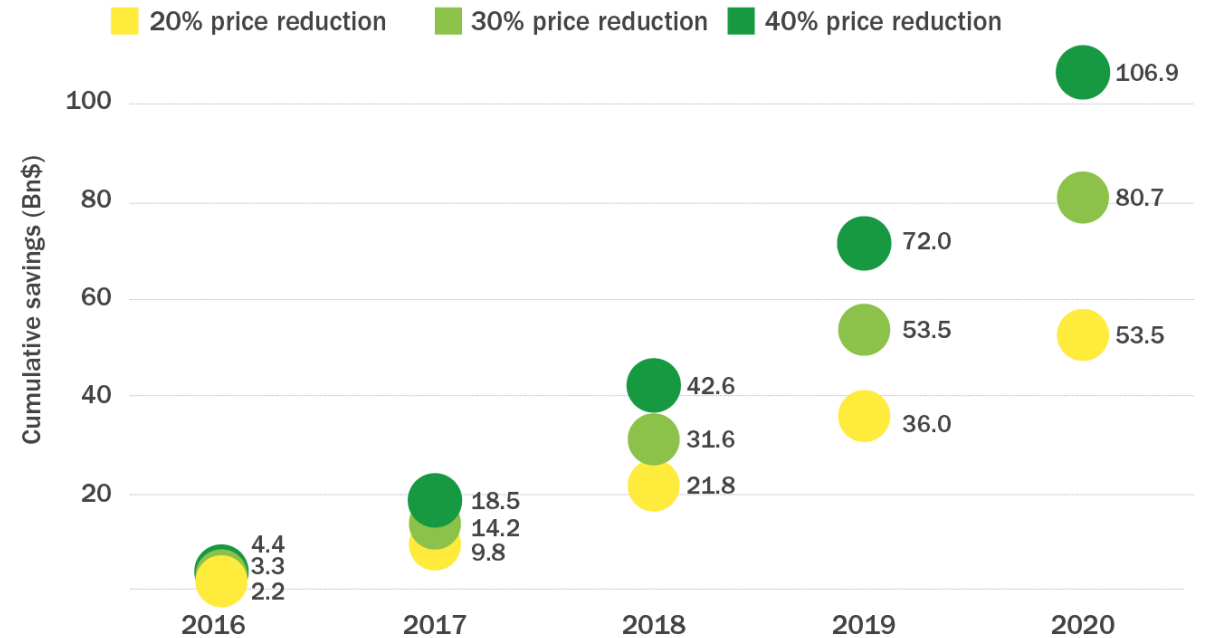
Building on the experience and success of over 300 biosimilar medicines approvals, covering over 10 therapeutic areas



Savings produced by biosimilar medicines contribute to the sustainability of healthcare systems

- Biosimilar medicines could produce cumulative savings of nearly 107 billion USD in Europe and the US combined, between 2015 and 2020*¹

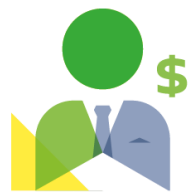
Potential cumulative savings from eight key biosimilar medicines in France, Germany, Italy, Spain, the UK, and the US¹



Biosimilar medicines have already delivered savings of around 1.6 billion USD in the five largest European markets alone²

Footnotes: *Savings potential in five largest European markets plus US biosimilar accessible market dependent on change in price per treatment day. The accessible market analysis is based on adalimumab, insulin glargine, etanercept, infliximab, rituximab, peg-filgrastim, trastuzumab, and follitropin alpha. Savings potential in biosimilar accessible market at different price levels is calculated based on extrapolated size of the originator market between 2016 and 2020, and historic CAGR and analogues. Accumulation of savings potential between 2016–2020 is shown. Conversion rate: 1 EUR = 1.091 USD.

References: 1. QuintilesIMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. 2016.; 2. Lynch C. *Pharma Horizon* 2016;1:2–3.



Globally, biosimilar medicines have the potential to offer healthcare systems huge savings for the same outcomes



Canada - \$94 million CAD

Combined savings from use of etanercept, filgrastim, infliximab and insulin glargine biosimilars in 2018⁵

U.S.A - 2,2 billion USD (2019)

Biosimilar savings totalled 2,2 billion USD in 2019 and 4,5 billion over the past 10 years⁴

Europe –15 billion EUR

between 2016 and 2020

based on a 30% price reduction across eight key reference products, driven by biosimilar competition¹

Japan – 46 billion JPY

between 2017 and 2019 with CAGR 61%²

South Africa – 6.4 million USD

(84.5 million Rand) per annum

A 50% price reduction following the introduction of the biosimilar trastuzumab would translate into 670 more patients being treated (2016)³

Biosimilar medicines represent a cost-effective alternative to the reference products

References: 1. QuintilesIMS. Delivering on the potential of biosimilar medicines; 2. Ministry of Health, Labour and Welfare Japan; 3. Generic & Biosimilar Medicines Southern Africa Available at: <https://gbmsa.org/>. Accessed October 2020; 4. IQVIA 2020 Report; 5. [Biologics in Canada. Part 2: Biosimilar Savings, 2018](#). Accessed October 2020.

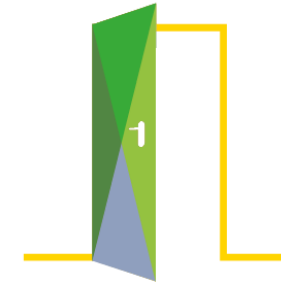
Summary: Biosimilar medicines — rising to the cost challenge



In the absence of competition, biological medicines place a **huge financial burden** on global healthcare systems¹



In many developed markets, key biological medicines are **coming off patent**¹



Patent expiry presents a **significant opportunity** for the introduction of biosimilar medicines¹



Around the globe, biosimilar medicines are being introduced, **enhancing competition** in the marketplace¹



In the five largest European markets alone, biosimilar medicines have saved **1.6 billion USD**²



The **potential savings** offered by biosimilar medicines could help support the **long-term sustainability** of healthcare systems¹

References: 1. QuintilesIMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. 2016.

2. Lynch C. *Pharma Horizon* 2016;1:2–3.

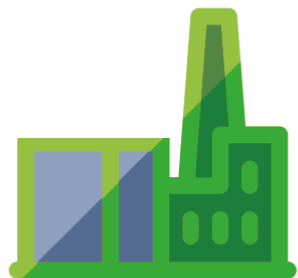
Chapter 4

Biosimilar medicines — a commitment to scientific excellence

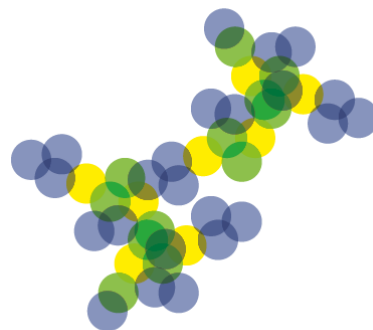
With biosimilar medicines, patients and healthcare providers benefit from high quality and efficacious therapeutic alternatives.

But how are biosimilar medicines developed, and how is their efficacy and safety ensured?

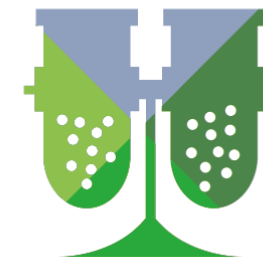
Biological medicines display an inherent degree of minor variability (microheterogeneity), which is tightly controlled¹



Biological medicines are made in living organisms and purified through **complex manufacturing processes**²



Biological medicines consist of relatively large and often highly **complex molecular entities**³



Any biological medicine will display **microheterogeneity**, even **between different batches of the same product**. This normal feature is tightly controlled³

The heterogeneity of biological medicines not only reflects the natural variation of these molecules, but also the variability of the production process^{1,3}

Throughout their lifecycle, biological medicines undergo changes to their manufacturing process^{1,2}

Changes in the manufacturing process of a biological medicine are very common and can include:³

- Upscaling the process
- Yield improvement
- New purification methods
- Change of cell line
- Change of manufacturing site

Following any change, comparability testing must be performed to ensure that the safety and efficacy is maintained across the different versions of the same biological medicine⁴

Number of approved manufacturing changes for monoclonal antibodies according to risk category

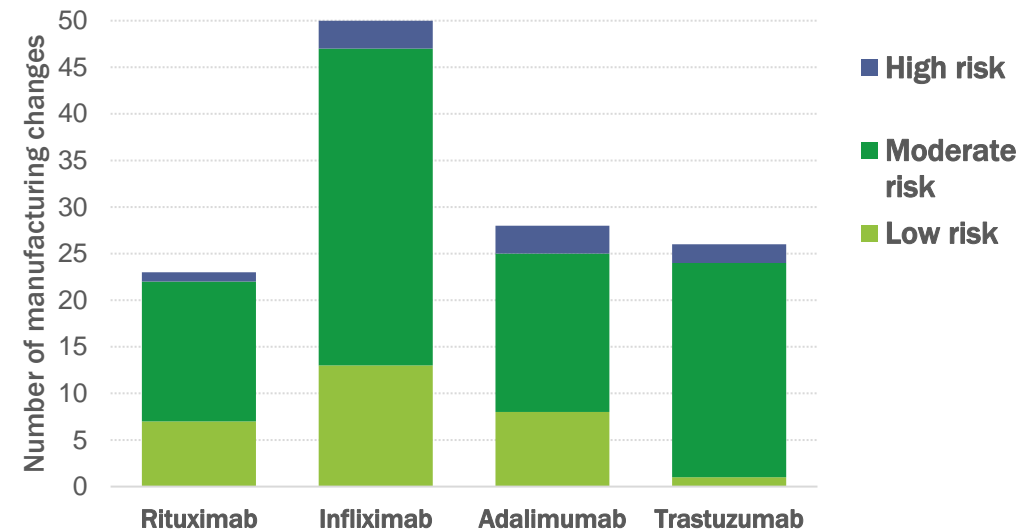
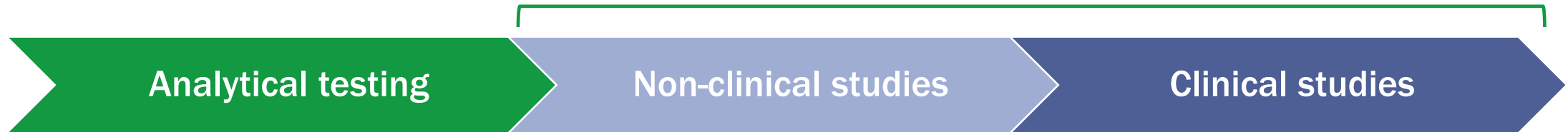


