

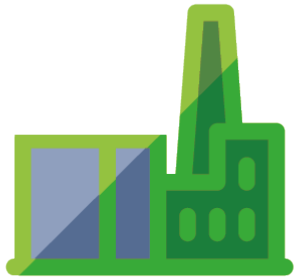
## Chapter 4

# Biosimilar medicines — a commitment to scientific excellence

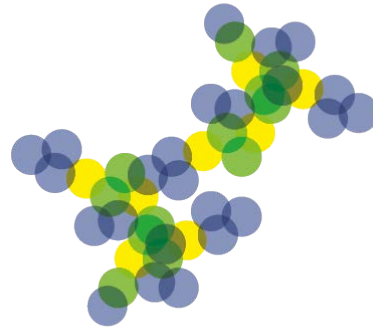
With biosimilar medicines, patients and healthcare providers benefit from high quality and efficacious therapeutic alternatives.

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

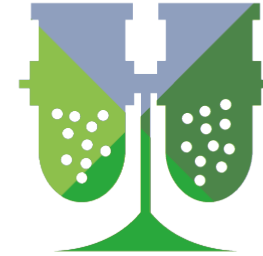
# Biological medicines display an inherent degree of minor variability (microheterogeneity), which is tightly controlled<sup>1</sup>



Biological medicines are made in living organisms and purified through **complex manufacturing processes**<sup>2</sup>



Biological medicines consist of relatively large and often highly **complex molecular entities**<sup>3</sup>



Any biological medicine will display **microheterogeneity**, even **between different batches of the same product**. This normal feature is tightly controlled<sup>3</sup>

The heterogeneity of biological medicines not only reflects the natural variation of these molecules, but also the variability of the production process<sup>1,3</sup>

# Throughout their lifecycle, biological medicines undergo changes to their manufacturing process<sup>1,2</sup>

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

- 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<sup>4</sup>

Number of manufacturing changes for monoclonal antibodies according to risk category

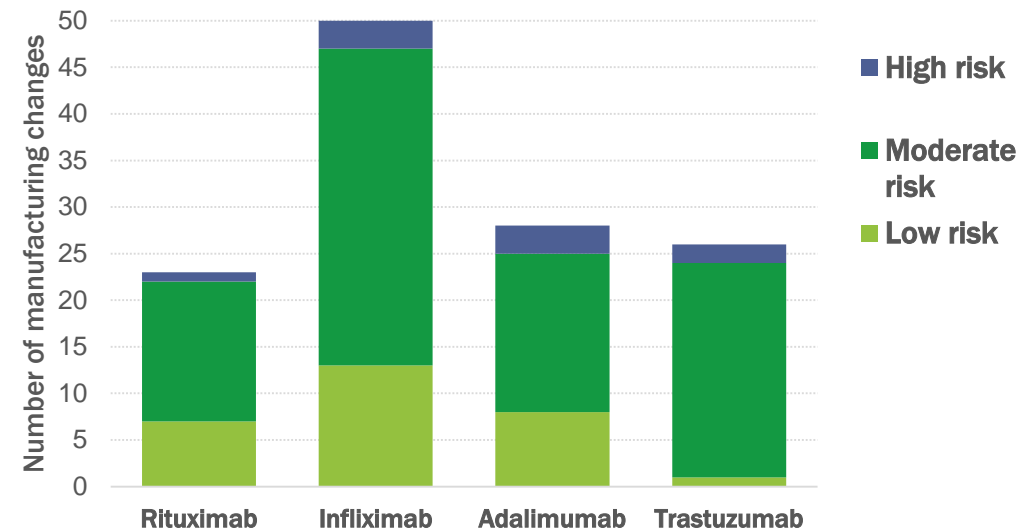


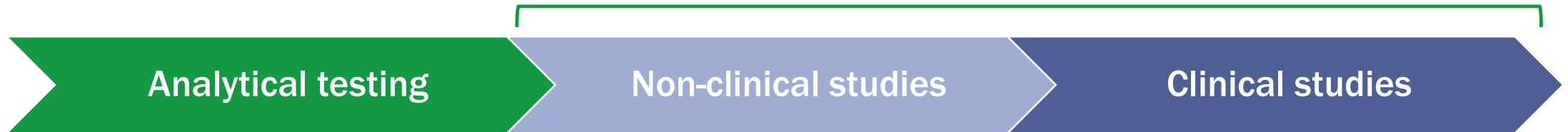
Figure adapted from Vezér *et al.* 2016<sup>2</sup>

