Biosimilar Medicines in Dermatology: Key Aspects

After the recent enactment of a specific approval pathway for biosimilars and publication of the first draft guidelines on biosimilar product development by the FDA, biosimilars are expected to be available in the US soon.

BY PROFESSOR BEGOÑA CALVO

Several biopharmaceutical products are approved for the treatment of moderate to severe psoriasis and other immune mediated disorders. They include biologic drugs such as the soluble tumor necrosis factor (TNF) receptor fusion protein etanercept (Enbrel, Amgen/Pfizer), the chimeric monoclonal antibody infliximab (Remicade, Janssen), the human monoclonal antibody adalimumab (Humira, AbbVie), and others, such as interferon-gamma. Many of these medicines have structures based on monoclonal antibodies that differ in size and in their capacity to bind to the target ligand, e.g. to TNF.[1-3]

The patents of many of these innovator biopharmaceuticals will expire within a few years in the US (Humira: 2016; Remicade: 2018; Enbrel: 2028), despite attempts by pharmaceutical companies involved to delay the expiry date. This represents an opportunity for the drug industry of biosimilars (subsequent versions of innovator biopharmaceutical products, also referred to as follow-on biologics in USA or subsequent entry biologics in Canada).

Biologics are large, complex molecules derived from living cells using recombinant DNA or monoclonal antibodies technologies. In general, biosimilar and biological innovator products are used at the same dose to treat the same disease. Due to their large and complex molecular structure, biologics have inherent variability, and they can never be exactly replicated, unlike small molecule drugs that are chemically synthesized (Figure 1).[4]

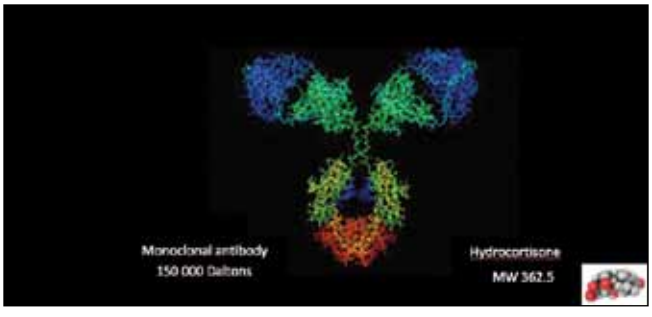
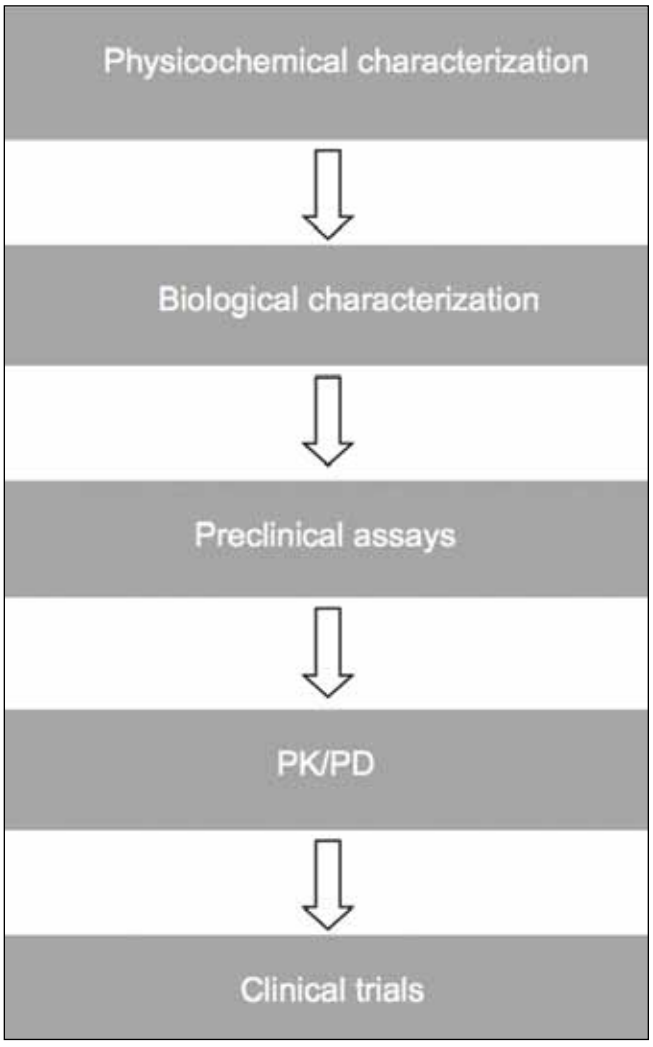


Figure 1. Structural comparison between the molecules of a monoclonal antibody and hydrocortisone. Molecular weight (MW).