Figure adapted from Vezér et al. 2016²

The acceptable variability of the reference biological medicine over its lifecycle designates the goalposts for biosimilar product development^{5,6}

Changes to manufacturing of biological medicines are approved following a stepwise comparability exercise¹

Comparability bridging studies and adherence to specific pharmacovigilance regulations may be required, depending on the nature of the changes made to the manufacturing process²

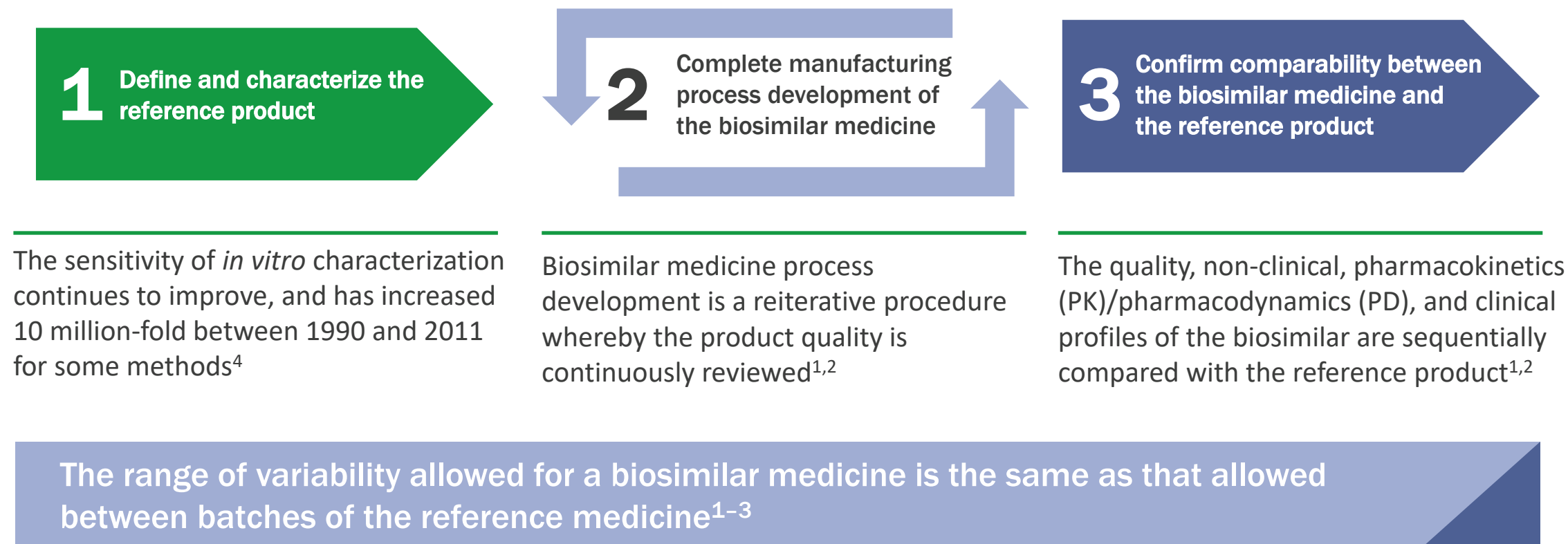


- Originator manufacturers rely almost exclusively on analytics and extrapolation of indications to obtain approval for the process changes^{3,4}
- Regulators have over two decades of experience in evaluating and approving these changes, based on comparability exercises in line with internationally agreed standards⁵
- When comparability has been demonstrated, the new version of the product can be introduced to the market without informing prescribers, pharmacists, or patients⁶

The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process of an already licensed biological medicine^{7,8}

References: 1. Chirino AJ, Mire-Sluis A. *Nat Biotechnol* 2004;22:1383–91; 2. European Medicines Agency and Heads of Medicines Agency. [EMA/168402/2014](#). Accessed March 2020; 3. Cornes P, Muenzberg M. *Pharma Horizon* 2016;1:30–34; 4. Weise M, et al. *Blood* 2014;124:3191–6; 5. McCamish M, Woollett G. *Clin Pharmacol Ther.* 2013;93:315–7; 6. Kurki P, et al. *BioDrugs* 2017 [Epub ahead of print]; 7. Weise M, et al. *Blood* 2012;120:5111–7; 8. EMA. [Guideline on similar biological medicinal products](#). Accessed March 2020.

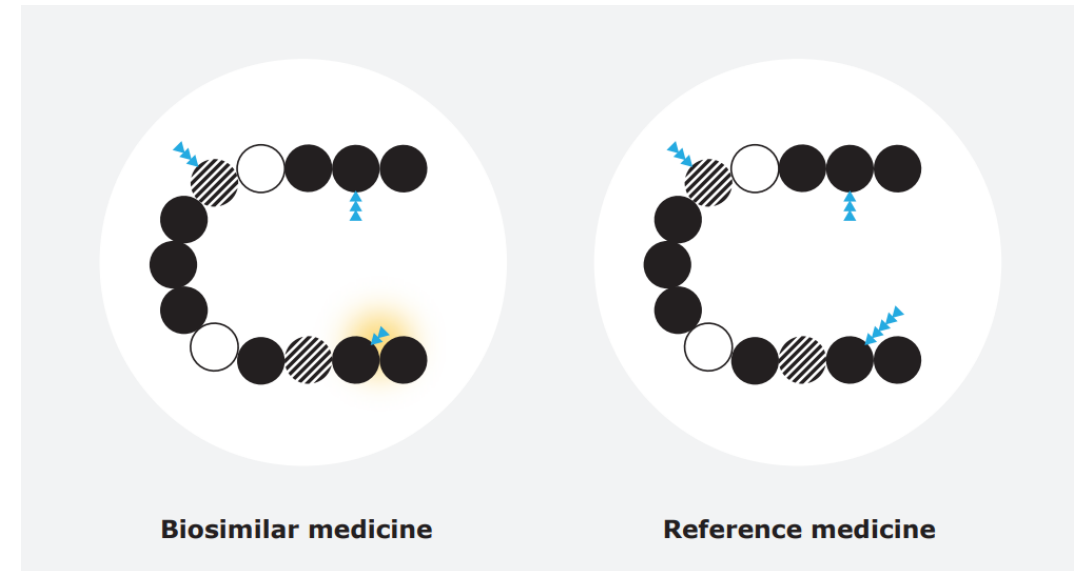
Biosimilar medicine development is target-orientated, comparative, and follows a stepwise approach¹⁻³



References: 1. FDA. Available at <https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval> Accessed Sept. 2020; 2. EMA. [Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues](#). Accessed March 2020; 3. EMA. [Guideline on similar biological medicinal products](#). Accessed March 2020; 4. Mire-Sluis: [The regulatory implications of the ever increasing power of mass spectrometry and its role in the analyses of biotechnology products-where do we draw the line?](#) . Accessed March 2020.

Example of variability between a biosimilar and the reference medicine

- Variability (yellow shadow) between a biosimilar and the reference medicine is comparable to what may occur between different batches of the same biological medicine
- Minor variability, e.g. in glycosylation (represented by small blue triangles) may be allowed, while the protein's amino acid sequence (circles) and biological activity are the same



Quality comparability establishes highly similar physiochemical properties and biological activity^{1,2}

- Analytical and functional comparability studies are the foundation of biosimilar medicine development^{1,2}
- Analytical testing is a more sensitive means of detecting differences than randomized clinical trials^{1,2}
- The biosimilar medicine and the reference product must be highly similar at a molecular level^{1,3}
 - The primary structures (amino acid sequences) must be identical
 - Higher-level structures must be indistinguishable
- Impurities, biological activity, and post-translational modifications are also compared^{1,2}
- The degree of quality similarity will determine the scope and the breadth of the required non-clinical and clinical data to rule out differences in clinical performance^{1,2}



Non-clinical comparability establishes that functionally, the biosimilar medicine and the reference product are similar^{1,2}

- The biosimilar medicine must display highly similar functionality to the reference biological medicine
- Multiple *in vitro* (and in exceptional cases, *in vivo*) assays are used to measure the binding of the biosimilar medicine to target antigens or receptors



PK/PD comparability establishes that the biodistribution of the biosimilar and the reference product are similar

- Comparative pharmacokinetic (PK) and/or pharmacodynamic (PD) studies in humans are designed to further support comparability data, or to detect potential differences between the biosimilar medicine and the reference product¹
- The PK study is a major gatekeeper in the clinical biosimilarity exercise
- In certain cases, the comparative analytical, non-clinical, and human PK/PD (clinical immunogenicity) studies may be sufficient to definitively confirm biosimilarity to the reference product^{1,2}



Clinical comparability complements and confirms the comparability demonstrated at the previous steps

- Tailored clinical comparability [where appropriate] **confirms** that the structural concordance **translates into clinical performance**, and is designed to rule out clinically relevant differences in safety or efficacy¹
- Comparative clinical trials, where needed, are performed in a scientifically justified 'clinical model' that is sensitive to small differences²⁻⁶
- Clinical safety (including immunogenicity) is important throughout the clinical development program. Safety data is captured during the initial pharmacokinetic (PK) and/or pharmacodynamic (PD) studies, and the comparative clinical study, where required²⁻⁶



The biosimilar medicine is only approved if there are no clinically meaningful differences from the reference product

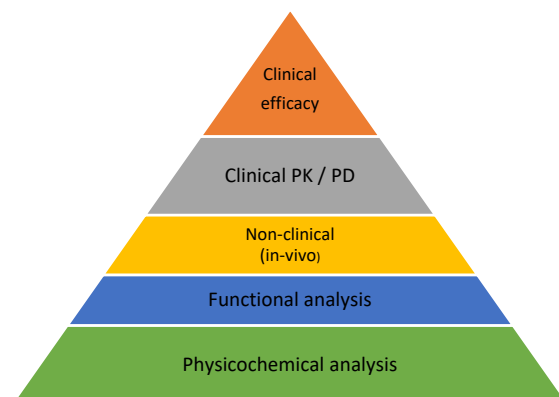
How can we tailor biosimilar development?

- Continuously apply evolving regulatory sciences;
- Maintain robust regulatory standards that have resulted in an impeccable track record of biosimilar medicines;
- Adapting the biosimilar framework with the latest knowledge is reflected in objectives of EMA¹, MHRA², WHO³
 - e.g. EMA objective: “Further develop the biosimilar framework, adapting the clinical part of the development to the latest scientific knowledge concerning the comparability assessment”¹.
 - MHRA Objective: “Develop and publish guidance on a new innovative UK licensing procedure for biosimilar products to operate from 1 January 2021 to reduce the burden on clinical trial data generation”².