The acceptable variability of the reference biological medicine over its lifecycle designates the goalposts for biosimilar product development<sup>5,6</sup>

**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. Available at: <http://bit.ly/2pSMkfV>. Accessed July 2017; 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 stepwise comparability exercise<sup>1</sup>

Comparability bridging studies and adherence to specific pharmacovigilance regulations may be required, depending on the nature of the changes made to the manufacturing process<sup>2</sup>

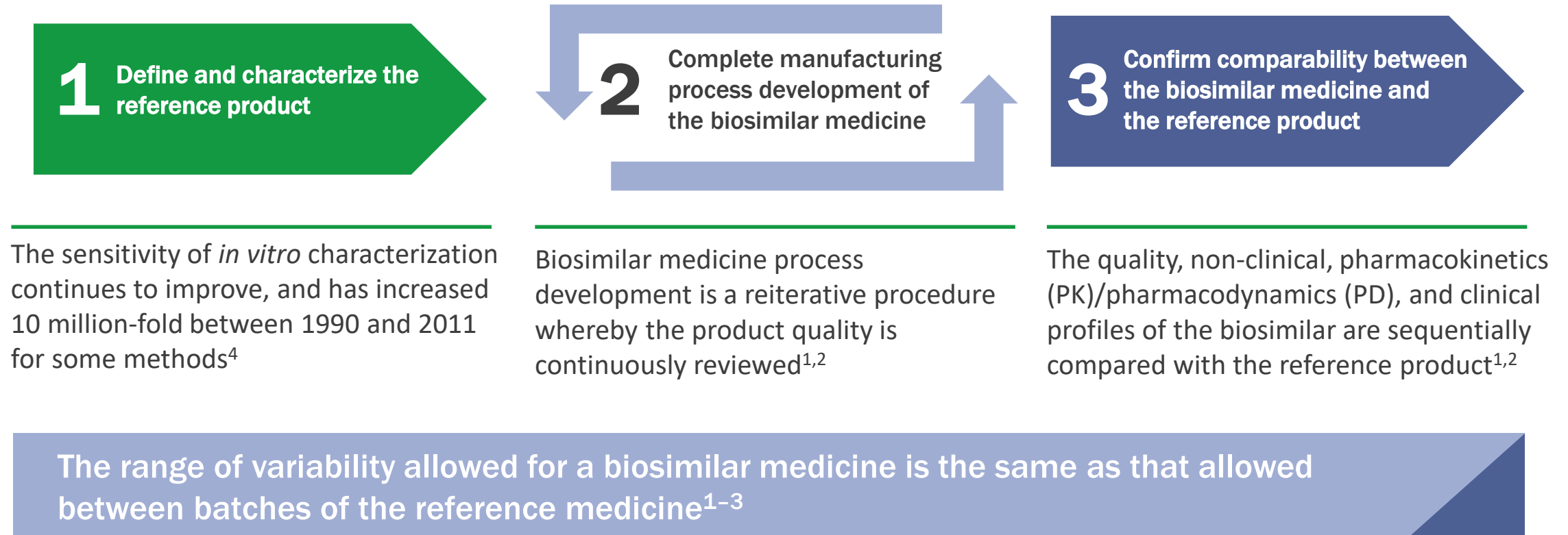


- Originator manufacturers rely almost exclusively on analytics and extrapolation of indications to obtain approval for the process changes<sup>3,4</sup>
- Regulators have over two decades of experience in evaluating and approving these changes, based on comparability exercises in line with internationally agreed standards<sup>5</sup>
- When comparability has been demonstrated, the new version of the product can be introduced to the market without informing prescribers, pharmacists, or patients<sup>6</sup>

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<sup>7,8</sup>

**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. Available at: <http://bit.ly/2bSxaP2>. Accessed April 2017; 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. Available at: <http://bit.ly/2ckWrzf>. Accessed July 2017.