DIFFERENCES BETWEEN GENERIC DRUGS AND BIOSIMILARS

Marketing approval of generic versions of low molecular weight drugs only requires the generic to demonstrate chemical identity and bioequivalence with regard to the innovator drug.

Nevertheless, the existing legal framework for generic drugs does not apply for biosimilars approval. The conventional methods used to obtain small molecule drugs generate highly purified products that can be readily and identically reproduced in different laboratories. In contrast, obtaining biosimilar medicines involves differences in manufacturing processes and in biological materials compared to the original product (Figure 2).



(PK/PD: pharmacokinetic/pharmacodynamic studies)

Figure 2. Biosimilar development process.

These processes have inherent variability so that their subproducts may also be variable (Table 1).[5] This is because the biosimilar manufacturers have no access to the production data of the innovator biologic product, which are protected by the patent. It is therefore practically impossible to produce an identical copy of the original product, although a molecule that is biologically and clinically comparable, i.e. a biosimilar, can be manufactured.

Variations in glycosylation, purification, formulation and storage of a biologic product may alter its safety and efficacy profiles. Moreover, the impurities existing in the final product as a result of the production process (biological materials, product related impurities, etc.) may also influence its biological and clinical properties. A modification in the three-dimensional structure of a protein may also have important effects on immunogenicity. Usually, the primary safety concern not only for biosimilars, but also for all biotechnological medicinal products, is immunogenicity.

WORLDWIDE REGULATORY STATUS OF BIOSIMILARS

Biosimilar medicines are a reality in the European Union (EU), where the first biosimilar was approved in 2006. Following the European Medicines Agency's (EMA) success, the Food and Drug Administration (FDA) adopted a similar approach to the EMA's with regards to the marketing approval of these products. Thus, the concept of biosimilar was established in the USA.[6] The EMA has issued several guidelines containing details of clinical, non-clinical, and quality requirements for biosimilar development; one of the most recent is related to monoclonal antibodies biosimilars.[7-10] The most relevant European scientific guidelines establish that the biosimilars approval process varies according to the product, due to the significant differences between them. Therefore, the required amount of nonclinical and clinical data is determined on a case-by-case basis.[4]

The current EU guidelines have resulted in the approval of biosimilar therapeutics with comparable efficacy and safety profiles for the recommended indications of their respective reference originator biologics. The European guidelines have served as a starting point in the development of a process for approving biosimilars in the US and worldwide. In addition, FDA legislation goes a step further than the EMA, offering the possibility to adopt full interchangeability for biosimilars.[11]

After the approval of a biosimilar product, healthcare professionals and consumers can have the assurance that the product meets FDA safety and efficacy standards. At the same time, the availability of biosimilars should result in a significant cost savings for national health care programs and consumers.

In the US, biologic medicines have been registered through two main pathways. Medicines such as erythropoietins were approved under the Public Health Services (PHS) Act. The PHS Act was amended by the Patient Protection and Affordable Care Act (Affordable Care Act), signed into law in 2010, to create an abbreviated licensure pathway for biologic products that are demonstrated to be biosimilar to or interchangeable with an FDA-licensed biologic product. This pathway is covered by the Biologics Price Competition and Innovation (BPCI) Act.[6,11]

Under the BPCI Act, a biological product may be demonstrated to be biosimilar to an already-licensed FDA biologic product (the reference product) if the available data show the product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and there are no clinically significant differences

A 351(k) application shall include information demonstrating that the biological product:

- Utilizes the same mechanism(s) of action for the proposed condition(s) of use (to the extent known for the reference product);
- Condition(s) of use proposed in labeling have been previously approved for the reference product;
- Has the same route of administration, dosage form, and strength as the reference product;
- The manufacturing facility meets standards to assure purity, safety and potency.

Figure 3. BPCI Act highlights for biosimilars approval.

between the biologic product and the reference product in terms of safety, purity, and potency of the product. The new pathway for highly similar products to originator biologic medicines is called 351(k) (Figure 3).[6]

In the same way, regulatory agencies from Canada, Japan, and Australia follow criteria close to those of the EMA.[12] On the other hand, India, China and some countries in Central and South America have lax regulation, not comparable to the previously mentioned ones. These countries have approved alternative biologicals, posing significant analytical, pharmacokinetic, or clinical differences compared to the innovator product, so that they cannot be registered in regulated markets like EU, US, or Japan.