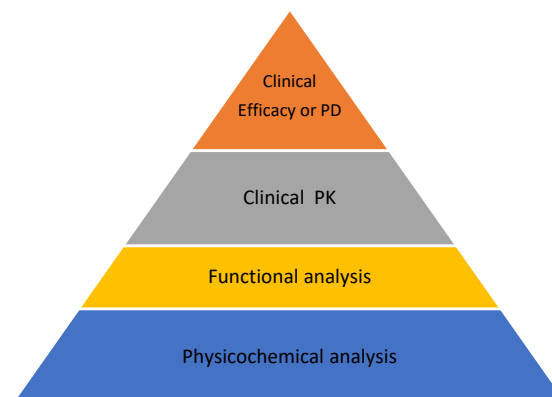


1. [EMA Regulatory Science to 2025, EMA/110706/2020](#), published 2020, accessed 16 April 2020
2. MHRA Business plan 2020-21, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/889864/MHRA_Business_Plan_2020_to_2021.pdf, accessed 17 June 2020; [MHRA draft biosimilar guideline](#), accessed October 2020
3. [WHO - Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 21 to 25 October 2019](#), accessed 21 April 2020; see also Backup-slide “WHO Discussion)

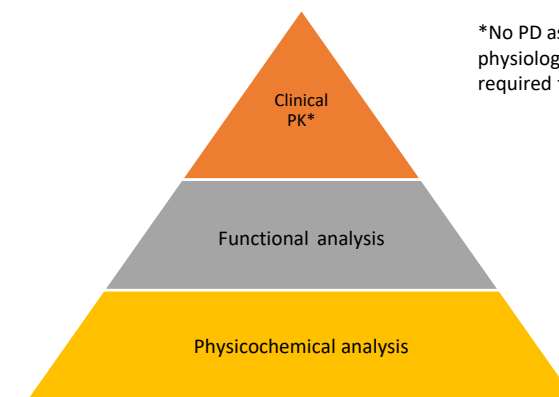
Evolution of biosimilar development options for therapeutic proteins



**Biosimilar development
as setup 2004**



**Today's accepted
regulatory options**



**Proposed additional option
of tailored development**

*No PD as early measure of physiological response required for clinical efficacy

5 step approach	4 step approach	3 step approach
1. Physicochemical analysis	1. Physicochemical analysis	1. Physicochemical analysis
2. Functional analysis	2. Functional analysis	2. Functional analysis
3. Non-clinical (in-vivo)	<i>An in vivo animal study is usually not considered necessary</i>	
4. Clinical PK/PD	3. Clinical PK	3. Clinical PK (Additional confirmation of immunogenicity/safety only if needed)
5. Comparative clinical efficacy	4. Comparative clinical efficacy or, instead clinical PD with sufficiently qualified PD marker	Confirmation of biosimilar efficacy provided by functional analysis and clinical PK

Current resources



Current Opinion | [Open Access](#) | Published: 06 August 2019

An Efficient Development Paradigm for Biosimilars

[Christopher J. Webster](#), [Anny C. Wong](#) & [Gillian R. Woollett](#)

[BioDrugs](#) **33**, 603–611(2019) | [Cite this article](#)

3111 Accesses | **4** Altmetric | [Metrics](#)

Abstract

The current development paradigm for biosimilars required by regulators in highly regulated jurisdictions is derived from the development of novel drugs and is unnecessarily burdensome and inefficient. It requires the accumulation of data from analytical, nonclinical (including in vivo studies in some jurisdictions), and clinical studies (including powered efficacy studies in most cases); this paradigm is known as ‘totality of evidence’ (ToE) and does not admit a conclusion of biosimilarity from analytical data alone. The record of biosimilar approvals in these jurisdictions shows that no biosimilar candidate that has been found highly similar to its reference in analytical and pharmacokinetic studies has failed to be approved. We propose a new paradigm (‘confirmation of sufficient likeness’, CSL) that emphasizes the demonstration of analytical resemblance between the biosimilar candidate and its reference, and permits the conclusion of biosimilarity upon this basis. CSL does not entail bridging studies between reference products, in vivo nonclinical studies, or powered efficacy studies and is, therefore, substantially more efficient than ToE while maintaining equivalent scientific rigor. Such efficiency will contribute to the attractiveness as well as the sustainability of biosimilars as a therapeutic modality.

Review Article | [Open Access](#) | Published: 20 September 2019

Evolution of the EU Biosimilar Framework: Past and Future

[Elena Wolff-Holz](#) , [Klara Tittso](#), [Camille Vlemmings](#) & [Martina Weise](#)

[BioDrugs](#) **33**, 621–634(2019) | [Cite this article](#)

5425 Accesses | **5** Citations | **1** Altmetric | [Metrics](#)

Abstract

The approval of biosimilars in the EU follows a comprehensive scientific assessment based on stringent regulatory standards. While the initial approach to biosimilars was understandably cautious and conservative in that uncharted territory to protect patients’ safety, the analytical and scientific progress and accumulated experience with biosimilars continues to reshape regulatory requirements, generally leading to a reduced burden of clinical trials. This trend is expected to continue, for example, by increasingly employing pharmacodynamic endpoints and biomarkers, but much work remains to make this happen, especially for complex molecules with several or unknown mechanisms of action. We reviewed the available guidance and European Public Assessment Reports (EPARs) of biosimilars approved in the EU via the centralised procedure. This review focuses on the nature and extent of clinical confirmation of biosimilarity considered necessary in addition to analytical and functional data. Cases with conflicting results from different parts of the comparability exercise are discussed, with the aim of identifying whether certain elements of the comparability exercise are more important than others in determining biosimilarity. Taken together, analytical and functional comparison is the foundation of any biosimilar development. In addition, pharmacokinetic similarity is an indispensable prerequisite for any biosimilar approval, so careful planning on behalf of the applicant is mandated to avoid potential failure of such studies, for example, because of large interindividual variability, underpowered trial designs or other methodological causes. Comparative pharmacokinetic studies are a basic requirement for biosimilar development and are usually more sensitive than clinical efficacy trials when detecting potential product-related differences. This may explain why a demonstration of equivalent efficacy could not overrule a finding of dissimilar pharmacokinetic profiles in two cases of biosimilar pegfilgrastim. However, the outcome of efficacy trials depends not only on drug exposure but also on proper pharmacological action of the biological substance in vivo. Therefore, the objectives of both types of studies differ. Efficacy trials should usually be designed as equivalence trials to ensure that the efficacy of the biosimilar is neither decreased nor increased compared with the reference product. However, some remaining uncertainty regarding potentially increased efficacy of the biosimilar may be acceptable in exceptional cases, provided that the data from other parts of the comparability exercise clearly support a conclusion of biosimilarity and safety is assured. In contrast, uncertainties regarding potentially inferior efficacy of the biosimilar may not be acceptable at all. We conclude that the EU biosimilar regulatory framework is robust and able to adapt to advancing knowledge and experience and to strike a balance between regulatory standards, patient safety and feasibility of biosimilar development.

Review Article | [Open Access](#) | Published: 07 April 2020

The Path Towards a Tailored Clinical Biosimilar Development

[Martin Schiestl](#) , [Gopinath Ranganna](#), [Keith Watson](#), [Byoungjin Jung](#), [Karsten Roth](#), [Björn Capsius](#), [Michael Trieb](#), [Peter Bias](#) & [Julie Maréchal-Jamili](#)

[BioDrugs](#) **34**, 297–306(2020) | [Cite this article](#)

3245 Accesses | **3** Altmetric | [Metrics](#)

Abstract

Since the first approval of a biosimilar medicinal product in 2006, scientific understanding of the features and development of biosimilar medicines has accumulated. This review scrutinizes public information on development programs and the contribution of the clinical studies for biosimilar approval in the European Union (EU) and/or the United States (US) until November 2019. The retrospective evaluation of the programs that eventually obtained marketing authorization and/or licensure revealed that in 95% (36 out of 38) of all programs, the comparative clinical efficacy studies confirmed similarity. In the remaining 5% (2 out of 38), despite meeting efficacy outcomes, the biosimilar candidates exhibited clinical differences in immunogenicity that required changes to the manufacturing process and additional clinical studies to enable biosimilar approval. Both instances of clinical differences in immunogenicity occurred prior to 2010, and the recurrence of these cases is unlikely today due to state-of-the-art assays and improved control of process-related impurities. Biosimilar candidates that were neither approved in the EU nor in the US were not approved due to reasons other than clinical confirmation of efficacy. This review of the development history of biosimilars allows the proposal of a more efficient and expedited biosimilar development without the routine need for comparative clinical efficacy and/or pharmacodynamic studies and without any compromise in quality, safety, or efficacy. This proposal is scientifically valid, consistent with regulation of all biologics, and maintains robust regulatory standards in the assessment of biosimilar candidates. Note: The findings and conclusion of this paper are limited to biosimilar products developed against the regulatory standards in the EU and the US.

Approval of all indications of biosimilar medicines is based on the totality of evidence

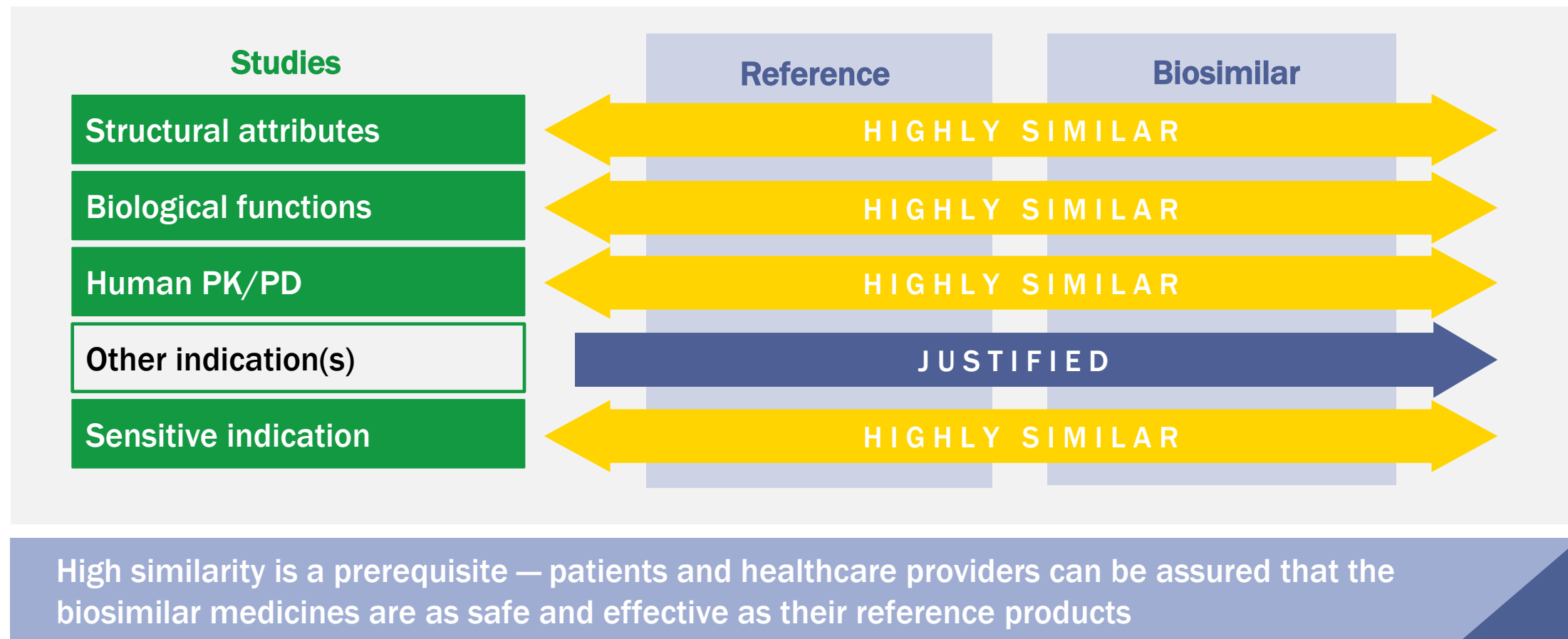
- A biosimilar may be approved for one or more indications for which its reference product is licensed, but for which there was no head-to-head clinical comparison
- These indications are individually evaluated based on sound science
- The approvals are based on extrapolation of data, which is an established regulatory and scientific principle. This approach is also used by regulators in the approval of changes to the reference product manufacturing process, and in pharmaceutical development of all biological medicines