# Biosimilar medicine development is target-orientated, comparative, and follows a stepwise approach<sup>1-3</sup>



**References:** **1.** FDA. Available at: <http://bit.ly/2qySWih>. Accessed July 2017; **2.** EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: <http://bit.ly/1liuZfS>. Accessed July 2017; **3.** EMA. Guideline on similar biological medicinal products. Available at: <http://bit.ly/2ckWrzf>. Accessed July 2017; **4.** Anthony Mire-Sluis, Presented at 9th Symposium on the Practical Applications of Mass Spectrometry in the Biotechnology Industry; September 11–14, 2012, San Diego, CA USA. Available at: <http://bit.ly/2pSEUcP>. Accessed July 2017.

# Quality comparability establishes highly similar physiochemical properties and biological activity<sup>1,2</sup>

- Analytical and functional comparability studies are the foundation of biosimilar medicine development<sup>1,2</sup>
- Analytical testing is a more sensitive means of detecting differences than randomized clinical trials<sup>1,2</sup>
- The biosimilar medicine and the reference product must be highly similar at a molecular level<sup>1,3</sup>
  - 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<sup>1,2</sup>
- 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<sup>1,2</sup>



**References:** 1. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Available at: <http://bit.ly/2qySWih>. Accessed July 2017; 2. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: <http://bit.ly/1liuZfS>. Accessed July 2017; 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<sup>1,2</sup>

- 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 product<sup>1</sup>
- 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<sup>1,2</sup>





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

- Clinical comparability **confirms** that the structural concordance **translates into clinical performance**, and is designed to rule out clinically relevant differences in safety or efficacy<sup>1</sup>
- Comparative clinical trials are performed in a scientifically justified 'clinical model' that is sensitive to small differences<sup>2-6</sup>
- 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<sup>2-6</sup>

The biosimilar medicine is only approved if there are no clinically meaningful differences from the reference product<sup>7</sup>



**References:** 1. Gudat U. *Pharma Horizon* 2016;1:35–38; 2. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Available at: <http://bit.ly/2qySWih>. Last accessed July 2017; 3. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: <http://bit.ly/1liuZfS>. Accessed July 2017; 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].

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

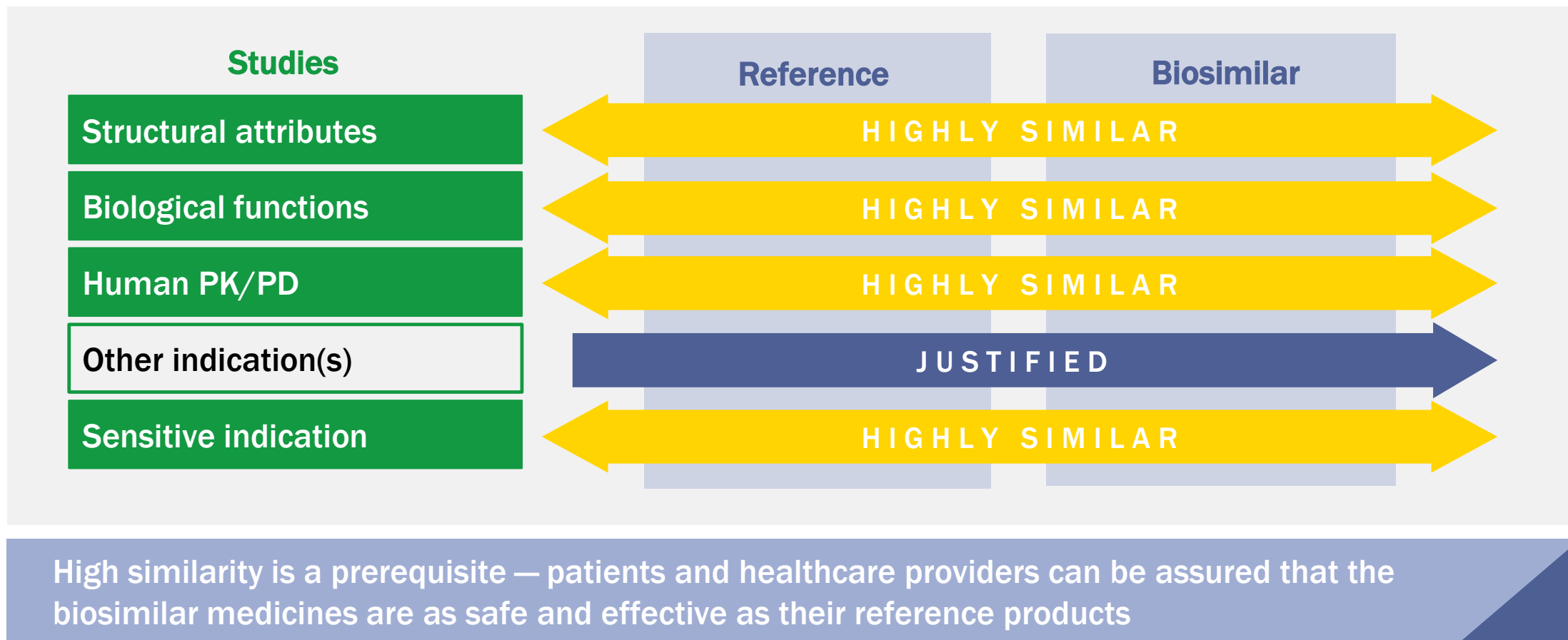
- A biosimilar may be approved for one or more indications for which its reference product is licensed, but for which there was no head-to-head clinical comparison
- These indications are individually evaluated based on sound science
- The approvals are based on extrapolation of data, which is an established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

