A Comparison of US and EU Biosimilars Regimes

SUMMARY STATEMENT

Economic barriers, along with regulatory complexity and uncertainty, are shaping the biosimilars industry into something entirely different from the generic small molecule pharmaceutical industry. The sharp demarcation between branded and generic small molecule pharmaceutical companies may not exist in the biologics context. The emerging biosimilars industry may present opportunities for both pioneering and follow-on companies. The regulations, both in the United States and Europe, are still in a very early, formative stage. This presents an opportunity for commentary and an exploration of comparative advantage. This article presents an overview of the US and EU biosimilars regulations, in order to help legal and executive decision makers at biopharmaceutical companies begin to think about the range of expenditures that may be necessary for approval of a biosimilar.

A COMPARISON OF US AND EU BIOSIMILAR REGULATIONS

At the end of March 2010 the United States enacted the Biologics Price Competition and Innovation Act (BPCI), the long awaited US pathway to biosimilars. Europe has had an established pathway for biosimilars since 2005. FDA has indicated it will seek to learn from the European experience with biosimilars as it promulgates regulations pursuant to BPCI. This article will explore the basics of the BPCI, compare and contrast it with the European approach, and suggest some possible near and medium turn scenarios for biosimilars in the United States.

The Biologics Price Competition and Innovation Act

The BPCI provides an application pathway for follow-on biological products, codified in 42 USC 262(k). The Act further categorizes such follow-on products as "biosimilar" or fully "interchangeable." While there is no incentive for a company to be the first-to-file a biosimilar application (in contrast with Hatch-Waxman) there is a one-year market exclusivity associated with being the first to file an "interchangeable" product (but this period may be expanded depending on the outcome of patent litigation, as set forth in 42 USC 262(k)(6)).

The BPCI defines a biosimilar product as "(A). . . highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B). . . no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[1] The interchangeable product must meet all the same requirements as a biosimilar and in addition have the same route of administration, dosage form and strength as the reference product.[2] An interchangeable "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[3]

The BPCI defines a biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide)or analogous product. . . applicable to the prevention, treatment, or cure of a disease or condition of human beings."[4]

The regulatory definition of a protein is yet to be determined by FDA. Will the regulatory definition, once established, mesh with Congress' presumed intent to distinguish proteins created recombinantly, via biological processes, from proteins - presumably shorter chain proteins, such as short peptides - that are created via chemical reaction? The FDA has indicated that some peptides are not proteins even if created in living cells. Would this mean that short-chain therapeutic polypeptides such as might be made, for example, via plasmid vector in a bacterium or yeast, not be covered by BPCI? These and other questions will hopefully be answered as FDA rulemaking proceeds.

1 42 USC 262(i)(2)
2 42 USC 262(i)(3); 42 USC 262(k)(IV)
3 42 USC 262(i)(3)
4 42 USC 262(i)(1)

It should be noted that there is no such thing as a "biogeneric" because unlike in the small molecule context the follow-on can never be an exact, to the atom, duplicate. "Interchangeable" is the closest any biologic regulatory regime can come to 'generic'. Of course this raises the question: what is similar enough?

Regulations Governing Biosimilarity

In the small molecule (Hatch-Waxman) context, the substitutable small molecule must have the "same active moiety" as well as identical ingredient (chemical structure of active property), strength, and route of administration as the pioneer product. In contrast, in the biological context, molecules may not be identical even from batch to batch within a single manufacturing facility. Given that follow-on biologics will be made in different facilities and via a different process (because of patent or trade secret protection) than the pioneer product, the difference between putatively similar biologics could be structurally quite significant. Therefore the biosimilars regulations must, by biochemical necessity, provide more flexible definitions. The BPCI provides that a biosimilar can have significant differences from the pioneer product but still be "highly similar" so long as any differences in purity, potency and safety are not "clinically meaningful".[5] The question then becomes, how will FDA determine if a difference between a pioneer and follow-on biologic is sufficiently "clinically meaningful" so as to require FDA rejection of the follow-on? FDA began holding hearings on these issues in November, 2010.

Since then the FDA has obtained commentary from industry and interested parties on the range of structural differences that would be acceptable within the "highly similar" standard (or, put another way, would be an unacceptable "clinically meaningful" difference) in the BPCI, but has not yet promulgated a specific rule as of the date of this writing.

Some parties have set forth standards that make interchangeability practically impossible. For example, the American Medical Association and others argued for the need for clinical testing before approval, as well as clear labeling and no automatic substitution right for pharmacists, essentially asking the FDA to set a regulatory bar so high that "interchangeability" becomes an impossible threshold to meet.

Setting aside the question of interchangeability for the moment, what degree of testing should be required for mere biosimilarity? Does the crux of biosimilarity lay in the achievement of the same clinical results to the pioneer product? That is to say, should FDA require the same multi-year span of data that the pioneer originally used to convince the FDA to approve the product in the first place?

As discussed below, this is not the requirement in Europe. The European Medicines Agency ("EMA") regulations do not require the applicant to obtain comprehensive data on patient benefit. The EMA requires the follow-on applicant demonstrate "similar efficacy and safety compared to the reference product."