While no one piece of information is sufficient to demonstrate biosimilarity, when taken together, the evidence forms a comprehensive picture in each and every approved condition

Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise¹

Similarity space



Abbreviations: PK, pharmacokinetic; PD, pharmacodynamic

References: 1. Windisch J. The Science of Biosimilars. Sandoz Training Workshop, London, April 2015 [Data on file].

Figure adapted from Windisch J.

Biosimilar medicine development requires significant investment and state-of-the-art technologies

- **Significant investment**, costing 100–300 million USD and taking up to eight years to develop, is needed to achieve a successful similarity exercise ¹
- **Highly sophisticated analytical tools** allow for a detailed characterization of the biosimilar medicine and the reference product^{3,4}
- Due to technological advances, biosimilar medicines are usually **better characterized** than their reference products, which were characterized at the time of their initial approval 10 or 20 years earlier^{5,6}
- Biosimilar medicines are manufactured, distributed, and monitored according to **the same standards as other medicines**, and regulatory authorities perform periodic inspections of the manufacturing sites²

Patients and healthcare providers can trust biosimilar medicines, as they are approved according to the same high standards and by the same regulators as all other medicines

Summary: Biosimilar medicines — a commitment to scientific excellence



Biological medicines display an **inherent degree of minor variability**, which is tightly controlled¹



Throughout their lifecycle, biological medicines **undergo manufacturing changes**²



Tailored clinical comparability, [where appropriate] complements and confirms the comparability demonstrated at the previous steps³



Scientific principles for **establishing biosimilarity** are the **same as** those for **demonstrating comparability**⁴



Stepwise comparability exercises ensure there are no clinically meaningful differences between the biosimilar and the reference product^{5,6}



Development of biosimilars requires **significant investment** and state-of-the-art technologies⁴



WHO, EMA/EU, FDA/USA, HC/Canada, PMDA/Japan, TGA/Australia and others, all **require extensive evidence** that a biosimilar is highly similar to a reference product, and that there are no meaningful differences⁷

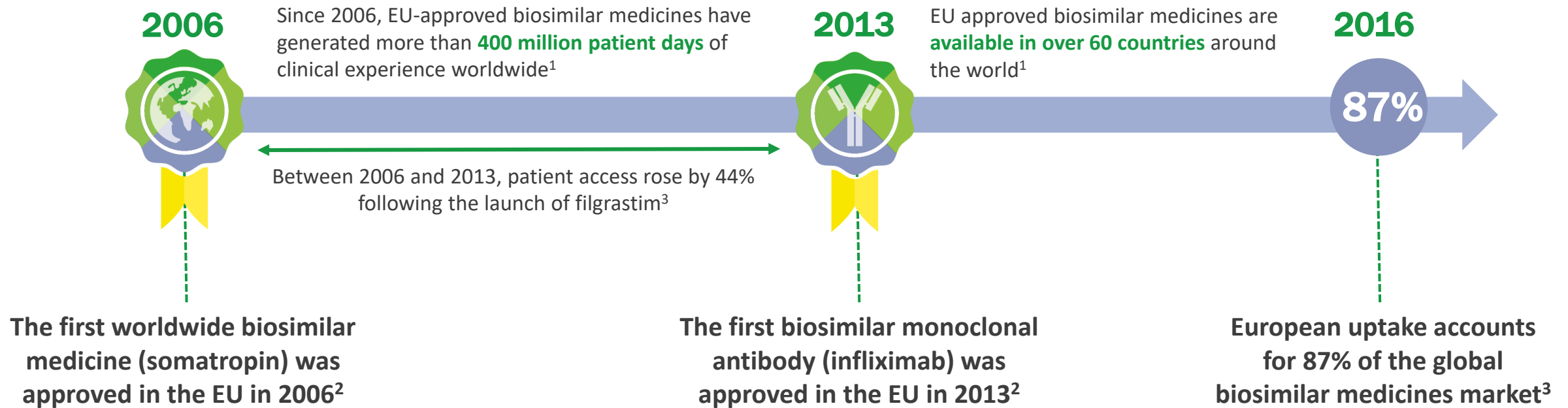
References: 1. Schneider C. *Ann Rheum Dis* 2013;72:315–8; 2. McCamish M, Woollett G. *Clin Pharmacol Ther* 2013;93:315–7; 3. Gudat U. *Pharma Horizon* 2016;1:35–38 4. Biosimilar Medicines Group handbook 2016; 5. FDA. Available at <https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval> Accessed September 2020; 6. EMA. [Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues](#). Accessed March 2020; 7. Weise M, et al. *Blood* 2014;124:3191–6.

Chapter 5

The benefits of biosimilar medicines

Biosimilar medicines have demonstrated similarity with reference biologicals in terms of structure, function, safety and efficacy, but what are their benefits?

Europe is a pioneer of biosimilar medicines and has the largest clinical experience



There is nearly 15 years' worth of real-world evidence demonstrating the benefits that biosimilar medicines offer to patients and healthcare systems¹

Biosimilar medicines offer benefits to patients, healthcare professionals, and payers¹



Patients^{1,2}

- More patients gain access to biologic treatments, and at earlier stages of the therapy cycle
- Improved access drives better outcomes for patients



Healthcare professionals^{1,2}

- Access to a wider spectrum of treatment options
- Development of value-added services for patients via benefit-sharing models
- Reduced pressure on the prescribers' budget



Payers^{1,3}

- Creation of a more competitive market with a broader range of cost-effective treatment options
- Generation of savings across healthcare systems, supporting their sustainability

Biosimilar medicines increase the treatment options available to patients, healthcare professionals, and payers¹



Availability of biosimilar medicines increases patient access to biologic therapies



- According to WHO, biosimilar medicines provide a good opportunity to **expand access** and to become a **game-changer** for access to medicines for certain complex conditions¹
- In countries with low initial usage or availability of biological products, the launch of biosimilar medicines appears to **lead to increased access**^{2*}

Product/Country	Treatment days per capita (Year before biosimilar entrance)	Volume change of treatment days following introduction of biosimilar
HGH		
Romania	0.02	152%
Czech Rep	0.08	68%
Poland	0.04	82%
G-CSF		
Romania	0.02	2542%
Bulgaria	0.02	581%
Slovakia	0.05	509%
Anti-TNF		
Bulgaria	0.10	190%
Czech Rep	0.24	59%
Slovakia	0.49	93%

Biosimilar medicines allow access to highly innovative treatments

Abbreviations: G-CSF, granulocyte-colony stimulating factor; HGH, human growth hormone; TNF, tissue necrosis factor; WHO, World Health Organisation.

Reference: 1. WHO. [WHO to begin pilot prequalification of biosimilars for cancer treatment](#).. Accessed March 2020; 2. QuintilesIMS. [The impact of biosimilar competition on price, volume and market share - update 2017](#). Accessed March 2020.



Swedish launch of biosimilar filgrastim led to improved patient access



Initiation of treatment with filgrastim reference medicine required the formal approval of **three physicians**



Launch of filgrastim biosimilar

Following the launch of biosimilar filgrastim:

- Treatment costs for granulocyte colony-stimulating factor (G-CSF) treatment of febrile neutropenia were reduced
- Regional authorities relaxed restrictions on the prescribing of G-CSF treatments
- Prescriptions do not need additional authorization

Driven by the use of biosimilar filgrastim, clinical use of G-CSF increased five fold in the Southern Healthcare region



Biosimilar medicines allow access for more patients, and at earlier stages in the treatment cycle

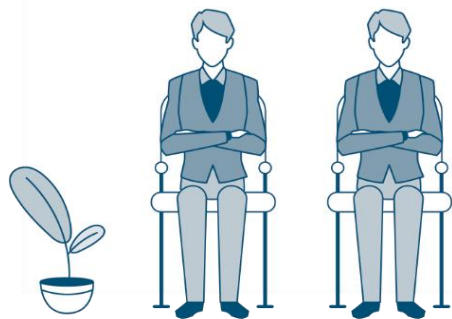


In Bavaria¹, biosimilar competition led to rheumatic patients receive faster access to biological therapy²

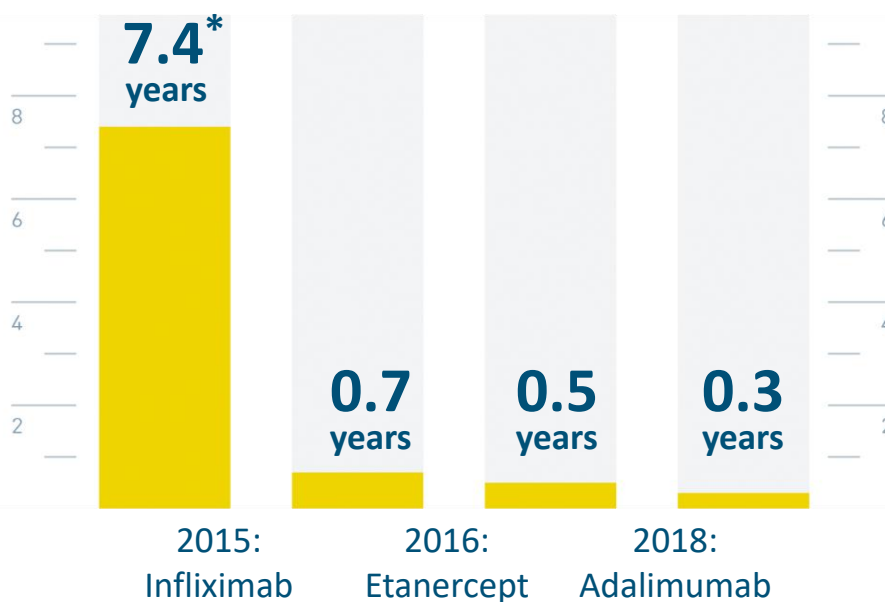


Waiting time for
biologic therapy

In years



Market launch of Biosimilars against
rheumatism:



