

# Biosimilar Drugs

FREQUENTLY ASKED QUESTIONS



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## BIOSIMILARS: DEFINITIONS, DESCRIPTION, AND NOMENCLATURE

### 1. What is the scientific definition of a biosimilar?

A biosimilar is a biologic product that is similar, but not identical, to a reference product, and therefore requires separate marketing approval upon patent expiration of the reference product. Biosimilars are not generic versions of biologics.<sup>1</sup> (See Figure 1.) The active ingredient in a generic small molecule drug is a single molecular structure and can readily be reproduced by chemical synthesis, but the active substance in a biologic product is a collection of large protein isoforms, thus making reproduction more complex.<sup>1,2</sup> (See Figure 2.)

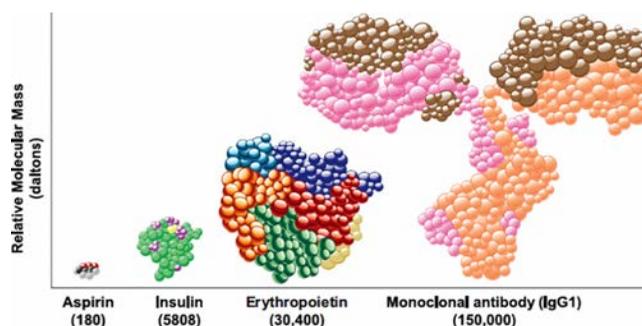
“Biosimilar” is the term used in Europe and the U.S., “follow-on pharmaceuticals” in Japan, “subsequent entry biologics” in Canada, and “biocomparables” in Mexico. The original version of a biologic is referred to as the “originator,” “innovator,” “pioneer,” or “reference” drug. A biologic drug in general is also referred to as a “biopharmaceutical,” “biodrug,” “biologic,” or “biological.”

### 2. What are the features of both reference and biosimilar biologics?

#### Origin and Manufacturing

Biologics, whether reference or biosimilar, are produced with living cells through the use of biotechnology, such as recombinant DNA technology, controlled gene expression, or antibody technologies.<sup>2,3</sup> Since biologics are made with cells in culture or whole organisms, such as plants, animals, and microorganisms, they are inherently more variable

Figure 2: Comparisons among Small Molecule, Simple Biologic, and Complex Biologic Drugs<sup>6</sup>

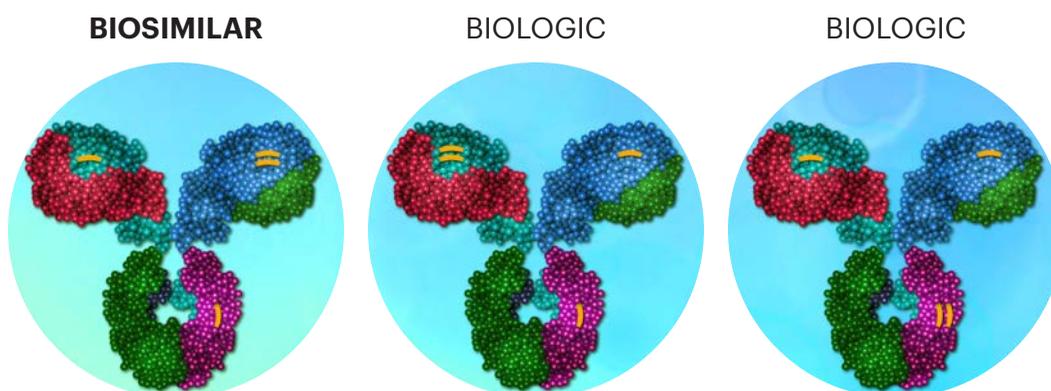


Adapted with permission from Mellstedt H. Clinical considerations for biosimilar antibodies. *European J Canc.* 2013;S11:1-11.

than a small-molecule drug, such as aspirin, which is made by chemical synthesis.<sup>2,7</sup> Recombinant DNA technology refers to the process of using enzymes to cut and paste together DNA sequences of interest. The recombined DNA sequences can be placed into vectors that carry the DNA into a host cell, where the customized recombined DNA sequence can be copied or translated.<sup>8</sup> First-generation biologics were made directly from human and animal by-products, such as human blood and porcine insulin. Second-generation biologics, however, are made by genetically engineering DNA within living organisms.<sup>9</sup> The benefit of this is notable in the example of immunological compatibility of genetically-engineered insulin versus porcine insulin, which can cause long-term immunological complications in some patients.<sup>7</sup> The use of recombinant DNA technology to produce insulin is shown in Figure 3. Figure 4 depicts the manufacturing process for biologics.

