Chapter 4

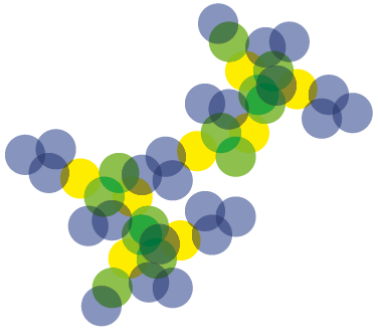
Biosimilar medicines — a commitment to scientific excellence

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

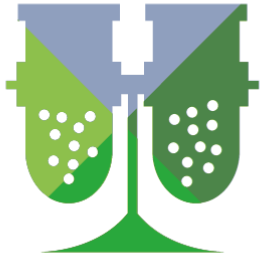
But how are biosimilar medicines developed, and how is their efficacy and safety ensured?

Biological medicines display an inherent degree of minor variability (microheterogeneity), which is tightly controlled[1]

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 controlled[3]

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

References: 1. Schneider C. *Ann Rheum Dis* 2013;72:315–8; **2.** Gudat U. *Pharma Horizon* 2016;1:35–38; **3.** Weise M, *et al. Blood* 2012;120;5111–7.

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 medicine**[4]

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

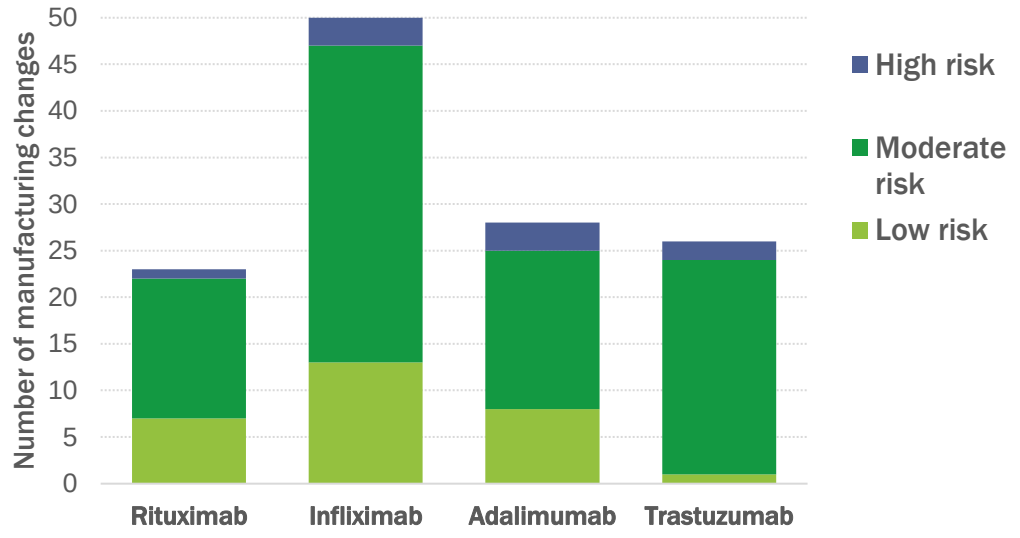


Figure adapted from Vezér *et al.* 2016[2]

The acceptable variability of the reference/comparator biological medicine over its lifecycle designates the goalposts for biosimilar product development[5,6]

References: 1. McCamish M, Woollett G. *Clin Pharmacol Ther* 2012;91:3:405–17**; 2.** Vezér B, *et al. Curr Med Res Opin* 2016;32:829–34; **3.** Schiestl M, *et al. Nat Biotechnol* 2011;29:310–2;
4. ICH Q5E guideline on comparability of biotechnology-derived products after a change in the manufacturing process. 2016. Accessed March 2020;
5. McCamish M, Woollett G. *mAbs* 2011;3:209–17; **6.** McCamish M, Woollett G. *Clin Pharmacol Ther* 2013;93:315–7.