Duration of therapy with a
synthetic medicine



*until 2015, exclusively synthetic standardised therapy or original biological agents were available³

Biosimilar infliximab, etanercept and adalimumab translated in a significant reduction of the duration of synthetic medicines therapy for rheumatic patients from 7,4 years to 4 months²



Biosimilar medicines make biotherapeutics a cost-effective option, broadening treatment choice



- Biosimilar medicines are often able to reach an acceptable incremental cost-effectiveness ratio (ICER) in situations where reference products are not¹
- In the UK, biosimilar medicines have introduced new treatment options for ankylosing spondylitis, and for treatment-induced anaemia in patients with cancer^{1,2}

Ankylosing spondylitis



According to 2008 UK National Institute for Health and Clinical Excellence (NICE) guidelines, **infliximab (originator) should not be used at all**

2015 NICE guidance **recommends use of infliximab biosimilar medicines** in adults with non-radiographic axial spondyloarthritis

Cancer-treatment-induced anemia



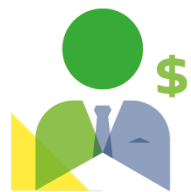
According to 2008 NICE guidelines, **epoetin** is clinically effective for cancer treatment-induced anaemia, but **is not cost-effective**

According to 2014 NICE guidelines, **epoetin is both clinically effective and cost-effective**

Biosimilar medicines empower physicians, providing cost-effective treatment options¹

Abbreviations: NICE, The National Institute for Health and Care Excellence.

References: 1. Simon-Kucher & Partners. [Payers' price & market access policies supporting a sustainable biosimilar medicines market](#). Accessed March 2020; 2. [NICE](#). Accessed March 2020.



Globally, biosimilar medicines have the potential to offer healthcare systems huge savings for the same outcomes



Canada - \$94 million CAD

Combined savings from use of etanercept, filgrastim, infliximab and insulin glargine biosimilars in 2018⁵

U.S.A - 2,2 billion USD (2019)

Biosimilar savings totalled 2,2 billion USD in 2019 and 4,5 billion over the past 10 years⁴

Europe –15 billion EUR

between 2016 and 2020

based on a 30% price reduction across eight key reference products, driven by biosimilar competition¹

Japan – 46 billion JPY

between 2017 and 2019 with CAGR 61%²

South Africa – 6.4 million USD

(84.5 million Rand) per annum

A 50% price reduction following the introduction of the biosimilar trastuzumab would translate into 670 more patients being treated (2016)³

Biosimilar medicines represent a cost-effective alternative to the reference products

References: 1. QuintilesIMS. Delivering on the potential of biosimilar medicines; 2. Ministry of Health, Labour and Welfare Japan; 3. Generic & Biosimilar Medicines Southern Africa Available at: <https://gbmsa.org/>. Accessed October 2020; 4. IQVIA 2020 Report; 5. [Biologics in Canada. Part 2: Biosimilar Savings, 2018](#). Accessed October 2020.

Sharing the benefits of clinical use of biosimilar medicines

- In Germany, the medical association KV Westfalen-Lippe, and the statutory health insurance provider Barmer GEK, agreed a contract geared towards **improving care of patients** with inflammatory bowel disease
- Under the contract, patients with ulcerative colitis or Crohn's disease will be primarily treated with **infliximab biosimilars**
- **Absolute savings** generated from prescribing infliximab biosimilar will be equally split between the treating physician and Barmer GEK

Benefit sharing models help physicians to see the tangible benefits from generated savings due to more cost-effective prescribing, leading to increased biosimilar medicine uptake and patient care

Summary: The benefits of biosimilar medicines



The use of biosimilar medicines has been **successfully implemented** within Europe for over a decade¹



Benefit sharing models involve all stakeholders and help to **demonstrate the cost benefits** associated with biosimilar medicine adoption³

Biosimilar medicines improve the treatment options available to:²⁻⁴



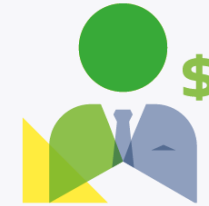
Patients

Biosimilar medicines allow access for more patients, and at earlier stages in the treatment cycle



Healthcare professionals

Biosimilar medicines empower physicians, providing cost-effective treatment options



Payers

Globally, biosimilar medicines introduce competition by representing a cost-effective alternative to reference biologicals, and generate savings

Biosimilar medicine policies are necessary to drive uptake and provide the benefits of biosimilar use

References: 1. Biosimilar Medicines Group. [Factsheet on Biosimilar Medicines 2016](#). Accessed March 2020; 2. Medicines for Europe. [Biosimilar Medicines Handbook 2016](#). Accessed March 2020; 3. Simon-Kucher & Partners. [Payers' price & market access policies supporting a sustainable biosimilar medicines market](#). Accessed March 2020; 4. Cornes P, Muenzberg M. *Pharma Horizon* 2016;1:35–38.

Chapter 6

Building on the experience and success of biosimilar medicines

Biosimilar medicines are increasingly becoming an integral part of modern healthcare systems, so what does the future hold?

Biosimilar medicines are internationally recognized for expanding access to life-changing treatments

“Globally, regulators have confidence in the rigour of the scientific review and approval process for biosimilars.”¹

International Coalition of Medicines Regulatory Authorities (ICMRA) Statement about confidence in biosimilar products



“Biosimilars can provide more treatment options for patients, and possibly lower treatment costs, enabling greater access for more patients.”²

Dr Janet Woodcock, Director, Centre for Drug Evaluation and Research, Food and Drug Administration (FDA)



“Whether it's in the public or the private sector, we need to provide sustainable healthcare and biosimilars are clearly a good way to improve affordability.”³

Professor Josep Tabernero, Former President, European Society of Medical Oncology (ESMO)

Biosimilar medicines are cost-effective therapeutic alternatives to reference biological products¹

Reference: 1. ICMRA statement about confidence in biosimilar products (for healthcare professionals) Available at <https://bit.ly/2lXwwTJ>. Accessed October 2020; 2. Woodcock J. [Biosimilars Implementation](#). Accessed March 2020; 3. Tabernero J. [Europe ready to embrace first copies of biotech cancer drugs](#). Accessed March 2020.

Health Ministers recognize the value and benefits of biosimilar medicines use for healthcare



The Honourable Greg Hunt
Health Minister
Australia

“ 7 of the top 10 most expensive medicines on the PBS are all from the bio family. That's why what's occurring with biosimilars is so important, because it helps to expand the sustainability of the health system & helps to bring down the cost of these medicines ”

October 2, 2019, NSW Parliament House



The Honourable Adrian Dix
Minister of Health
Province of British Columbia (B.C.), Canada

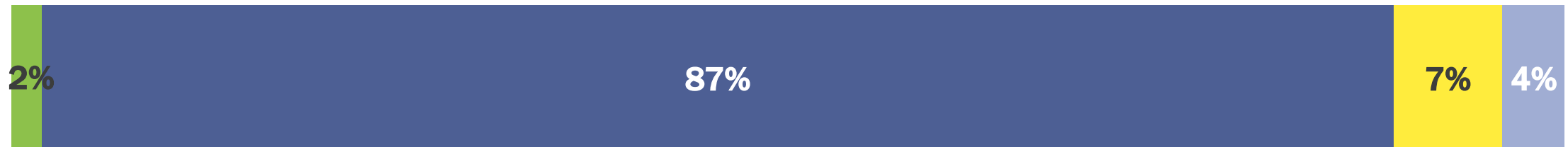
“ Biosimilars are a necessary step to ensure PharmaCare provides existing coverage for more people and funds new drugs well into the future ”

Globally, there is a huge opportunity for biosimilar medicines to provide competition to existing biological medicines