Methods for manufacturing biologics are more complex than for small molecule drugs, and involve several steps

Figure 1: Comparison Between a Reference Biologic and a Biosimilar<sup>3</sup>

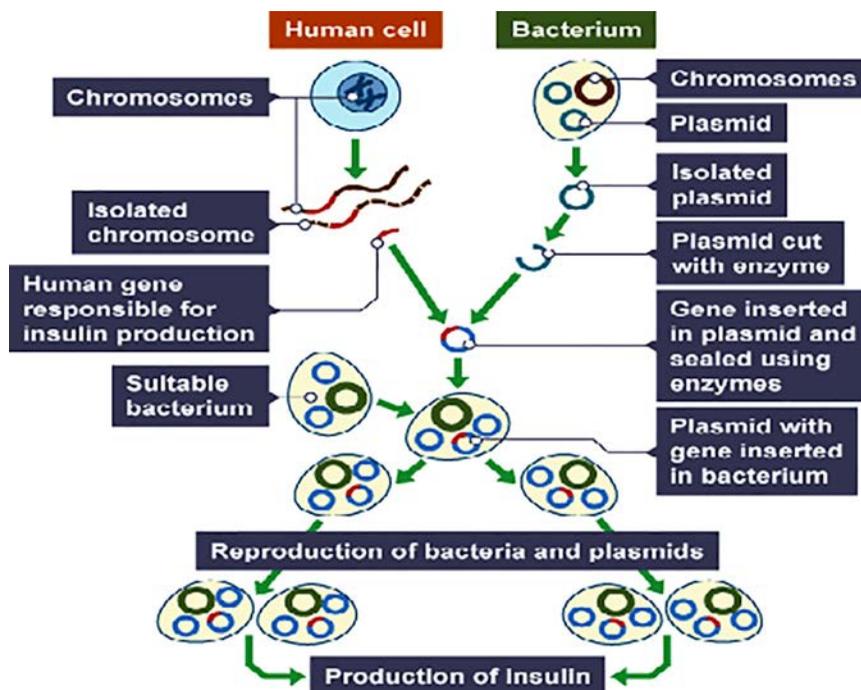


The organisms from which the biosimilar and reference drug are produced may not be identical, and the production process of the reference drug remains confidential, even after the patent for the process expires.<sup>4</sup> As a result, the biosimilar and the reference biologic are not exact duplicates. Inherent variability also exists for the reference biologic, and it must be noted that no batch of any reference product is identical to the previous one, as depicted by the difference between the middle molecule and one to its right. Note the different orientation of yellow lines in each molecule, which represent minor alterations in post-translational modifications that should not affect clinical efficacy.<sup>5</sup>

that are subject to variations affecting the biological and clinical properties of the product.<sup>11,12</sup> The sensitivity of biologics to manufacturing conditions is much greater than for chemical small molecules.<sup>13</sup> It is natural for proteins, once isolated from the host cells that produced them, to undergo certain chemical changes, such as oxidation

