

Biosimilars: The Way Forward In the United States

Background

The European Medicines Agency has been approving biosimilars since 2006. It therefore has a lot of experience in this respect. The situation is different in the United States. Although originator biological medicines have been approved in the US since 2006, these have not been approved as biosimilars. This difference is due to the historical way that biological medicines have been registered in the US.

Biological medicines have been registered by two main pathways in the US. These are under the Food Drug and Cosmetics Act (low molecular weight heparins, growth factor, insulins) and under the Public Health Services Act (e.g., erythropoietin). These different mechanisms of approval in the US, provide unique opportunities for registration of biological medicines that do not exist in Europe. For instance, Enoxaparin, a low molecular weight heparin was registered as a generic under 505(j), the generic pathway. Consequently, this medicine is fully substitutable for the originator product. The 505(b)(2) route has also been used to register medicines like Omnitrope.

The challenge in the US was how would “copies” of originator biological medicines registered under the Public Health Service Act via 351(a) be registered. There has been much discussion on this over the years. After initially arguing strongly that such “copies” could not be made due to safety concerns, the prohibitive costs to global healthcare systems made it imperative that a way be found to make the very thing argued against feasible. What was previously perceived to be impossible has suddenly become do-able.

In 2009, President Obama signed into law the Healthcare Act. The Biologics Price Competition and Innovation Act of 2009 (BPCI) amended the Public Health Service Act, creating an abbreviated pathway for the registration of medicines that are demonstrated to be highly similar to originator biological medicines. A new pathway for highly similar biological medicines was created, known as 351(k).

The 351(k) pathway stated what would be needed to enable registration of these highly similar medicines. The following would need to be conducted:

1. Analytical studies
2. Animal studies (including toxicity studies)
3. A clinical study or clinical studies
 - a. Including assessment of immunogenicity, PK, PD
 - b. One or more indications licensed for the Reference Product

Meetings held with the pharmaceutical industry and other stakeholders in recent months and years had made clear that more meat would need to be put on the bone of the 351(k) language. The long awaited FDA guidelines were issued by FDA on the February 9th, 2012.

The initial three guidelines are the first in a set of guidelines that the FDA will undoubtedly issue over the coming months and years. The purpose of these guidelines is to clarify what is required to secure registration for biosimilars. The three guidelines issued on February 9th, 2012 are as follows:

1. Guidance for Industry: **Scientific Considerations** in Demonstrating Biosimilarity to a Reference Product, February 2012, CDER, CBER

2. Guidance for Industry: **Quality Considerations** in Demonstrating Biosimilarity to a Reference Protein Product, February 2012, CDER, CBER
3. Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

Basic Tenet of the Guidelines

The basic tenet of the guidelines is that a biological medicine must be demonstrated to be highly similar to a biological medicine already registered under 351(a) (Public Health Service Act). A biological medicine registered under 351(a) that is no longer under patent is a medicine with which the FDA has quality, safety and efficacy experience. There is a tremendous amount of postmarketing experience with these medicines. A medicine that has been demonstrated to be highly similar to this medicine can benefit from the experience already in existence. On this basis the manufacturer will be able to conduct an abridged development program for the biosimilar medicine.

The extent to which the program can be abridged will be dependent upon the extent to which the medicine is demonstrated to be highly similar to the biological medicine. If the medicine is demonstrated to have differences, this is going to raise questions about its quality, safety and efficacy in relation to the originator biological medicine, and therefore result in additional studies being required to attempt to allay concerns.

Biobetters

The three new guidelines do not address biobetter medicines, except to indicate that biobetter medicines will not fall under 351(k), but under 351(a) of the Public Health Services Act. Consequently, the extent to which a biobetter development program can be abridged will need to be carefully explored with the company's experts, and consultants before meeting with the FDA to propose an approach.

What are the Principles and Concepts that Will Underlay the Review Process for Biosimilars?

There are a number of principles that will underlay the review process, as laid out in 351(k) and the guidelines. FDA has made it clear in the guideline that the review division will make the final decision. Despite this, the company should propose and justify any approaches to be taken scientific principles and data. The review division will expect to be able to review data in a stepwise fashion as it is accrued. In this respect, the Quality Guideline will be very important in that it lays out the types of comparison studies to be carried out for the biosimilar product against the reference biological product. The biosimilar company would be well advised to develop a finger print of the originator product and then seek to create a biosimilar product that is as close to this as possible. Because the basic tenet of the guidelines and 351(k) is that the biosimilar product is highly similar to the reference product, the extent to which the proposed biosimilar varies from the originator reference product, will be the extent to which extensive animal and human studies will need to be conducted to determine the degree of risk that would exist were the product to be registered and marketed.