Percentage of global biological medicine sales by region



Percentage of global biosimilar medicine sales by region



US



Europe



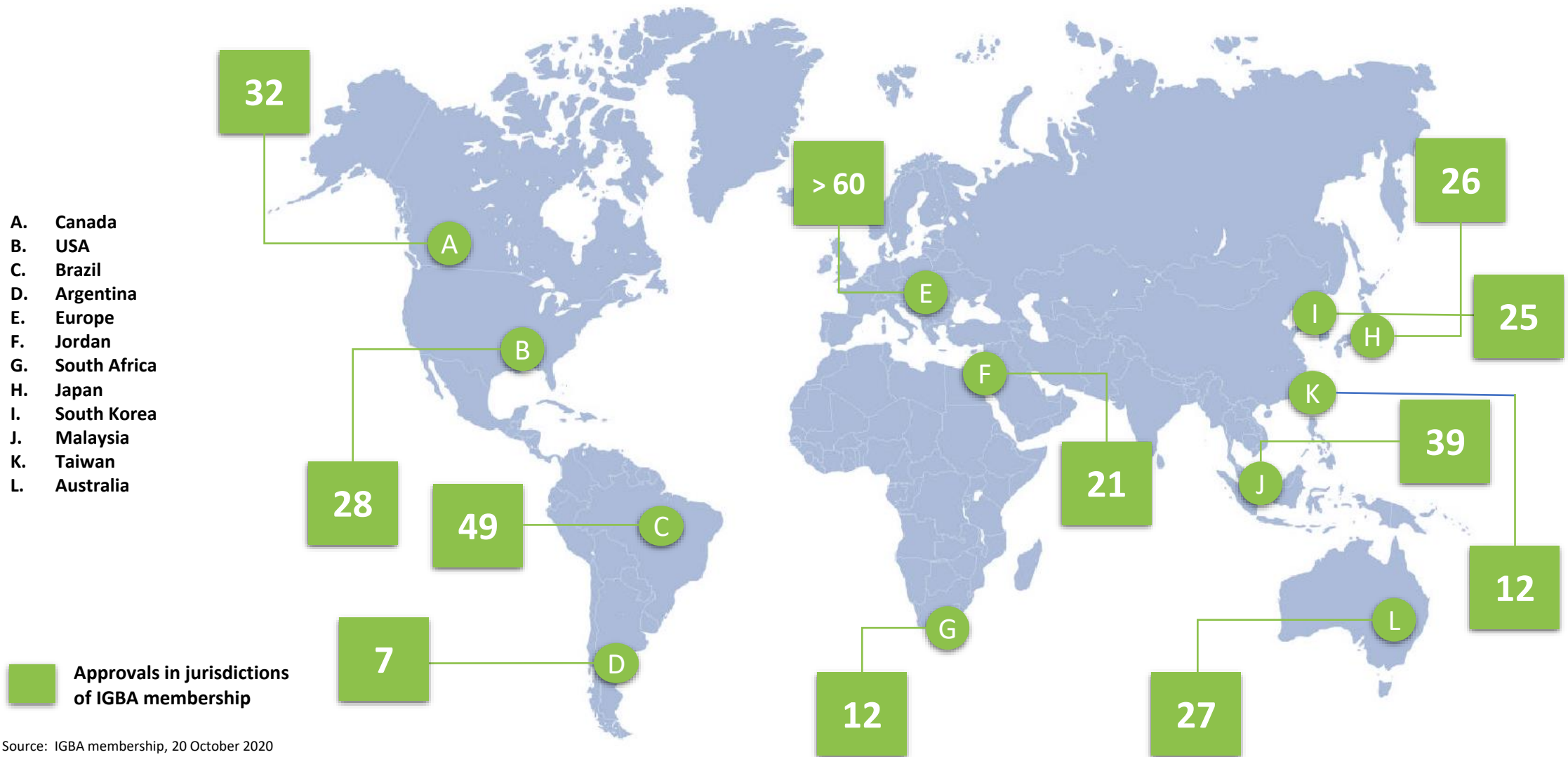
Japan



Other

Experience of biosimilar medicines in Europe is expected to support faster uptake in other regions

Building on the experience and success of over 300 biosimilar medicines approvals, covering over 10 therapeutic areas





Switching biological medicines is considered safe¹

- **Europe is leading the way** in switching from the reference to a corresponding biosimilar medicine²
- European Public Assessment Reports (EPARs) , available on the EMA website, provide **substantial evidence** for the safety of a switch²
- In Japan, a switching study from reference product filgrastim to the biosimilar demonstrated the same clinical efficacy and safety, but at a **reduced cost**³
- **Large clinical experience** in Europe supports switching not only between new versions of the same product, but also between a reference and its biosimilar medicine²
- The lack of safety signals in Europe **provides further reassurance** of the safety of switching between the reference and the biosimilar medicine²
- **The available switching data (over 170 studies) do not indicate that switching from a Reference Product to a Biosimilar is associated with any major efficacy, safety or immunogenicity issues**⁴
- A prescribing healthcare professional **transferring** a patient on treatment from an originator to a biosimilar medicine is an **accepted clinical practice in many countries**⁵

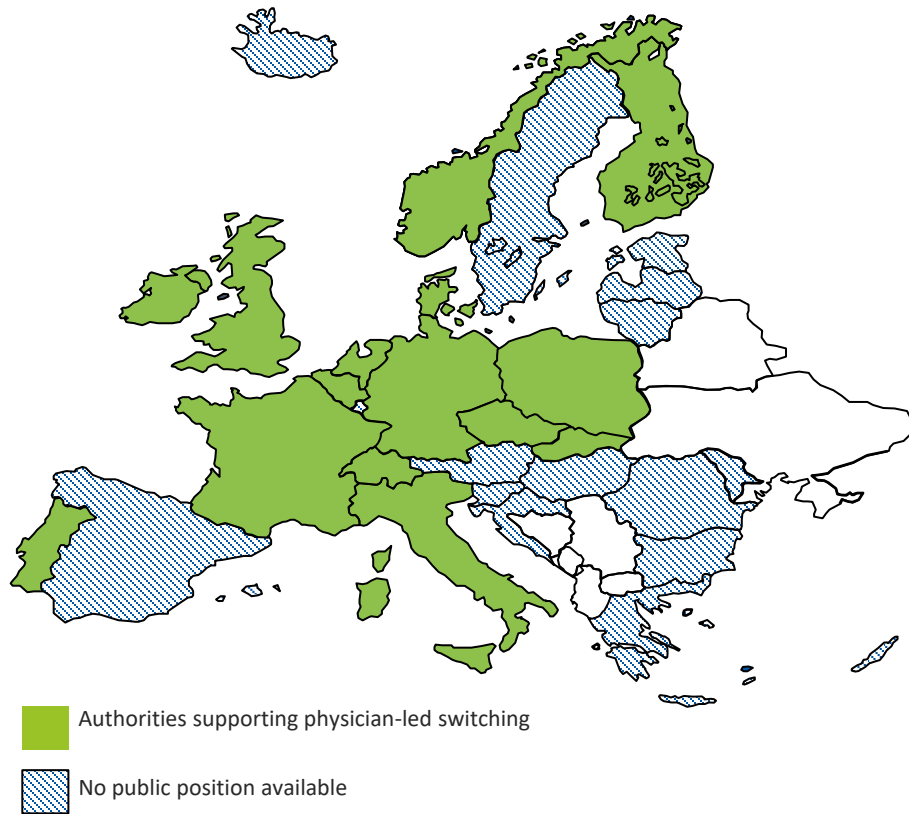
Under the supervision of the treating physician, patients can be safely switched from the reference product to the biosimilar medicine and vice versa³

References: ; 1. Glintborg B, et al. *Ann Rheum Dis* 2017; [Epub ahead of print]; 2. Kurki P, et al. *BioDrugs*. 2017;3(2):83–91; 3. Kamada I, et al. *RSMP* 2017;7(1):3–15. 4. Source: [Barbier, Ebbers, Declerck, Simoens, Vulto and Huys - The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biotherapeutics and Biosimilars: A Systematic Review \(2020\)](#). Clinical Pharmacology & Therapeutics. <https://doi.org/10.1002/cpt.1836> . Accessed November 2020; 5. ICMRA statement about confidence in biosimilar products (for healthcare professionals). Available at <https://bit.ly/2IXwwTJ>, Accessed October 2020.

Widespread support for switching biosimilar medicines under supervision of a healthcare person



National guidance



Regulatory guidance

BioDrugs
DOI 10.1007/s40259-017-0210-0

CURRENT OPINION

Interchangeability of Biosimilars: A European Perspective

Pekka Kurki¹ · Leon van Aerts² · Elena Wolff-Holz³ · Thij
Venke Skibeli⁵ · Martina Weise⁶

“In our opinion, switching patients from the original to a biosimilar medicine or vice versa can be considered safe.”

Clinical guidance*



Biosimilars: a position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers

ECCO Position Statement

Josep Tabernero,¹ Malvika Vyas,² R
Paolo G Casali,³ Andres Cervantes,
Jacek Jassem,¹⁰ George Pantherou,
Christoph C Zielinski,¹⁴ Rolf A Stahe
Keith McGregor,² Fortunato Ciardiello

ECCO Position Statement on the Use of Biosimilars for Inflammatory Bowel Disease—An Update

Silvio Danese,^{a,b} Giannata Fierino,^c Tim Raine,^d Marc Ferrante,^e

ilian Panes,^k

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Jonathan Kay,¹ Monika M Schoels,² Thomas Dörner,³ Paul Emery,⁴ Tore K Kvien,⁵
Josef S Smolen,^{2,6} Ferdinand C Breedveld,⁷ on behalf of the Task Force on the Use of
Biosimilars to Treat Rheumatological Diseases

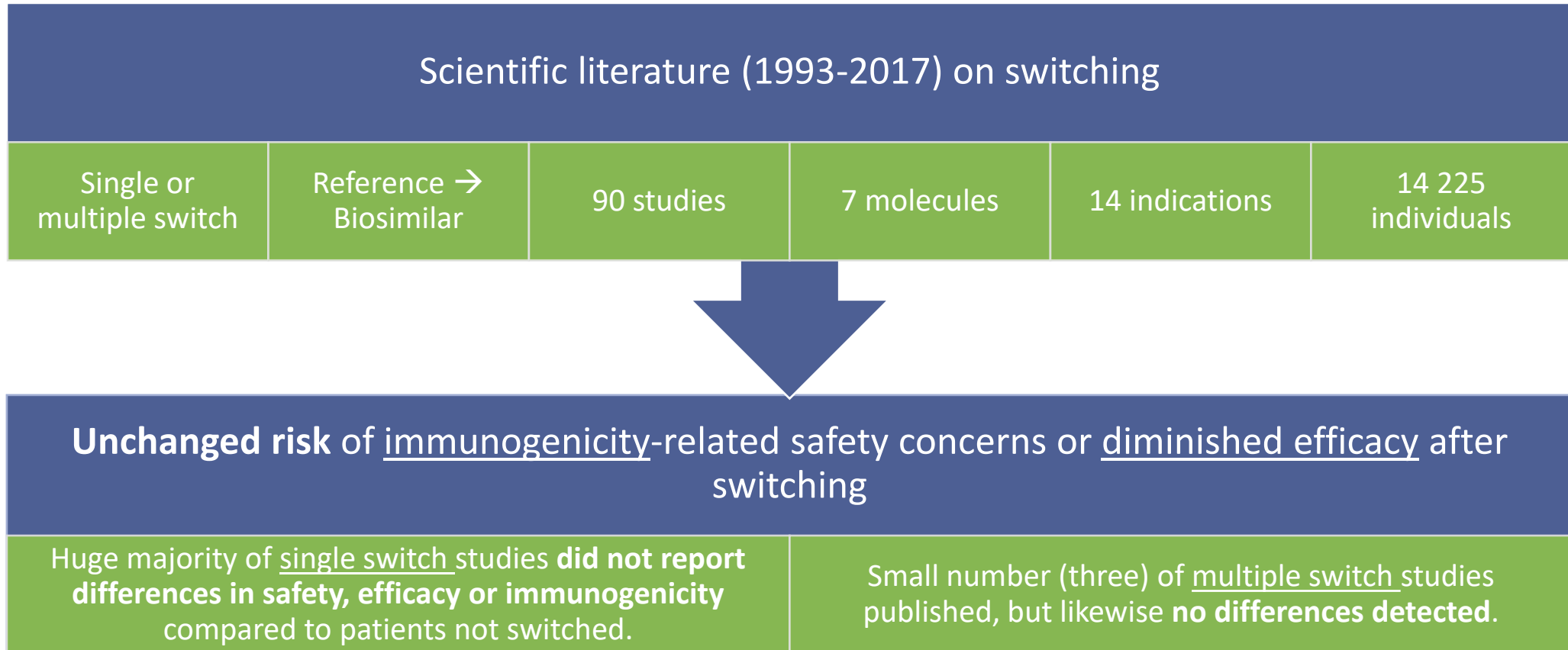


Source: Medicines for Europe Internal Biosimilar Mapping

* Medicines for Europe [Overview of biosimilar physician-led switching \(EU\) updated Sept 2020](#)