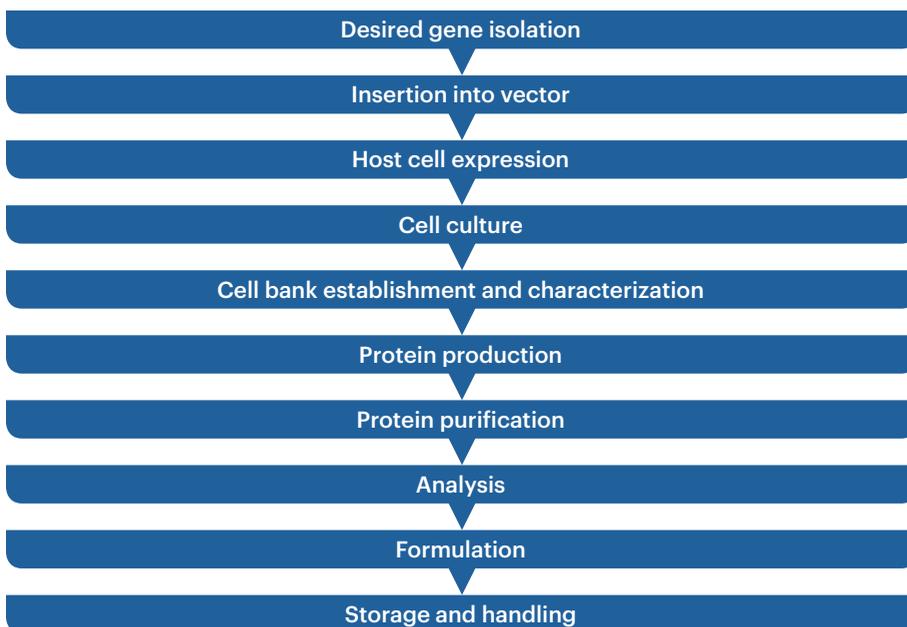
and deamidation. Subtle time-dependent changes in the shape of a protein can trigger undesirable effects, such as protein insolubility, loss of biological function, or increased immunogenicity because of exposure of antigenic segments of the molecule that would usually be hidden from the immune system.<sup>7</sup>

**Figure 3: Recombinant DNA Technology for Making Insulin<sup>10</sup>**



Adapted with permission from BBC. GCSE Bitesize. Home > Science > Edexcel Triple Science Topics > Using Biology > Biotechnology. Available at: [http://www.bbc.co.uk/schools/gcsebitesize/science/triple\\_edexcel/using\\_biology/biotechnology/revision/5/](http://www.bbc.co.uk/schools/gcsebitesize/science/triple_edexcel/using_biology/biotechnology/revision/5/). Accessed October 10, 2014.

**Figure 4: Manufacturing Process for Second-Generation Biologics<sup>2</sup>**



Adapted with permission from Sekhon BS, Saluja V. Biosimilars: an overview. *Biosimilars*. 2011;1:1-11.

### Structure and Function

Other defining characteristics of a biologic are its size and molecular diversity. A biologic carries information, the complexity of which is defined by its unique three-dimensional shape, molecular structure, and sheer size. A larger molecule will have a greater number of atoms, making it more complex, and therefore, more biologically sophisticated. Small molecules are uniform in their composition because they are chemically synthesized with precision, and any contaminants or unwanted byproducts can be removed through purification. Biologics, however, comprise a wide range of closely related variants, or are intentionally a mixture of different biomolecules. Because of their size, biologics move less freely in the body than small-molecule drugs, which can travel most anywhere, and almost always remain undetected by the immune system. Larger molecules, however, may have difficulty crossing cell membranes or the blood-brain barrier, and they are much more likely to trigger an immune response.<sup>9</sup>

### Immunogenicity and Allergenicity

Nearly all therapeutic proteins in biologics induce antibodies. They may decrease efficacy or may induce severe side effects by neutralizing endogenous factors.<sup>2,14</sup> Unintended immune responses to biologics include anaphylaxis, organ-specific immunopathy, autoimmune reactions, and systemic hypersensitivity. Unintended immunogenicity can cause altered pharmacodynamics, pharmacokinetics, and certain immunopathies. Many biologics are intrinsically immunomodulatory. It is probable that most adverse reactions to biologics described as allergy are due to activation/release of proinflammatory mediators, a phenomenon known as “cytokine release syndrome,” “cytokine storm,” and “sterile sepsis.”<sup>15</sup>

Many drug allergies do not likely involve a specific immune response to a drug. Small-molecule drugs must form haptens, known to be harmful, in order to induce a genuine allergic reaction. However, biologics do not need to be biotransformed into hapten-protein complexes in order to induce a drug allergy.<sup>2</sup>

### 3. What are the therapeutic applications of biologic drugs?

Biologics include a wide range of therapeutics, including recombinant hormones, growth factors, blood products, monoclonal antibody-based products, recombinant vaccines, and advanced technology products (gene and cell therapy biologics). These therapies have revolutionized the management of many diseases, including solid tumors, hematologic malignancies, autoimmune diseases, and hormone deficiencies.<sup>2,16</sup> The first generation of biologics was manufactured in the 1980s using recombinant technologies, and the first biologic drug was Humulin, approved by the Food and Drug Administration (FDA) in 1982.<sup>17</sup> Other examples of biologic drugs include rituximab, filgrastim, and epoetin. Biologics are one of the fastest growing therapeutic products in the pharmaceutical industry.<sup>2</sup>