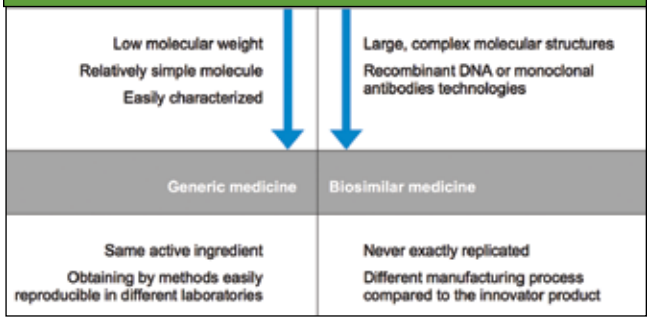
As can be gathered, in developed countries, the approval process for biosimilars is different from that of generic drugs. These products only need to demonstrate they are bioequivalent to the original product, while for biosimilars demonstration of analytical similarity, comparative pharmacokinetic and pharmacodynamic (PK/PD) studies are also required.

Furthermore it is possible to extrapolate the biosimilar product efficacy to other indications of the innovator product whose pathogenic mechanism is similar. This extrapolation does not need additional clinical trials, although the final decision is carried out by regulatory authorities. Immunogenicity evaluation throughout clinical trials is also required as well as a pharmacovigilance program after product marketing.

INTERCHANGEABILITY

Generic therapeutic substitution is the replacement at dispensation of an alternative, therapeutically equivalent drug than what was originally prescribed by a physician. According to the Affordable Care Act, a biosimilar product would be interchangeable with the reference product if

TABLE 1. GENERIC VS BIOSIMILAR MEDICINES.



it can be expected to produce the same clinical result as the reference product and, 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 that the risk of using the reference product without such alternation or switch.

The American Academy of Dermatology Association (AADA), in order to ensure patient safety, recommends that generic therapeutic and biosimilar substitution can be made provided that the following minimum thresholds are met:

- In the case of biosimilars, the biosimilar has a unique nonproprietary name to eliminate confusion, to allow providers to accurately track the therapeutic in a patient's permanent record, and to allow for the collection of adverse event information;
- In the case of biosimilars, the biosimilar has been designated by the FDA as interchangeable with the prescribed biologic for the specified indicated use;
- The prescribing physician provides explicit permission to the pharmacist that a generic therapeutic or biosimilar may be used as a substitute to the original therapeutic or biologic medication;
- The patient (or patient's authorized representative) must be informed and educated about a generic therapeutic or biosimilar substitution at the point of sale;
- The pharmacist notifies the prescriber in writing or electronic communication within 24 hours prior to the substitution; and
- Upon notification of a substitution, the pharmacy and the prescribing physician are encouraged to retain a permanent record in the patient's medical record of the generic therapeutic or biosimilar substitution.

It is imperative that data be collected regarding efficacy and safety and, therefore, that these products have different names so that medical records can fully reflect the exact medication prescribed and taken. Data on the frequency of biosimilar switching in clinical practice is scarce, but it seems

> "Dermatologists need a thorough understanding of the issues associated with biosimilars to facilitate interpretation of the clinical impact of different treatments."

most frequent for erythropoietins. No evidence has been found from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns.[13]

PATIENT SAFETY

Pharmaceutical companies in regulated markets are legally required to monitor the use, effects, and side effects of their medicines. They have systems to detect, assess and understand the reasons of any adverse drug reactions (ADR) seen during the use of medicines. Each manufacturer must have its pharmacovigilance system approved, which is also inspected by the regulatory authorities.

Since even small differences may affect safety, tracking of adverse events associated with the use of both reference and biosimilar products, and the ability to readily identify the manufacturer and the product name is an issue that must be addressed. The ADR reports should include, in addition to the International Nonproprietary Name (INN), other indicators, such as brand name, manufacture's name, lot number, and country of origin of the batch used.[14]

After the introduction of these biosimilars in the US, healthcare costs should be reduced, since they are cheaper than original products. This will help governments to control the healthcare expenditure and make these treatments more accessible to patients.