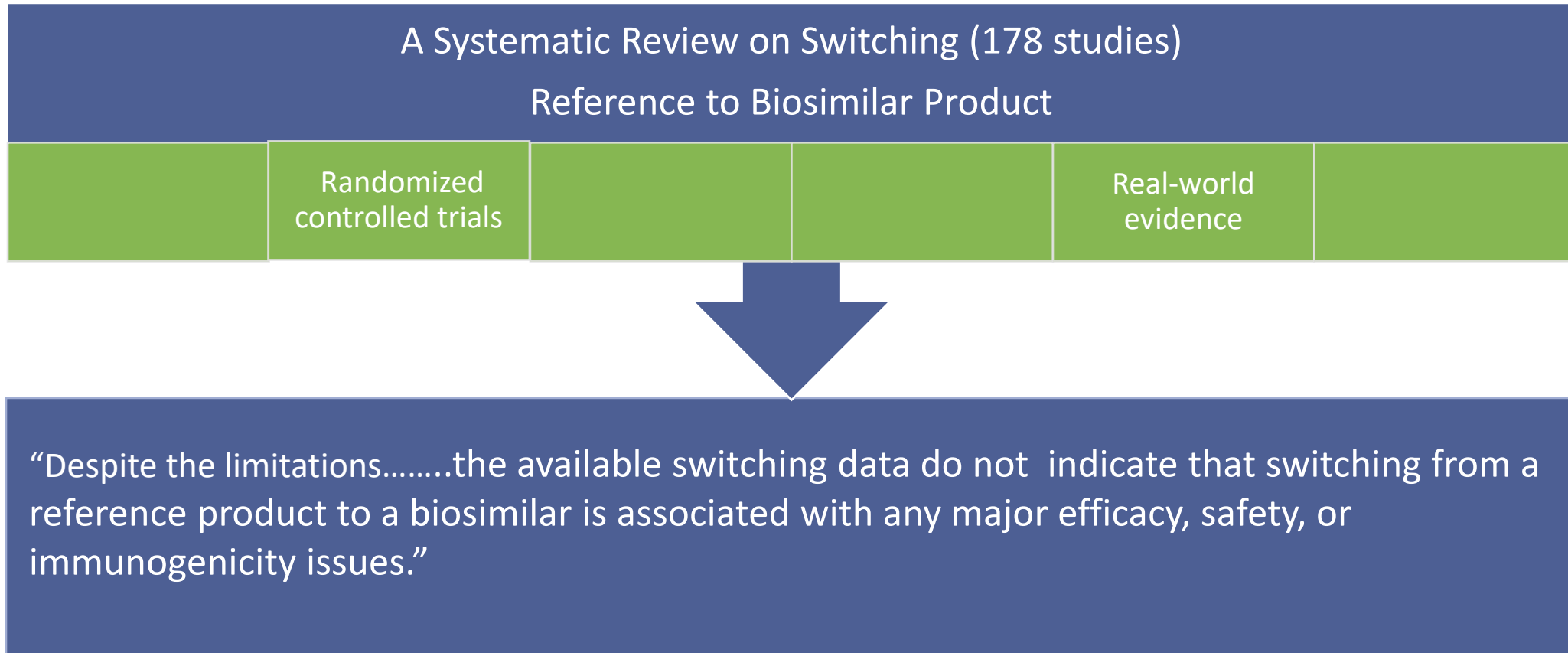


Switching studies confirm no differences in safety, efficacy or immunogenicity (2018)

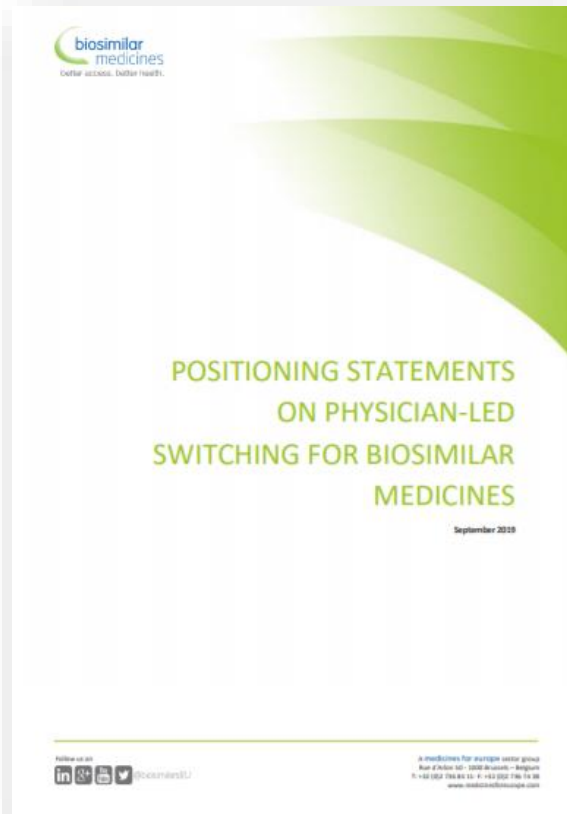




No major efficacy, safety, or immunogenicity issues when switching from a reference product to a biosimilar (2020)



EU: Clinical use and experience inform medical societies' positions

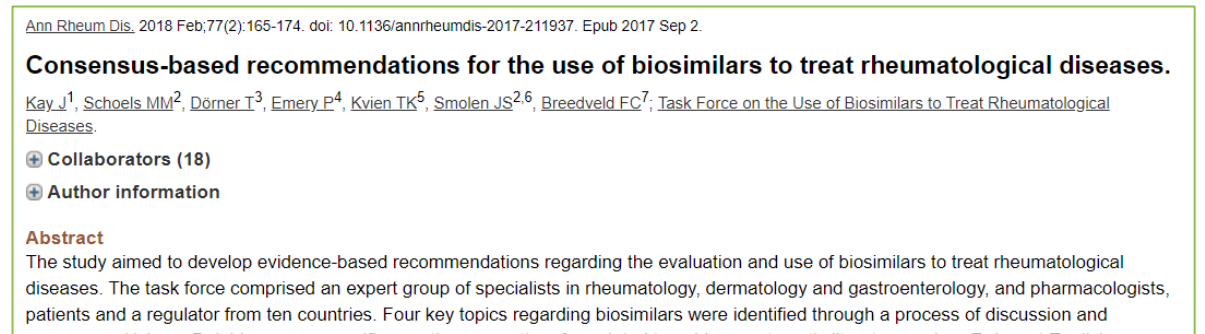


[Overview of biosimilar physician-led switching \(EU\)](#), updated in Sept. 2020

2015



2017



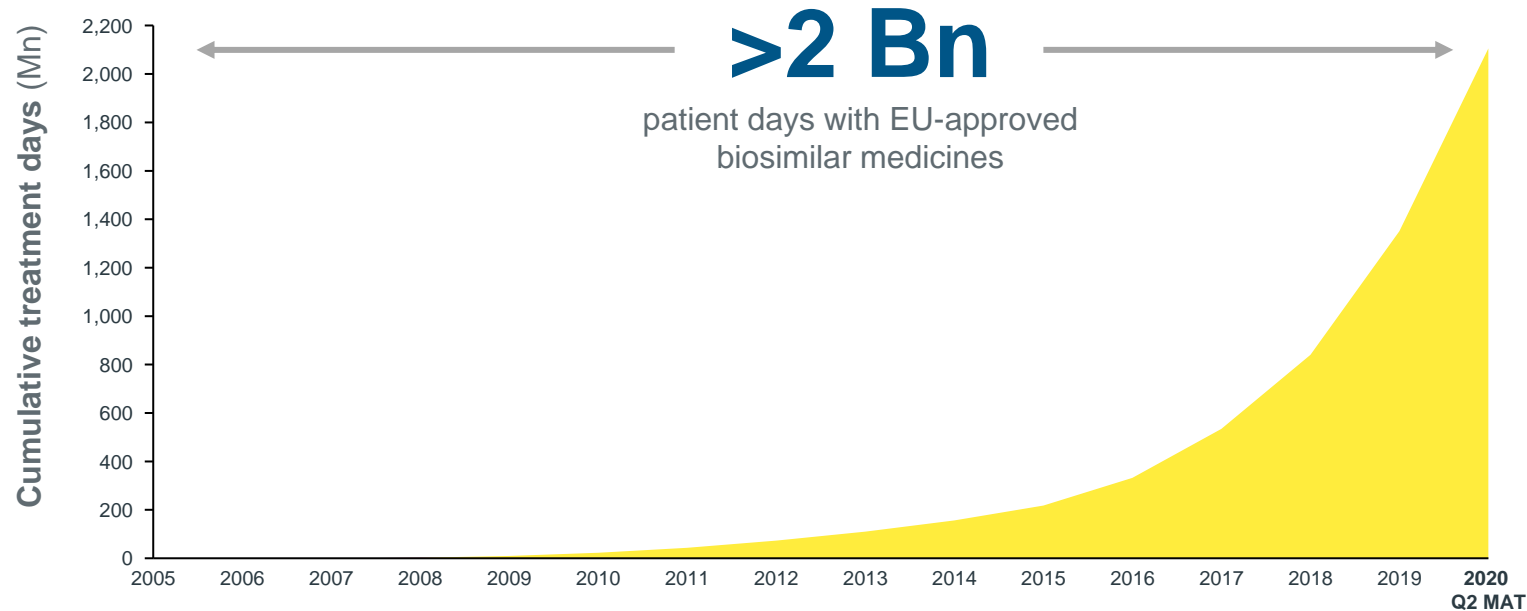
A number of medical societies have revised their initial positions and recommendations on the use of biosimilar medicines, recognising the positive clinical experience and benefits for patients

Transitioning approach to biosimilars medicines in two Canadian Provinces

- British Columbia¹ and Alberta²— have implemented **well-controlled switching policies** for patients on their public drug programs taking etanercept, infliximab, insulin glargine and rituximab for chronic conditions, saving hundreds millions of dollars that has been reinvested into their healthcare systems



The total clinical experience with biosimilar medicines exceeded 2 billion patient treatment days in Europe