### 4. What is the Food and Drug Administration (FDA) definition of a biosimilar?

“The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity, and potency of the product.”<sup>18</sup> Because it is well recognized that no batch of any biologic, whether reference or biosimilar, is identical to the one previous to it, this statement emphasizes the importance of a biosimilar being similar to the reference product in all relevant functional and structural aspects to the extent that technical and scientific variations during manufacturing and the inherent variability of biologics will not have an impact on safety and efficacy.<sup>5</sup> Achieving this level of quality requires a comparative exercise which confirms that the existing knowledge is adequately predictive to ensure that any differences in quality characteristics have no adverse impact upon safety or efficacy.<sup>19</sup>

The FDA defines these four classifications for proposed biosimilars as part of a comparative analytical characterization continuum:<sup>20</sup>

**Not Similar** due to certain differences in the results of the analytical characterization. At this point, further development through the 351(k) regulatory pathway is not recommended unless, for example, modifications are made to the manufacturing process for the proposed biosimilar product that are likely to lead to a highly similar biological product.<sup>21</sup>

**Similar** means that the sponsor must present additional information to determine if the product is highly similar to the reference product. For example, additional analytical data or other studies may be deemed necessary to determine if observed differences are within an acceptable range to consider the proposed biosimilar product to be highly similar to the reference product.<sup>21</sup>

**Highly Similar** if it meets the statutory standard for analytical similarity given the results of the comparative analytical characterization. The product sponsor would then conduct targeted and selective animal and/or clinical studies to resolve any residual uncertainty and demonstrate biosimilarity.<sup>21</sup>

**Highly Similar with Fingerprint-Like Similarity** if it meets the statutory standard for analytical similarity “based on integrated, multiparameter approaches that are extremely sensitive in identifying analytical differences. The results of these fingerprint-like analyses permit a very high level of confidence in the analytical similarity of the proposed biosimilar and the reference product.” The product sponsor would then conduct targeted and selective animal and/or clinical studies to resolve any residual uncertainty and demonstrate biosimilarity.<sup>21</sup> This last category of fingerprint-like similarity foreshadows the FDA’s possible position regarding interchangeability. An exacting process is necessary to determine the level of biosimilarity required for possible interchangeability with reference drugs.<sup>20</sup>

The FDA definition of an interchangeable biological product is “one that has been shown to be biosimilar to the reference product, and can be expected to produce the same clinical result as the reference product in any given patient. In addition, to be determined to be an interchangeable biological product, it must be shown that for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”<sup>22</sup>

## 5. How do biosimilars compare with generic small molecule drugs?

### Manufacturing

Small-molecule generics are made with the same chemical synthetic pathway that was used to make the reference drug. Once chemists know the pathway, they are able to chemically synthesize a generic chemical drug whose structure and behavior will be identical to the original, thus producing consistent results. Copying biologics is more difficult because they are made from cells, and often their complex structures are not fully understood. Small changes in the manufacturing process can lead to variations in the final product, which can in turn affect safety and clinical effectiveness. Even biologics produced in the same manufacturing facility will have some variation between lots. Therefore, establishing biosimilarity to a reference product requires more preclinical and clinical