How Should a Company Approach the Development of Biosimilars

Any company that will be developing biosimilars should plan to meet with the FDA on a regular basis during development. The frequency of meetings will depend on the type of data that have arisen in the process of developing the biosimilar. These meetings should be seen as opportunities to discuss the data and provide justifications for the approach to be taken moving forward. Far too many (mainly small and emerging companies) seek to use the FDA like a consulting organization. This is ill-advised

with any development program, and should be avoided with biosimilar developments. Meetings should take place with the FDA after the data have been thoroughly reviewed. Data that clearly show that the proposed biosimilar medicine is not highly similar to the reference product should lead to some soul searching in terms of next steps, rather than to another meeting with the FDA to discuss them. A proposed schedule of meetings is shown below:

- Initial Meeting – discuss the proposed strategy and the proposed analytical, animal and clinical studies.
- Second Meeting – present, analyze and discuss the analytical data gathered to that point in the development program. What are the potential concerns and issues in terms of the similarity of the proposed biosimilar medicine to the reference product? Present the proposed animal studies to be conducted. Agree the animal studies, and their study designs.
- Third Meeting – present, analyze and discuss the animal data gathered to that point in the development program. What are the initial concerns and issues in terms of the similarity of the proposed biosimilar medicine to the reference product? How might these be addressed by additional animal studies before progressing to the human studies? Present the proposed human studies to evaluate the immunogenicity, PK/PD. Agree the study designs for the human studies.
- Fourth Meeting – present, analyze and discuss the human data and any additional animal data that are available. Provide justification for the position on additional human studies that the company will take.
 - Are additional human studies required?
 - If additional human studies are not considered to be required, provide justification and a proposed post marketing surveillance program.

What should a Company Do that has Approvals for Biosimilars in Other ICH Countries?

The Scientific Guideline provides a pathway for companies with biosimilar medicines registered in other ICH countries to seek registration in the US. The pathway will require bridging studies, the types of which are outlined in the Scientific Guideline and the Quality Guideline. The reference product that was used to procure registration in another ICH region or country, will need to be demonstrated to be equivalent to that of the reference product registered by FDA under 351(a). If this bridging can be successfully completed, the data package used to secure registration in another ICH country or territory would be reviewed by the FDA. This could save companies a lot of time and money. Although this approach seems like a shortcut, bear in mind that any difficulties in demonstrating the bridge will lead to a need to conduct additional studies to address the concerns arising.

What Should a Company Do that has Approvals for Biosimilars in Non ICH Countries?

Companies that have secured registration for biosimilar products outside of the ICH regions should seek expert regulatory advice and input. Many countries outside of the ICH regions have adopted and implemented the EU guidelines for biosimilars in recent years. The extent to which companies in these territories have had to comply with these guidelines to seek registration is not clear. Some biological copies were approved before recent regulatory systems for biosimilars were adopted in these non ICH territories. A detailed gap analysis will need to be conducted by an expert global regulatory affairs consulting firm.

Whilst postmarketing safety data would be useful, the availability of these data is often a challenge because of the limitations of voluntary reporting systems, and the lack of proper mechanisms in many countries, to collect these type of data. These data would certainly be invaluable to provide assurance regarding safety, as part of a total data package that is compliant with the FDA and EU guidelines.

Developing a Global Regulatory Strategy for Biosimilars

Most large pharmaceutical companies that will be working in the biosimilar space intend to seek registration of their products in all the major regions, as well as other territories. The availability of the FDA guidelines now makes it more feasible to create a global regulatory strategy and to have constructive discussions with the EU, Japan and US FDA. Throughout the process of developing the biosimilar, the approaches to be taken to demonstrate quality, safety and efficacy, must be agreed with the major health authorities.

Conclusion

In an era when the FDA receives its fair share of criticism, it is to be commended for the construction of three well thought out and rational draft guidelines. The open system of discussion that the FDA used to receive input from the various stakeholders before putting pen to paper to write these draft guidelines is unlike anything else available elsewhere around the world. It will be abundantly clear to anyone that took part in the November 2010 meeting held with the various stakeholders, that many of the questions that arose at that time have been addressed in these guidelines. Where there was obvious confusion, and perhaps a little too much pushing against the safety railings by the generic industry, the FDA has sought to address those issues clearly and firmly. For instance, the argument that comparability testing conducted by originator companies is no different to biosimilars was deeply flawed. Hopefully, FDA has put that issue to rest permanently.

Moving forward, the Agency clearly needs to be cautious. The stepwise approach is to be commended, and will allow the industry and the FDA to move forward as a team. The stakes are high. The stakes are high for large pharma as well as small and emerging companies. Some of us remember the tragic death of the research subject that effectively killed the gene therapy field. It is to be hoped that the stepwise and cautious approach being taken by the FDA will avoid such an outcome for the biosimilar medicines field.

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