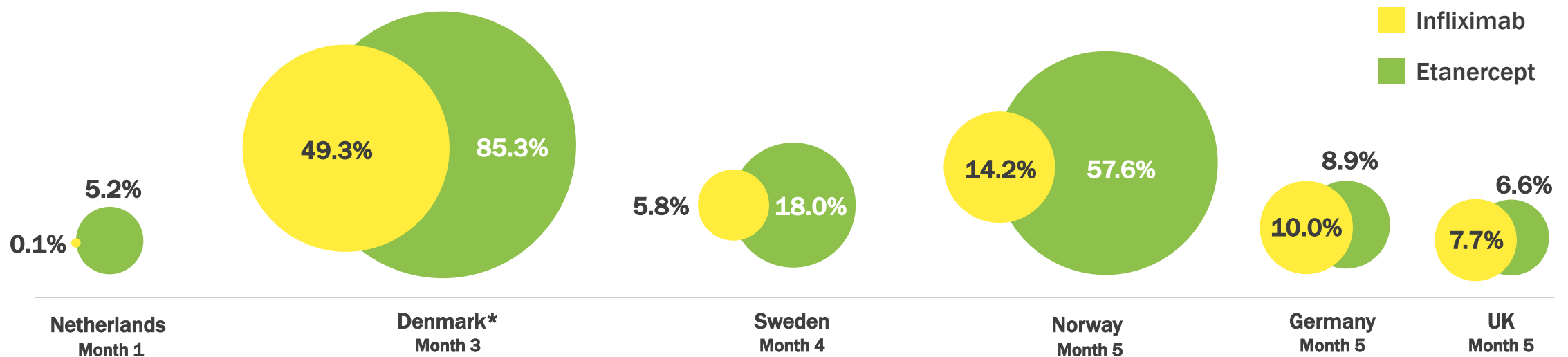


Over the last 10 years, the cumulative patient treatment days for EU approved biosimilar medicines have doubled every ~1.5 years

Increasing experience with biosimilar medicines supports faster uptake of subsequent new biosimilar medicines

- Infliximab was the first biosimilar monoclonal antibody (mAb) to be launched in Europe
- Uptake of a subsequent complex biosimilar, etanercept, was generally similar or improved compared with that of infliximab

Comparison of post-launch market share of biosimilar infliximab with that of etanercept for the same time period

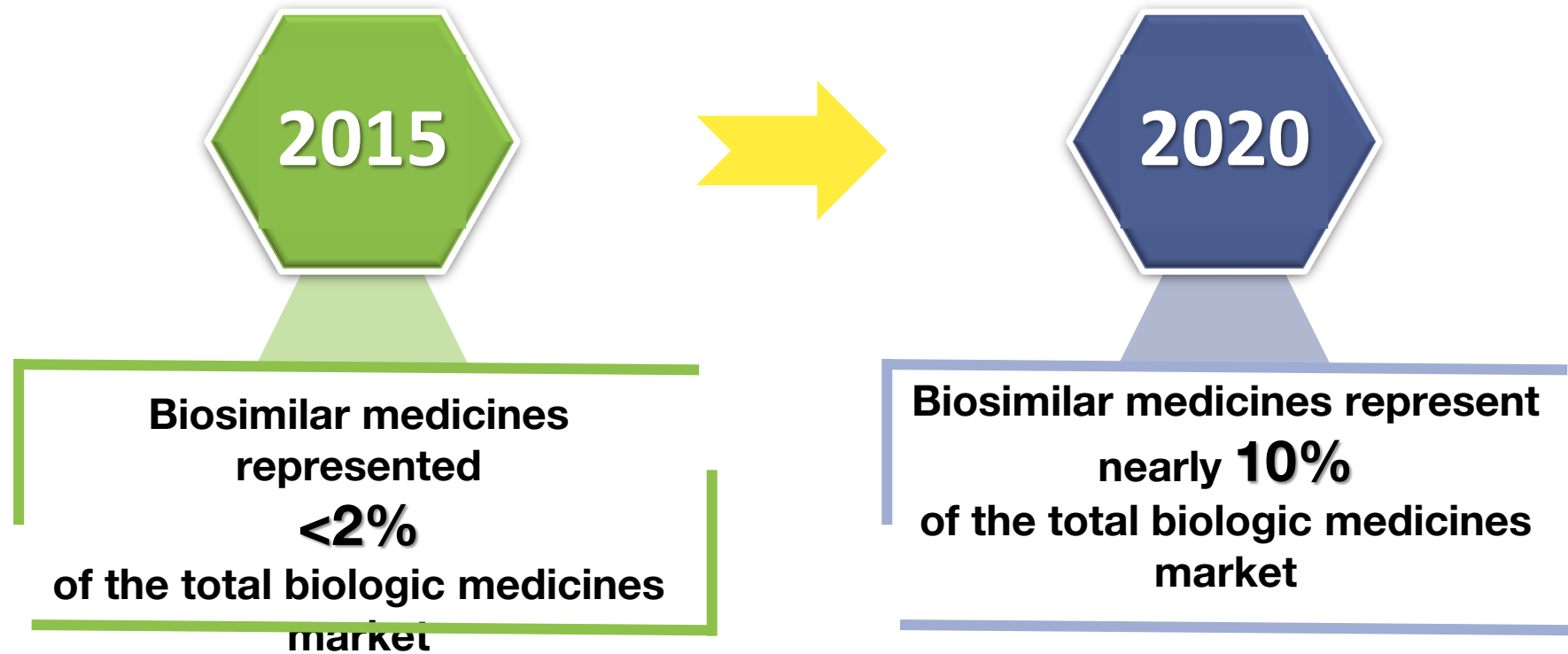


The launch and uptake of multiple biosimilar medicines provides a competitive biologics marketplace

*Denmark data from MIDAS monthly restricted database

Reference: QuintilesIMS. MIDAS July 2016.

In Europe, biosimilars have captured 7% more of the biologics market¹ over a 5-year period



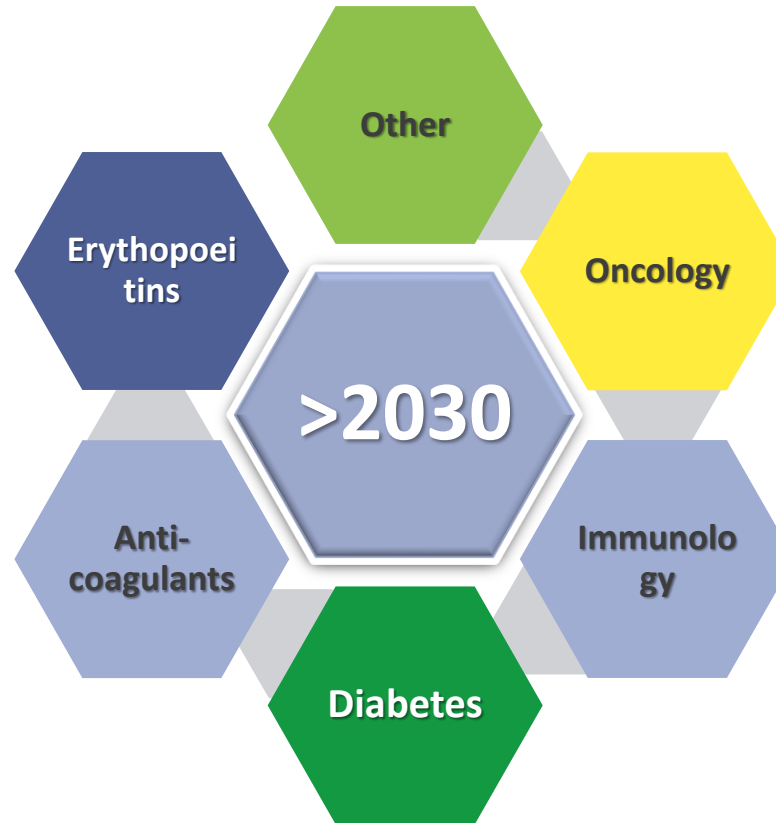
In the last 5 year period, biosimilar market growth in the EU mainly relates to immunology and oncology biosimilar market growth

The growing number of available biologic therapies offers future opportunities for biosimilar medicines development

e.g.: denosumab, aflibercept, ranibizumab

e.g.: darpepoietin

e.g.: insulin aspart, liraglutide



e.g.: cetuximab, daratumumab, ipilimumab, nivolumab, pegaspargase, pembrolizumab, pertuzumab, ramucirumab

e.g.: abatacept, belimumab, certolizumab pegol, interferon beta, golimumab, natalizumab, secukinumab, tocilizumab, ustekinumab

Over the next 10 to 15 years, more than 30 biologic medicines (mainly monoclonal antibodies) will lose market protection and open to biosimilar competition in existing and new therapy areas, including for orphan indications

Availability of biosimilar medicines improves the security of the supply chain

- The FDA and EMA have identified manufacturing problems, delays in supply, and lack of available active ingredients as the **most frequent causes of drug shortages**¹
- Drug shortages can **compromise patient safety and clinical outcomes**, and increased healthcare costs, due to delays or changes in treatment regimens¹
- Biosimilar medicines **help prevent future biologic shortages** and ensure access to effective and safe treatment options¹



“[...] the biosimilar market will see a more diverse range of companies, greater competition, and improved supply chain security.”²

Alex Kudrin, Biopharmaceutical Consultant, United Kingdom

Biosimilar medicines offer improved access to more cost-effective healthcare, today and in the future

Summary: Building on the experience and success of biosimilar medicines



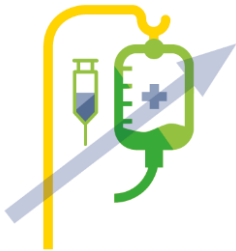
The benefits offered by biosimilar medicines are **internationally recognized**¹



Around the world, **multiple biosimilar medicines** have been approved²⁻⁶



Switching from a reference product to a biosimilar medicine is considered safe⁷



Experience with biosimilar medicines **improves uptake**⁸



A **strong pipeline** supports the continuous introduction of new biosimilar medicines¹



Availability of biosimilar medicines **safeguards the supply chain**, ensuring patient access to key therapeutics

References: 1. QuintilesIMS Institute for Healthcare Informatics. Delivering on the Potential of Biosimilar Medicines. 2016; 2. [European Medicines Agency](#). Accessed March 2020; 3. [Ministry of Health, Labour and Welfare \(MHLW\)](#). Accessed March 2020; 4. Health Canada. Data on file; 5. Food and Drug Administration. [Purple Book](#). Accessed March 2020; 6. [Australian Register of Therapeutic Goods \(ARTG\)](#). Accessed March 2020; 7. Ebbers HC, et al. *Expert Opin Biol Ther*. 2012;12(11):1473-85; 8. QuintilesIMS MIDAS MTH July 2016.