testing than is usually necessary for generic small-molecule drugs.<sup>23</sup>

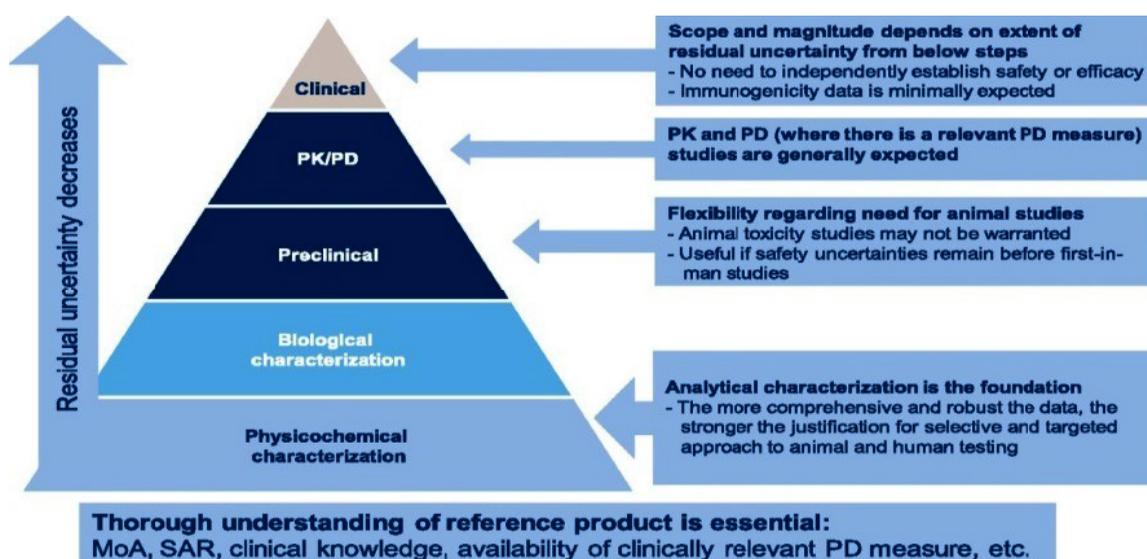
### Approval Process in the United States

Since implementation of the Hatch-Waxman Act, generics of small-molecule drugs approved under the Food, Drug, and Cosmetic Act can undergo an accelerated review known as an Abbreviated New Drug Application, whereby manufacturers must demonstrate bioequivalency, which can be established on the basis of pharmacodynamics and/or pharmacokinetics testing without additional clinical trials. Hatch-Waxman does not apply to biologics, and that is why a new pathway for approval was recently created.<sup>24</sup>

### Cost Savings

Generic drugs generally cost 30-80% of the brand-name product. By 2012, generic drugs accounted for 84% of all US prescriptions and had saved consumers an estimated \$1 trillion since 2002 alone. Biologics are among the most expensive drugs on the market, with average costs about 22 times that of nonbiologic drugs. In 2010, spending on the top seven biologics alone represented about 43% of Medicare Part B's total drug budget. Thus, there is substantial interest in promoting market competition through an accelerated biosimilar approval pathway. An analysis conducted by the Congressional Budget Office estimated that competition from biosimilars would reduce drug spending to about \$25 billion over 10 years, saving the federal government nearly \$6 billion. US federal and state regulatory, pricing, and reimbursement policies will play a key role in determining future cost savings.<sup>24</sup>

Figure 5: The Food and Drug Administration (FDA) “Totality-of-Evidence” Approach to Biosimilar Approval<sup>26</sup>



MoA=mechanisms of action; PD=pharmacodynamics; PK=pharmacokinetics; SAR=structure-activity relationship

Adapted with permission from Wish JB. The approval process for biosimilar erythropoiesis-stimulating agents. *Clin J Am Soc Nephrol.* 2014;9:1645-1651.

## FOOD AND DRUG ADMINISTRATION APPROVAL PATH AND REQUIREMENTS FOR BIOSIMILARITY

### 6. What is the FDA approval path for biosimilars?

Congressional interest in improving access to less costly biologic products led to the 2010 enactment of the Biologics Price Competition and Innovation (BPCI) Act of 2009, which was incorporated as Title VII of the Patient Protection and Affordable Care Act.<sup>25</sup> The BPCI Act amends the Public Health Service Act (PHS Act) and other statutes to create an abbreviated licensure pathway through PHS section 351(k) for biologic products shown to be biosimilar to, or interchangeable with, an FDA-licensed biologic reference product.<sup>18</sup> The 351(a) Biologics License Application (BLA) only covers biologic reference products, and sponsor data from preclinical and clinical testing are used to support approval. The 351(k) BLA for biosimilars, however, must incorporate extensive analytical testing and tailored clinical comparison with a reference product in order to obtain approval.<sup>18,26</sup> To clarify these requirements, the FDA has released several draft guidance documents (see list) to guide manufacturers through the new process of demonstrating that a therapeutic biologic product is biosimilar to its reference product. The documents discuss the science required to establish biosimilarity, proper manufacturing processes, as well as technical issues, such as identifying differences in excipients that may affect product degradation or clinical performance, and study design for obtaining pharmacokinetic and pharmacodynamic data. Future FDA guidance is anticipated for topics related to biosimilar product labeling and interchangeability.<sup>18,20</sup>

#### **FDA Draft Guidance for Industry**

"The Purple Book" contains lists to help clinicians see whether a particular biologic product has been determined by the FDA to be biosimilar to, or interchangeable with, a reference biological product, as well as the reference product exclusivity expiry date.