The main obstacle, besides the technological issues, the efficacy or safety incidences, and regulatory uncertainties, will be the tough legal battle the owners of patents in force will pitch. It is necessary to keep in mind that the biotech industry represents 20 percent of investment in research and development in the US, with a global market close to US $60 billion in 2012 only for monoclonal antibodies.[15]

CONCLUSIONS

Nowadays only a few biopharmaceutical products are out of patent. Therefore, only a few classes of biosimilars are approved in highly regulated markets. In the coming years other complex molecules, such as monoclonal antibodies, will be off-patent and the market of biosimilars will develop significantly.

In the US, after the recent enactment of a specific approval pathway for biosimilars and publication of the first draft guidelines on biosimilar product development by the FDA, biosimilars are expected to be available soon.

Although biopharmaceuticals interchangeability can pose barriers, it should be noted that the innovative products also change over time, e.g. if any modification is introduced in the production process. The scientific principles underlying the biosimilars comparability exercise versus the reference product are the same as those for changes in the manufacturing process of a given biopharmaceutical, for which guidance and experience already exist.[16]

The expected benefits of biosimilars are reductions in acquisition expenses and consequently better access to biopharmaceuticals. It has been estimated that a 20 percent price reduction of off-patent biotherapeutics would save the US federal government $9 billion to $12 billion over the next 10 years.[17,18]

Dermatologists need a thorough understanding of the issues associated with biosimilars to facilitate interpretation of the clinical impact of different treatments.

After the approval of a biosimilar product by a stringent regulatory authority, healthcare professionals and consumers can have the assurance that the product will meet FDA safety and efficacy standards. ■

Dr. Calvo is in the Pharmaceutical Technology Department, Faculty of Pharmacy, at the University of the Basque Country in Vitoria-Gasteiz, Spain.

1. Enbrel (etanercept) [package insert]. Thousand Oaks, CA: Immunex Corp; 2010.
2. Humira (adalimumab) [package insert]. North Chicago, IL: Abbott Laboratories; 2010.
3. Strober BE, Armour K, Romiti R, et al. Biopharmaceuticals and biosimilars in psoriasis: What the dermatologist needs to know. J Am Acad Dermatol. 2012; 26 (2):317-22.
4. Zuñiga L, Calvo B. Biosimilars approval process. Regul Toxicol Pharmacol . 2010; 56:374-7.
5. Genazzani AA, Biggio G, Caputi AP, et al. Biosimilar drugs: concerns and opportunities. BioDrugs. 2007; 21, 351–6.
6. FDA. Biologics Price Competition and Innovation Act of 2009, x7002(b)(3). Technical report, Food and Drug Administration, Silver Spring, MD, USA, 2009.
7. Weise M, Bielsky MC, De Smet K, et al. Biosimilars: what clinicians should know. Blood. 2012; 120 (26): 5111-7.
8. Committee for Medicinal Products for Human Use (CHMP). Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues.EMA/CHMP/BMWP/403543/2010. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf . [Accessed 2013 January 15].
9. Committee for Medicinal Products for Human Use (CHMP). Concept paper on the revision of the guideline on similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues. EMA/CHMP/BMWP/572828/2011. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/10/WC500115611.pdf [Accessed 2013 January 15].
10. Calvo B, Zuñiga L.Therapeutic Monoclonal Antibodies: Strategies and challenges for biosimilars development. Current Med Chem. 2012; 19 (26):4445-50.
11. Calvo B, Zuñiga L. The US approach to biosimilars. The long-awaited FDA approval pathway. Biodrugs. 2012; 26 (6): 357-61.
12. Wang J, Chow S. On the regulatory approval pathway of biosimilar products. Pharmaceuticals. 2012; 5: 353–68.
13. Ebbers,HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Exp Opin Biol Ther. 2012; 12: 1473-85.
14. European Medicines Agency, Eudravigilance expert working group: Volume 9A: Implementation questions & answers, Version 1.2; February 29, 2008. http://www.ema.europa.eu/pdfs/human/ phv/11197208en.pdf. [Accessed January 15, 2013].
15. BCC Research. Biologic Therapeutic Drugs: Technologies and Global Markets. Available from URL: http:// www.bccresearch.com. [Accessed 2013 January 15].
16. ICH Guideline topic QE5: Comparability of biotechnological/ biological products subject to changes in their manufacturing process. Available from URL: http://www.ich.org/products/guidelines/quality.html. [Accessed 2013 January 15].
17. Simoens S. Biosimilar medicines and cost effectiveness. Clinicoecon Outcomes Res. 2011; 3:29-36.
18. Hackbarth GM, Crosson FJ, Miller ME. Report of the Congress: improving incentives in the Medicare program. Washington, DC: Medicare Payment Advisory Commission; 2009.