Changes to manufacturing of biological medicines are approved following a thorough comparability exercise[1] (either sequential or in parallel)

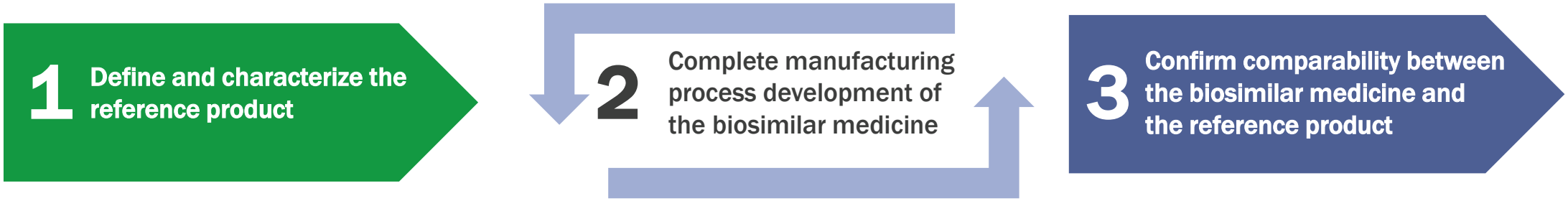
Comparability bridging studies and adherence to specific pharmacovigilance regulations may be required, depending on the nature of the changes made to the manufacturing process[2]

- 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 standards[5]
- When comparability has been demonstrated, the new version of the product can be introduced to the market without informing prescribers, pharmacists, or patients[6]

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 tailored multi-step approach[1–3] (either sequential or in parallel)



The sensitivity of *in vitro* characterization continues to improve, and has increased 10 million-fold between 1990 and 2011 for some methods[4]

Biosimilar medicine process development is a reiterative procedure whereby the product quality is continuously reviewed[1,2]

The quality, non-clinical, pharmacokinetics (PK)/pharmacodynamics (PD), and clinical profiles of the biosimilar are compared with the reference product[1,2]

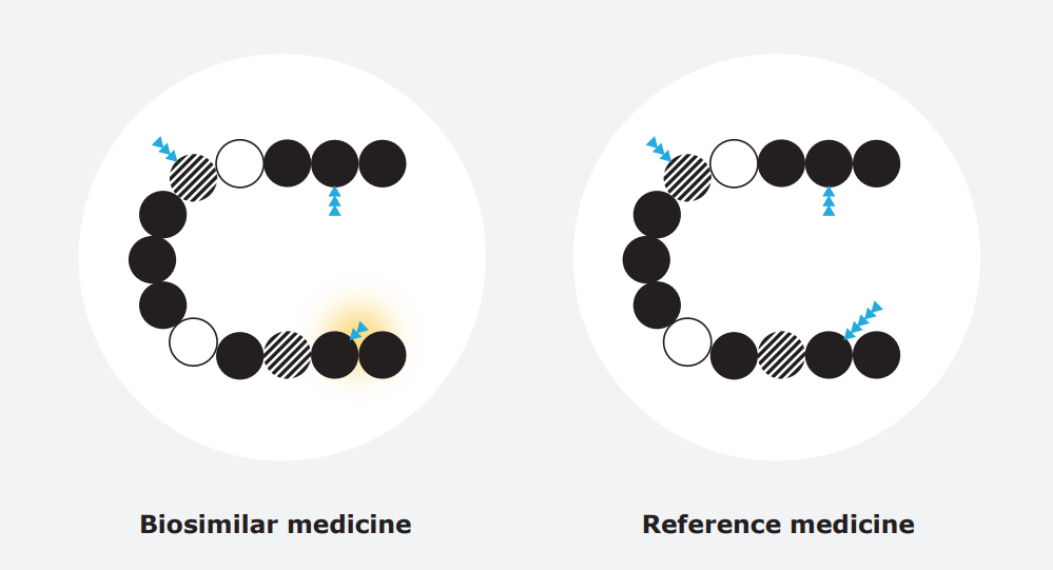
The range of variability allowed for a biosimilar medicine is the same as that allowed between batches of the reference medicine[1–3]

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 its 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



Text and figure page 4/36 Biosimilars in the EU – Information guide for Healthcare Professionals. Available at https://tiny.cc/# . Accessed September 2020

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]

References: 1. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Accessed April 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.** Weise M, *et al. Blood* 2012; 120; 5111–7.

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

References: 1. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Last accessed April 2020; **2.** EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Last accessed March 2020.