#### **Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, September 2014**

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm>

#### **Reference Product Exclusivity Biological Products Filed Under Section 351(a) of the PHS Act, August 2014**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407844.pdf>

#### **Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, May 2014**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf>

#### **Formal Meetings between the FDA and Biosimilar Biological Product Sponsors or Applicants, March 2013**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM345649.pdf>

#### **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, February 2012**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>

#### **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, February 2012**

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>

#### **Q&As Regarding Implementation of the BPCI Act of 2009, February 2012**

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm259797.htm>

**Figure 6: Orthogonal Approach to Fingerprint-Like Analyses<sup>18</sup>**

- Analytical testing is the primary focus of biosimilar development
- Fingerprint-like analysis demonstrates product attributes and combinations



**Biosimilar**



**Reference Biologic**

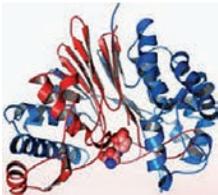
- New techniques and advances in analytics are available.
- More than 1 test method may be used to measure a single quality attribute.

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Analytic comparisons for a biosimilar are likely to be more extensive and comprehensive than those made for reference biologics after a manufacturing change.

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Figure 7: Characterization Study Matrix for Biosimilars<sup>18</sup>

<b>Physiochemical Properties</b> Primary Sequence Glycoforms Impurities Higher Order Structures Peptide Mapping		<b>Bioactivity Assays</b> Effector Function Receptor Binding Cytotoxicity Signal Transduction
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## 7. What level of evidence does the FDA require for demonstrating biosimilarity?

### “Totality-of-Evidence”

Confirming the quality, safety, and efficacy of a biosimilar requires appropriate and rigorous comparative exercises using state-of-the-art analytics. The FDA follows a “Totality-of-Evidence” approach to biosimilar comparative testing and approvals, as depicted in Figure 5. This approach builds upon the extensive clinical knowledge base of the biologic reference product, and includes a robust analytical characterization and preclinical foundation that reduces the need for extensive animal and clinical testing. Immunogenicity testing is an essential component along the development spectrum.<sup>23,27</sup>

### Physiochemical and Biological Characterization

A key feature of this approach is fingerprint-like identification of quality attributes measured by orthogonal methods, in which a variety of highly sensitive tests are used to characterize individual product attributes (such as post-translational changes) and their combinations. (See Figures 6 and 7.) This process involves obtaining batches of the biosimilar manufactured at different times during its shelf life and determining the range of quality attributes at each point in time.<sup>27</sup> A thorough physiochemical comparative exercise is essential for demonstrating biosimilarity, and bioactivity assays reduce residual uncertainties about biosimilarity.<sup>21,28</sup>

### Clinical Evaluation

The clinical studies for biosimilar approval are not designed to establish safety, because this would have already been achieved by the reference biologic during its development and approval process.<sup>28</sup> The type and magnitude of clinical data requirements depend on the complexity of the active substance and how well it can be characterized, on the availability of an accepted surrogate end-point to assess efficacy, on the type and seriousness of safety concerns, and the possibility to extrapolate efficacy and safety data to other indications of the reference product.<sup>21,25</sup> Human safety (including immunogenicity) data are always required, and at least one clinical study comparing immunogenicity of a biosimilar and reference biologic will generally be expected.<sup>21,28</sup>

## 8. What types of testing does the FDA require to assess and prove biosimilarity?

The 351(k) pathway is based on the principle of comparative testing after a manufacturing change for a reference biologic product, which is an international standard described in the International Conference on Harmonization Q5E.<sup>29</sup> The process begins with structural and functional characterization of both the biosimilar and reference products. The more rigorous the analysis and the fewer the differences between the reference and biosimilar products, the less additional testing required. The goal is to generate fingerprint-like analysis algorithms in order to demonstrate biosimilarity. Some of the studies required for this process are listed below.

