



*Transforming Clinical Trials*

## **Global Biosimilar Development**

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accompanies this whitepaper can be found at:  
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## TERMINOLOGY

Many terms have been used to describe copy biologics: “follow-on biologics”, “subsequent entry biologic”, “similar biotherapeutic product”, “similar biological medicinal product”, “bio-generic”, “non-innovator biologic” and “biosimilars”. Not all copy biologics are biosimilars, but all biosimilars are copy biologics.

Biosimilars, by definition, are copy Biologics with a clear and effective regulatory route of approval that requires comparability studies at all stages of development: quality, non-clinical and clinical. The comparability studies required for comparing the innovator reference product and the potential biosimilar product are crucial for the regulatory process and guarantee the quality and clinical performance of the biosimilar.

Unfortunately, inconsistency in nomenclature used for biosimilars has led to confusion in referring to some products. The confusion over terminology is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions which arise from misleading published reports on apparent problems with biosimilars. Several examples of this have already occurred.

A case of pure red cell aplasia (PRCA) in an end-stage renal disease patient associated with induction of antibodies to administered erythropoietin (EPO) was described in India<sup>1</sup>. The patient had received the EPO product Wepox (Wockhardt Limited, India) which is referred to as a follow-on product. In the paper the authors state that in Europe, follow-on EPOs are also referred to as biosimilar EPOs. However, there is no evidence that this product has been approved using the comparability approach required in the EU for biosimilarity and described in the WHO and other guidelines. This is, in fact, unlikely as the Indian Regulatory process does not include biosimilars (up to very recently with the new guidelines) and approves non-innovator products based on a stand-alone system<sup>2</sup>. Thus the product Wepox, which is not a biosimilar and should not be described as such, clearly misleads the reader by using incorrect terminology.

Another serious example of misuse of terminology in a publication appeared with the alarming title “Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies”<sup>3</sup>. This paper describes loss of response to EPO in a number of patients being treated with what are called biosimilar EPOs in Thailand. These products were produced in Argentina, China, India and South Korea, and 14 different such products approved for use in Thailand. None of these products were really biosimilars as all were approved using the process employed for chemical generics, i.e. no comparison with originator product was conducted.

## RECENT BIOSIMILAR REGULATORY UPDATE

The most important recent development has been in the US; the legislative route creating biosimilars for the US market was created by the enacted healthcare reform law, the Patient Protection and Affordable Care Act (PPAC Act), signed into law in March 2010. Among other changes, the PPAC Act amends the Public Health Service Act (PHS Act) to create an abbreviated approval pathway for biological products that are demonstrated to be “highly similar” (biosimilar) to or “interchangeable” with an FDA-approved biological product; Also in the PPAC Act, there is a provision demanding that individuals should take personal responsibility for paying for their healthcare by obtaining health insurance or pay a fine. The latter was legally challenged as unconstitutional, and on 28 June 2012 the US Supreme Court ruled in favour of the bulk of the PPAC Act, meaning that the biosimilars pathway, which is part of the act, is now also safe. The decision removes any hesitation biosimilar manufacturers may have had in using the Biologics Price Competition and Innovation Act of 2009 (BPCIA) due to the

- 1 Keithi-Reddy SR, Kandasamy S, Singh AK. Pure red cell aplasia due to follow-on epoetin. *Kidney Int.* 2008;74:1617-22.
- 2 Malhotra H. Biosimilars and non-innovator biotherapeutics in India: an overview of the current situation. *Biologicals.* 2011;39:321-4.
- 3 Praditpornsilpa K, Tiranathanagul K, Kupatawintu P, Jootar S, Intragumtornchai T, Tungsanga K, Teerapornlertratt T, Lumlerkul D, et al. Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies. *Kidney Int.* 2011;80:88-92.

uncertainty of its survival. With the biosimilars framework intact, efforts to shape the implementation of the pathway will certainly follow.

Other important development is the release of the adopted guideline on “Similar biological medicinal products containing monoclonal antibodies—non-clinical and clinical issues: EMA/CHMP/BMWP/403543/2010” in the EU in June 2012 with an effective date of 1 Dec 2012. This is a very important step in the development of biosimilar monoclonals; at one point several years ago, it was questionable whether we could have biosimilars for such complex molecules. Not only that, we have a clear regulatory pathway for monoclonals, but during the development, several issues were highlighted and resulted in the re-evaluation of existing guidelines to provide further clarifications with anticipated benefit for industry and assessors of biosimilar products. These include the selection of relevant species for non-clinical studies, need for clinical equivalence studies vs. non-inferiority and the possibility to extrapolate to other indications.

In the rest of the world, the latest exciting development is the release of national guidelines on the development of similar biologics in India in June 2012. Presently, several organisations are actively engaged in manufacturing and marketing similar biologics in India. So far, these similar biologics were approved by Review Committee on Genetic Manipulation (RCGM) and Central Drugs Standard Control Organization (CDSCO) using an abbreviated version of the pathway applicable to new drugs on a case-by-case basis. Since there are several such products under development in India, both regulatory agencies considered the need to publish a clear regulatory pathway outlining the requirements to ensure comparable safety, efficacy and quality of a similar biologic to an authorised reference biologic. Based on demonstration of similarity in the comparative assessment, a similar biologic may require reduced preclinical and clinical data package as part of submission for market authorisation.