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 product[1]
- 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]

References: 1. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Accessed March 2020; **2.** Ventola CL. *PT* 2013;38:270–4,277, 287. Evolution of the EU biosimilar Framework: Past and Future" (4) the European regulators Elena Wolff-Holz et.al.

Clinical comparability is generally confirmatory of the comparability demonstrated in the other steps

- Streamlined 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 efficacy[1]
- Comparative clinical trials, where needed, are performed in a scientifically justified 'clinical model' that is sensitive to small differences[2–6]
- 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 required[2–6]

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

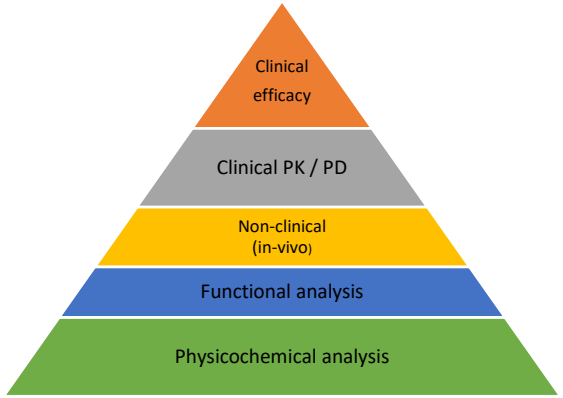
References: 1. Gudat U. *Pharma Horizon* 2016;1:35–38; **2.** FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Last accessed April 2020; **3.** EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Accessed March 2020; **4.** Ventola CL. *PT* 2013;38:270–4,277, 287; **5.** Schneider C. *Ann Rheum Dis.* 2013;72:315–8; **6.** Kurki P, *et al. BioDrugs* 2017 [Epub ahead of print].

How can we streamline biosimilar development?

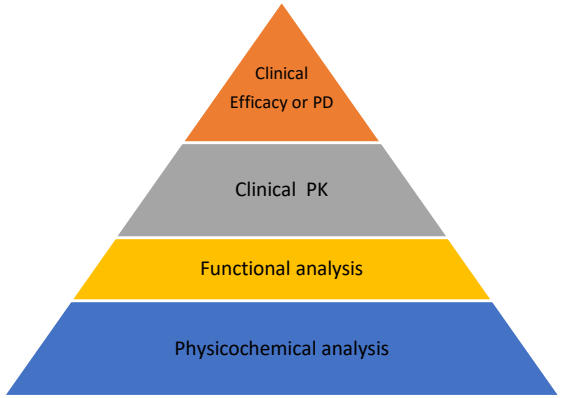
- Continuously apply evolving **regulatory sciences**;
- Maintain robust regulatory standards that have resulted in an impeccable track record of biosimilar medicines;
- Adapt the biosimilar framework in line with the latest knowledge as reflected in objectives of EMA[1], MHRA[2], WHO[3]
  - e.g. EMA 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 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 April 2020.

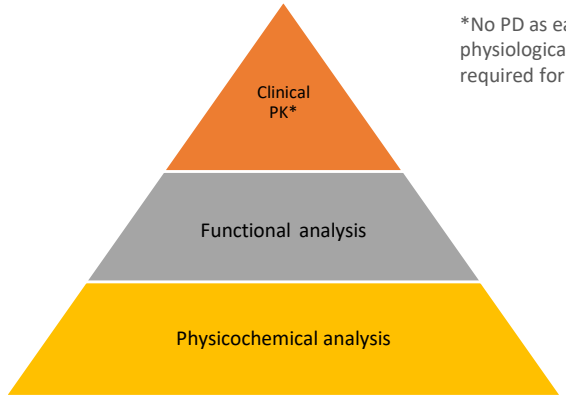
Continuous evolution of biosimilar development options for therapeutic proteins



Biosimilar development as setup 2004



Today's accepted regulatory options



Additional option of streamlined 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)	An in vivo animal study is usually not considered necessary	
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 on Biosimilar Development

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 biosin
jurisdictions is derived from the development

Review Article | Open Access | Published: 20 September 2019

Evolution of the EU Biosimilar Framework: Past and Future

Elena Wolff-Holz, Klara Tiitso, Camille Vleminckx & 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 co
stringent regulatory standards. While the initial a