- Analytical Studies:
  - Structural Analysis:
    - Primary amino acid sequence (minor N- or C-terminal truncations may be allowed that do not affect safety or effectiveness)
    - Primary, tertiary, and quaternary structure
    - Post-translational modifications (glycosylation and phosphorylation)
    - Other potential variants (protein deamidation, oxidation, and aggregation)
    - Intentional chemical modification (PEGylation site)
    - Lot-to-lot variability
  - Functional Assays:
    - Bioassays
    - Binding assays
    - Enzyme kinetics

There must be sufficient knowledge about the drug's mechanism of action in order to predict the clinical relevance of any observed structural differences.<sup>26</sup>

- Animal Studies:
  - Toxicity and immunogenicity studies
  - Pharmacokinetic (PK) and pharmacodynamic (PD) measurements

Animal studies may be done in order to resolve any residual uncertainties regarding safety. Animal data to assess toxicity, immunogenicity, and PK/PD can be more selective and targeted if the analytical data is comprehensive and robust.<sup>26</sup>

- Clinical Studies:
  - PK, PD, and immunogenicity studies sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.<sup>30</sup>

The amount of human testing will depend on the consistency in results from the structural and functional analyses, the knowledge base regarding the reference drug and its safety issues, and any concerns that remain after the previous steps in testing are complete. Usually, human PK/PD testing will be required, but most likely there will be no need to establish safety and efficacy independently for the biosimilar unless significant residual concerns remain. Immunogenicity studies that include assessment of binding antibodies and neutralizing antibodies may be required. The FDA will then make its determination regarding the approval on the basis of the totality of the evidence, and each application will be evaluated on a case-by-case basis.<sup>26</sup>

The FDA has the discretion to determine that an element described above is unnecessary in a 351(k) application, and conversely, it will not waive an element if the reviewers are unsure that the product will have clinical activity that is highly similar to the US-licensed reference product.<sup>30</sup>

## ADOPTION OF BIOSIMILARS: WHAT CLINICIANS SHOULD KNOW

### 9. What is the global experience with biosimilars?

The European Medicines Agency (EMA) was the first regulatory organization to develop guidelines for comparing a proposed biosimilar to a reference product, in terms of quality, safety, and efficacy. Product-specific guidelines for some biosimilar medicines, such as recombinant erythropoietin, are provided by the EMA/Committee for Medicinal Products for Human Use (CHMP). The EMA/CHMP Guidelines are considered the gold standard for establishing biosimilarity and are the basis for regulations in other countries, including Australia, Canada, Japan, Korea, and South Africa.<sup>31-33</sup>

It should be noted that the term “biosimilar” is misleading when used in reference to copies of biologics that have not proven similar to reference products, notably drugs developed for markets that are not highly regulated, such as those in Asia, Africa, and Central and South America.<sup>26</sup> Many of the countries in these areas do not have rigorous testing requirements and strict standards for approving drugs that are claimed to be similar to reference products. The inferior quality and adverse events that have been reported with products called “biosimilar” in these countries have made many healthcare providers and regulators wary about the safety and efficacy of biosimilars in general. However, biosimilars that have been approved in highly regulated markets, such as the European Union (EU), Canada, Japan, Australia, and New Zealand must meet

strict criteria for quality and similarity with their respective reference products, and the performance of such drugs after approval in these markets has been positive.<sup>34</sup> The long-term experience in the EU, which has had a rigorous pathway for the approval of biosimilar agents since 2005, has resulted in savings and increased access. Additionally, patient outcomes have not been adversely impacted because the same consistent and appropriate scientific regulatory standards for reference products have been applied to biosimilars.<sup>34</sup>

In the European Union, 17 out of 20 brand-name biosimilars, based on five reference products, have received marketing authorization since the regulatory approval pathway for biosimilars was established in 2005; two were withdrawn by the sponsors and only one was refused by the EMA.<sup>35</sup>

Biosimilars in Europe cannot be automatically substituted one for another as can be done with generic small-molecule drugs.<sup>31</sup>