Clearly the follow-on applicant will have to conduct testing and a clinical trial of some sort, but for the biosimilar pathway to have any practical meaning such trials must, as they are in Europe, be significantly shorter and less comprehensive than the original applicant's.

In a recent article in the New England Journal of Medicine, doctors from FDA's Center for Drug Evaluation and Research (CDER) voiced some optimism on the FDA's ability to use assay data to assess sufficient similarity.

> "[P]rogress in the characterization and understanding of biologics now permits demonstration that some products are highly similar to a reference product. [P]hysicochemical and functional assays have been used to characterize changes in manufacturing processes for some biologics, and then animal or clinical studies are used to resolve any remaining uncertainties about the comparability of the products created before and after such changes and to provide sufficient confidence that safety and efficacy are not diminished. . . There may be strategies that allow a "fingerprint"-like identification of very similar patterns in two different products. Such strategies were used in supporting the approval of a generic low-molecular-weight heparin product, enoxaparin — which, though it differs from proteins in important ways, is structurally complex. Although additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable

5) 42 U.S.C. 262(i)(1)

future, the scope and extent of such studies may be reduced further if more extensive fingerprint-like characterization is used."[6]

The scientists also indicated that they would look closely to the European approach and experience, integrating various types of information and taking a "totality of the evidence" approach. They then referred to the recent EMA draft guidance on biosimilar monoclonal antibodies (discussed below) as a source of guidance for the structure and conduct of biosimilarity clinical studies.

As high a standard as FDA sets for biosimilarity it will nevertheless be lower than for interchangeability. This may, as a practical matter, indeed make applications for a declaration of interchangeability highly unlikely. The CDER scientists note in passing that "a biologic will be considered interchangeable with a reference product if the developer demonstrates that it can be expected to produce the same clinical result in any given patient and that the risk associated with alternating or switching between the two products is not greater than that involved in continuing to use the reference product."[7]

The EMA's case-by-case approach to biosimilarity is articulated directly in its regulations. The FDA, even as it promulgates more specific rules in the near future, will likely also make its determinations on a case-by-case basis as a practical matter. Applicants, if they are to be successful, will need to marshal their best clinical, legal and regulatory professionals into the process. Each new application will be a significant learning experience for the entire industry.

Exclusivity

The BPCI grants a 12 year exclusivity to the pioneer product. Specifically, the FDA may not grant a biosimilar application until 12 years after the grant of the original biologic license to the pioneer. It would thus appear that a follow-on applicant can submit his application before the expiration of the pioneer's 12 year exclusivity but the FDA will not be able to act on it until the appropriate date.

There are also provisions in the BPCI to keep pioneers from "evergreening" their exclusivity. For example, a new exclusivity period does not begin to run if the pioneer files a subsequent application that changes dosage or route of administration or modifies the structure of the molecule in a way that "does not result in a change in safety, purity, or potency."

There is no equivalent to the Orange Book in the BPCI scheme. Instead, there is a private exchange of patent information and the biosimilar application itself is fully disclosed. Unlike in the Hatch-Waxman regime there is no automatic stay of an FDA approval.

The procedure is roughly as follows: after the follow-on application is accepted by FDA, but 180 days prior to marketing, the applicant must disclose the application to the original BLA holder. The original BLA holder then has 60 days to provide the follow-on applicant with a list of patents. The applicant then has 60 days to respond with detailed statements and a counter list of patents, which is then followed by a further response and negotiation period before the BLA holder can file a lawsuit.

The detailed mechanics of the process of information disclosure (including confidential information disclosure) and possible litigation between original BLA holders and follow-on applicants envisioned in the BPCI is far beyond the scope of this article. But there can be little doubt that the complexities and potential gamesmanship that may emerge could rival those of the Hatch-Waxman regime.

Europe

Europe is ahead of the United States when it comes to biosimilar adoption. The EMA approved its first biosimilar in 2006. Last year a biosimilar version of Amgen's Neupogen was approved.

The exclusivity period in Europe is the same for both biologics and chemical drugs: 10 years. Europe also requires follow-on biologics to adhere to the same post-marketing adverse-event vigilance and reporting requirements as the pioneer.

The Committee for Medicinal Products for Human Use (CHMP) is the EMA's equivalent of FDA's CDER and set forth the concept of a "comprehensive comparability exercise" in the original Guideline On Similar Biological Medicinal Products in 2005.[8]

6) http://www.nejm.org/doi/full/10.1056/NEJMp1107285

7) http://www.nejm.org/doi/full/10.1056/NEJMp1107285

8) CHMP/437/04 London, 30 October 2005

The CHMP has published over half-a-dozen "guidelines" related to biosimilar products, including guidelines on specific classes of biological products such as insulin and somatropin, as well as draft guidelines on monoclonal antibodies and a "concept paper" on low-molecular weight heparins. A complete assessment of these guidelines documents are beyond the scope of this article but will be the subject of a future article on European regulations. But for now we can say that, at a minimum, pharmacokinetic and pharamacodynamic (PK/PD) studies would be required to establish sufficient similarity.