## Similarity space



**Abbreviations:** PK, pharmacokinetic; PD, pharmacodynamic

**References:** 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 <sup>1</sup>
- **Highly sophisticated analytical tools** allow for a detailed characterization of the biosimilar medicine and the reference product<sup>3,4</sup>
- 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<sup>5,6</sup>
- 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<sup>2</sup>

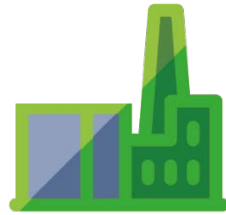
Patients and healthcare providers can trust biosimilar medicines, as they are approved according to the same high standards and by the same regulators as all other medicines

**References:** 1. Van Amum P. Biosimilars: Market weaknesses and strengths. Available at: <http://bit.ly/2qZOQ4s>. Accessed July 2017; 2. EMA. Biosimilar medicines. Available at: <http://bit.ly/1PCppri>. Accessed July 2017; 3. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. Available at: <http://bit.ly/2qySWih>. Accessed July 2017; 4. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: <http://bit.ly/1liuZfS>. Accessed July 2017; 5. Biosimilar Medicines Group handbook 2016. Available at: <http://bit.ly/1QCnNMR>. Accessed July 2017; 6. Brinks V, *et al.* *In Pharm Res* 2011;28:386–93; 7. European Medicines Agency and Heads of Medicines Agency. EMA/168402/2014. Available at: <http://bit.ly/2bSxaP2>. Accessed July 2017.

# Summary: Biosimilar medicines — a commitment to scientific excellence



Biological medicines display an **inherent degree of minor variability**, which is tightly controlled<sup>1</sup>



Throughout their lifecycle, biological medicines **undergo manufacturing changes**<sup>2</sup>



**Comparability exercises** are performed to ensure that these changes do not alter the product clinically<sup>3</sup>



Scientific principles for **establishing biosimilarity** are the **same as** those for **demonstrating comparability**<sup>4</sup>



**Stepwise comparability exercises** ensure there are no clinically meaningful differences between the biosimilar and the reference product<sup>5,6</sup>



Development of biosimilars requires **significant investment** and state-of-the-art technologies<sup>4</sup>



EMA/EU, FDA/USA, HC/Canada, PMDA/Japan, TGA/Australia all **require extensive evidence** that a biosimilar is highly similar to a reference product, and that there are no meaningful differences<sup>7</sup>

**References:** 1. Schneider C. *Ann Rheum Dis* 2013;72:315–8; 2. McCamish M, Woollett G. *Clin Pharmacol Ther* 2013;93:315–7; 3. Chirino AJ, Mire-Sluis A. *Nature Biotechnol* 2004;22:1383–91; 4. Biosimilar Medicines Group handbook 2016; 5. FDA. Available at: <http://bit.ly/2qySWih>. Accessed July 2017; 6. EMA. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available at: <http://bit.ly/1liuZfS>. Accessed July 2017; 7. Weise M, *et al. Blood* 2014;124:3191–6.