### 10. What points should the nephrology clinician evaluate when using both biologics and biosimilars?

#### Background

While there are currently no biosimilars approved in the US, the FDA has accepted its first application for a biosimilar, filed through the BPCI pathway in July 2014.<sup>35</sup> Many see this as the beginning of increased competition which will lead to better access to expensive, but essential therapies. Therefore, clinicians need to be informed about what to consider when using a biosimilar product. Requirements for labeling and interchangeability have not been determined by the FDA, but prescribers need to be aware when this may be established, at both the state and federal levels. Substitution of a biosimilar for a reference product or changing from one biosimilar to another constitutes a change in clinical management.<sup>36</sup>

After six years of successful use in Europe, data has demonstrated that biosimilar erythropoiesis-stimulating agents (ESAs) are safe and effective alternatives to brand-name epoetin alfa for treating anemia in patients with kidney disease. These new treatment alternatives have increased competition and decreased the price of ESAs across Europe, and the same should occur in the US once they are adopted here.<sup>37,38</sup> The investigation and use of these products, as well as reference biologic ESAs, has revealed four areas of interest pertinent to their clinical application: 1) immunogenicity; 2) route of administration; 3) differences in glycosylation; and 4) potency.<sup>39</sup>

Past experience with reference biologics outside the US had generated some concern about immunogenicity caused by changes in the manufacturing process. In 1998, for example, the makers of a reference biologic ESA changed the stabilizing agent from human serum albumin to polysorbate 80 and glycine. It is thought that the polysorbate 80, in combination with leached substances from the rubber stoppers in pre-filled syringes, increased the drug’s immunogenicity, and led to pure red cell aplasia (PRCA) when the drug was given subcutaneously (sc).<sup>26</sup> Even though the product was not a biosimilar,

**Table 1: Points to evaluate when using biosimilar ESAs<sup>39</sup>**

Pre-registration clinical trials, study design, sample size
Study population and how representative it is of the clinical population
Study duration, statistical methodology
Difference between the trial and reference drug (biologic activity, route of administration, median dosage, and endpoint)
The need to establish local protocols/care bundles to avoid inadvertent drug interchange, or when switching administration route (intravenous versus subcutaneous)
Safety, adverse events, potential for immunogenicity

Adapted with permission from Mikhail A, Farouk M. Epoetin biosimilars in Europe: five years on. *Adv Ther.* 2013;30:28-40.

the immunogenicity caused by one change in the manufacturing process highlights how such changes could potentially impact the profile of any biologic, whether it be a reference product or a biosimilar.

As biosimilar ESAs manufactured in Argentina, China, South Korea, and India came onto the Thai market, there was a surge in the prevalence of PRCA, and researchers found that 23 of 30 patients had antibodies to erythropoietin.<sup>40</sup> All of these patients received the biosimilar ESA sc, which supports the theory that an interaction between an unknown alteration in the ESA molecule and sc administration is a predisposing factor for the development of immune-mediated PRCA, as also seen in the experience with the reference biologic ESA described above. Regardless of the association with sc administration, it was concluded that stricter measures for approving biosimilar ESAs in Thailand are the primary safeguard against future problems.<sup>40</sup> None of the studies of intravenously (iv) administered biosimilar ESAs currently licensed in Europe has demonstrated any signs or symptoms of immune-mediated PRCA, and one biosimilar ESA is approved there for both iv and sc administration, as its safety and efficacy has been confirmed through comparative testing for both routes.<sup>26</sup>

Studies of biosimilar ESAs currently licensed outside of the US have shown a varying degree of glycosylation compared with the reference product; glycosylation plays a variety of roles in the biological properties and effects of therapeutic proteins, so it may be essential to assess the impact of carbohydrate content in different biosimilar ESAs.<sup>39</sup> Variations in carbohydrate structure may occur as a result of using different cell lines during manufacturing, thus affecting the PK and leading to a change in potency among different biosimilar ESAs.<sup>39</sup> For this reason, it is recommended that clinicians monitor hemoglobin levels when: 1) switching from a reference to a biosimilar ESA; 2) switching from one biosimilar ESA molecule to another; and 3) when switching to a different brand of the same molecule, so they can adjust the ESA dose accordingly.<sup>41</sup>

### **Points for the Clinician to Evaluate When Using Biosimilars**

With the current standard of fingerprint-like similarity being demonstrated through state-of-the-art orthogonal testing methods, a good safety record maintained in Europe over the past six years, and the rigorous FDA regulatory oversight that is currently in place, biosimilar ESAs should be a viable alternative to reference ESA products in the US. (See Table 1.)

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