Review Article | Open Access | Published: 07 April 2020

The Path Towards a Tailored Clinical Biosimilar Development

Martin Schiestl, Gopinath Ranganna, Keith Watson, Byoungin Jung, Karsten Roth, Björn Capsius, Michael Trieb, Peter Bias & Julie Maréchal-Jamil

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

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

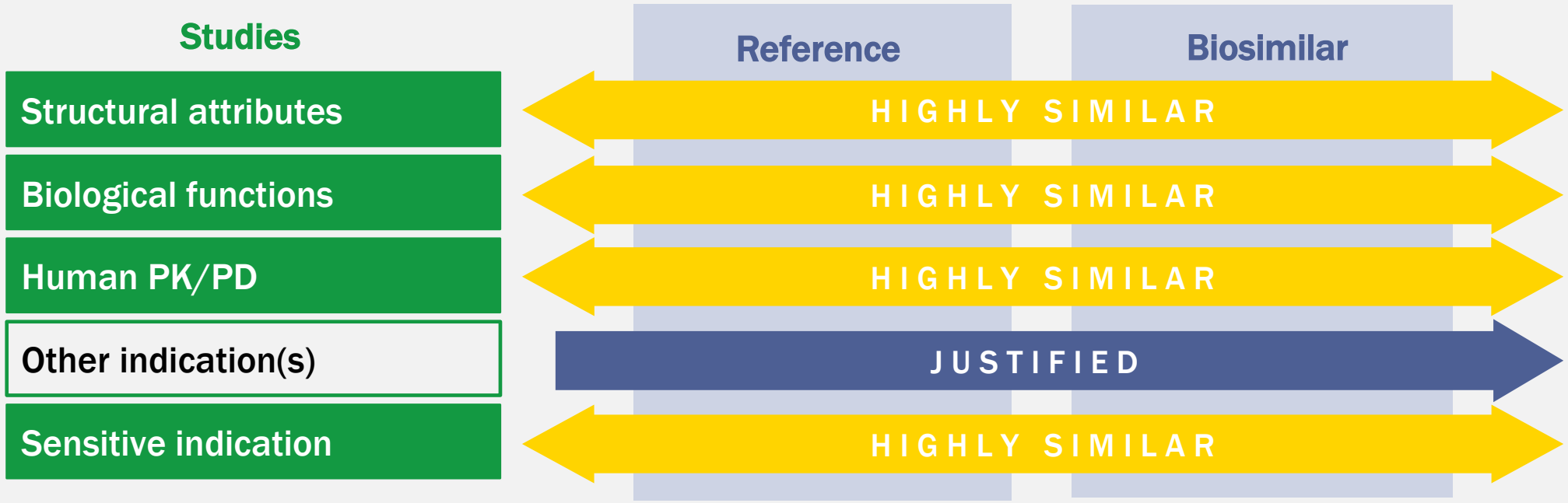
- A biosimilar medicine may be approved for one or more indications for which its reference product is licensed, but for which there was no head-to-head clinical comparison[1]
- These indications are individually evaluated based on sound science[1]
- The approvals are based on extrapolation of data, 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[1]

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

Reference: 1. Weise M, *et al. Blood* 2014;124:3191–6.

Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise[1]

Similarity space



High similarity is a prerequisite — patients and healthcare providers can be assured that the biosimilar medicines are as safe and effective as their reference products

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 sites[2]

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

References: 1. Van Amum P. Biosimilars: Market weaknesses and strengths; **2.** EMA. Biosimilar medicines. Accessed March 2020; **3.** FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Accessed April 2020; **4.** EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Accessed March 2020; **5.** Biosimilar Medicines Group handbook 2016. Accessed March 2020; **6.** Brinks V, *et al. In Pharm Res* 2011;28:386–93.

Summary: Biosimilar medicines — a commitment to scientific excellence

Biological medicines display an **inherent degree of minor variability,** which is tightly controlled[1]

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

Biosimilarity can be established using **streamlined clinical development,** [where appropriate] provided comparability is demonstrated through the totality of evidence[3]

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

Comprehensive 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 technologies[4]

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 differences[7]

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.