Although further along than the United States, the Europeans nevertheless continue to grapple with fundamental issues, such as proper nomenclature. In a recent article in Nature Biotechnology, members of the EMA's Biosimilar Medicinal Products Working Party (BMWP) argued for more specific definitions of the term biosimilar and criticized recent incorrect labeling of some protein products as biosimilars.

Of the dozen or so true biosimilars licensed in Europe thus far, almost all fall into three categories: somatropin, epoetin alfa, and filgrastim. These are all relatively small biologs. None of are as large or complex as the monoclonal antibodies - such as Rituxan or Herceptin - envisioned to be the subject of future biosimilar applications. On the other hand, these approvals have at least demonstrated proof of concept that biosimilars can be manufactured in different expression systems yet still be "similar." For example, the biosimilar Valtropin is expressed in yeast culture, whereas the original Humatrope is expressed in E coli systems. [9]

Near term predictions: 2012-2013

As noted, at the time of this writing the FDA has not yet approved a follow-on biologic under BPCI. [10] Nevertheless, several large "branded" biopharmaceutical companies have indicated that they will seek to market biosimilars in the future. For example Merck, through its Merck BioVentures subsidiary, is committed to biosimilar development and intends to market a biosimilar version of Enbrel.

Genentech (Roche) has taken the position that "the properties of the biologic often depend directly on the nature of the manufacturing process. Furthermore, proteins have unique structural organization patterns (referred to as "folding") that affect the way that they work in the body; even biologics that are chemically the same may have differing biological effects due to differences in the structural folding. An example of this folding effect is the difference between a raw egg and a cooked one: chemically the two are the same, but they are physically and biologically very different."[11] The company supports clinical trials for each biosimilar indication.

Amgen, in testimony before the FDA, asserted that half of the biosimilars developed in Europe had unexpected clinical outcomes, and therefore relying on pharmacokinetic and pharmacodynamic studies alone should never be enough.

On the other side, the large generic pharmaceutical companies such as Teva and Sandoz have indicated that they may, in the near term, forego the uncertain BPCI process and instead use the existing BLA process for their versions of popular biologic drugs, such as monoclonal antibodies.

One interesting idea aimed at avoiding clinical duplication is to allow follow-on applicants to purchase clinical trial data from pioneers. Another idea is to allow data from non-US licensed products.

The approval of a biosimilar that does not meet the definition of interchangeable will not result in the near-instantaneous market penetration that we observe in the Hatch-Waxman (small molecule) context. From an economic standpoint, the critical issue in biologics, as opposed to small molecules, may be in convincing doctors, patients and other healthcare stakeholders that the follow-on has demonstrated sufficient similarity to risk adopting it over the pioneer product. We can begin to get a sense of what will be acceptable to the FDA, but we have no way of knowing what will be acceptable to the market. This, along with the practical difficulties and expense of mass biological manufacturing, suggests that the major biosimilar competitors will likely be other large, pioneering biopharmaceutical companies.

9) EMEA biosimilars pathway presentation. June 2011

10 The July 2010 approval by FDA of Momenta Pharmaceuticals and Sandoz generic version of Sanofi-Aventis's blood-thinner Lovenox (enoxaparin sodium) came under the existing Hatch-Waxman regime for small molecules. In any event, enoxaparin sodium would likely not fit the definition of a biological product as set forth by BPCI and understood by FDA.

11) http://www.gene.com/gene/about/views/followon-biologics.html

Longer term predictions: 2016 and beyond

Recent forecasts for biosimilar monoclonal antibody sales reach upwards of $20B by 2020 , with the first monoclonal antibody (MAb) approvals to come (in Europe) by 2013.[12]

If biosimilar MAb products prove successful in Europe, with no more adverse effects than the pioneer MAb, this would likely prove influential to FDA.

In 2010 the top ten MAb were, in order: Remicade, Avastin, Rituxan, Humira, Herceptin, Erbitux, Lucentis, Tysabri, Xolair, and Synagis. Together they produced $45B in sales.[13] At least some of these monoclonal antibody products could see biosimilar versions by 2016. This will almost certainly be the case in Europe. Will such products, if they exist, be interchangeable by pharmacists with the original? At this stage that would seem unlikely. Nevertheless, the $20B by 2020 prediction in this context does not seem unreasonable.

In the final analysis it would appear that any biosimilar product, approved under either the EMA biosimilar regulations, the US BPCI, or simply as a new BLA, will require a level of clinical, marketing and education support that entry into the market by smaller generic small-molecule drug companies would be highly unlikely. In the biosimilar context the sharp line between "branded" and "generic" drug companies that we see in the Hatch-Waxman context may be blurred to the point of meaninglessness. It will likely be the large, pioneering biopharmaceutical companies that will create both pioneering and biosimilar biological products, and they will pursue the regulatory regime and jurisdiction best suited to market conditions as they emerge.

12) http://www.marketwatch.com/story/forecasted-sales-of-biosimilar-monoclonal-antibodies-for-oncology-indications-will-reach-more-than-4-billion-in-2020-2011-11-15

13) http://knol.google.com/k/krishan-maggon/top-ten-monoclonal-antibodies-2010/3fy5eowy8suq3/143#

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