## REFERENCE PRODUCT

In order to be cost-effective, a biosimilar product need to access global markets based on a single development programme that meets the requirements of all markets. In the EU the overarching EMA guideline for “Similar biological medicinal products” CHMP/437/04 states that “The chosen reference medicinal product must be a medicinal product authorised in the Community, on the basis of a complete dossier in accordance with the provisions of Article 8 of Directive 2001/83/EC, as amended.” So far “authorised in the community” has been interpreted as sourced in the EU as well. It was also believed that to change this will require legislative changes in each EU country, which can take a very long time and can be prohibitive.

On 26 June 2012 the EU commission agreed new change to the overarching EMA guideline on biosimilars, CHMP/437/04, which will incorporate changes to the wording to allow sourcing outside the EU without lengthy legislative process. Wording changes will make it clear that it has to be licensed in the EU but not necessarily sourced. It is expected that this will be completed by end of year 2012, but sponsors are encouraged to discuss with EMA before the official change is made. There will also be a need to consider bridging studies to bridge data from a reference product from outside the EU with the product within the EU.

The FDA draft guidance document, “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product”, state that data generated with non-US licensed product may be considered acceptable, provided adequate scientific justification is provided and an acceptable bridge is established but caution about interchangeability: The FDA “Q&A Regarding Implementation of the BPCIA” (Q.1.8) states that “At this time, as a scientific matter, it is unlikely that clinical comparisons with a non-U.S.-licensed product would be an adequate

basis to support the additional criteria required for a determination of interchangeability with the U.S.-licensed reference product.”

Japan requires reference product to be locally sourced, and so far there are no indications if they will change their position, although there is considerable pressure on them to align with other regions.

The rest of the world will accept non-locally sourced reference product with appropriate scientific justification.

Overall there is harmonisation but this is still to be tested. There are still several open questions: can we mix sources? What do the bridging studies look like and will all regions accept the same bridging study?

## DO WE HAVE A PATHWAY FOR ONE GLOBAL PROGRAMME FOR ALL REGIONS?

Despite progress, we are still a long way from harmonisation. In the current environment, the risks of a global programme meeting all the regional requirements are high, with many elements that are still unclear and can potentially hinder globalisation:

### GUIDELINES:

None of the guidance documents are descriptive. Instead, agencies will ordinarily provide feedback on a case-by-case basis on the components of a proposed product development program. This could potentially introduce differences in advice which is further complicated given the level of expertise differs from region to region.

### REFERENCE PRODUCT:

On the surface it appears that all regions are moving towards the same target, but until this is tested one must be cautious. There is no agreement across regions on what is an acceptable bridge and acceptable parameters if reference product is sourced outside “own” region. Furthermore the approved formulation and/ or presentations of the reference product may vary globally.

### STUDY DESIGN

#### *Sensitive model:*

All regions recommend the use of the most sensitive disease model for testing biosimilarity. The most sensitive model could be an indication not licensed globally. Would Agencies accept such an approach? EMA guidelines suggest so, but other Agencies are silent on this topic. Furthermore the FDA states in the guidance documents that similar study populations (across clinical programmes) are essential for supporting the constancy assumption. This can be interpreted as “repeat” of the originator pivotal studies in populations that are not necessarily the “most sensitive model”.

#### *Similarity:*

Different Agencies have still differing views on how to measure “similarity” through endpoints and equivalence margins leading to inflation of patient numbers and/ or duplication of studies. Although it is clear from EMA and the FDA that the aim is to establish not patient benefit (this has been established already by the reference product), but rather biosimilarity, there can be differences of opinion on what is the most appropriate endpoint and the acceptabil-

ity margin. In some instances the FDA has requested endpoints that have not been studied in the originators' pivotal studies, while EMA has accepted the same endpoints, leading to different study designs. Furthermore there is lack of historical data on such endpoints which makes it difficult to calculate the variability and hence the sample size, leading to further complications of the clinical programme.

### *Extrapolation*

Extrapolation across indications in different therapeutic areas is not readily accepted by all agencies globally. The "level" of scientific justification required by one Agency may differ significantly from another especially in cases where the mechanism of action is poorly understood.

### *Clinically meaningful*

What is "clinically meaningful" to one Agency may not be the case with another; there is no global definition, and it is "case-by-case" which could potentially lead to different views.

## WHAT DO WE NEED IN PLACE

### TO BE ABLE TO TRULY GLOBALISE BIOSIMILAR PROGRAMMES?

For true globalisation, it is critical that highly regulated agencies work together to provide the industry with global guidance:

*A unified set of guidance documents with more descriptive requirements setting clear design requirements:*

- *Population*
- *Endpoint*
- *Acceptability margin*
- *Immunogenicity testing*
- *Extrapolation requirements*

*One "reference product" sourced from a highly regulated market*

*Clear guidance on when "bridging" studies are required and design specifications*

How likely? Agencies are in continuous dialogue, but the legal framework in each country with local regulatory requirements will inevitably slow the process. To make changes, they must want to make the change—and they do in order to make expensive drugs more affordable and increase access of these drugs globally. Sponsors are encouraged to engage with all regions very early in the development and try to seek agreement on one global programme. Considerable experience has been gained in the EU on the concept of biosimilarity, not only from a conceptual but also from a data perspective. Information sharing among the Regulatory Agencies will help to build confidence across the globe and deliver global harmonisation.

## CONTACT INFORMATION:

### **Rodeina Challand**

*Executive Director, Biosimilars*

*Development at PRA*

ChallandRodeina@praintl.com

+44 118.918.1000