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FDA Hears Testimony on Approval Pathway for Biosimilar and Interchangeable Follow-On Biologics

On November 2-3, 2010, the FDA held an important hearing relating to a new piece of legislation intended to allow for market entry of "follow-on" biologic drug products.

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The Biologics Price Competition and Innovation Act ("BPCI Act" or "Act") was signed into law earlier this year as part of the omnibus Health Care Reform package passed by Congress.[1] Missing from the Act, however, are details of what an individual application for a follow-on biologic must contain in order to be approved by the FDA as either "biosimilar" or "interchangeable." The FDA held a hearing to seek input from a variety of stakeholders as to what sort of guidance and/or regulations it should issue relating to the Act. The FDA's public comment period on these issues will remain open through December 31, 2010. A webcast and transcript of the hearings may be obtained at http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm.

The FDA panel was interested in the following topics relating to the BPCI Act:

- Scientific and technical factors related to a determination of biosimilarity or interchangeability;
- The type of information that may be used to support a determination of biosimilarity or interchangeability;
- Development of a framework for optimal pharmacovigilance for biosimilar and interchangeable biological products;
- Scope of the revised definition of a "biological product";
- Priorities for guidance development;
- Scientific and technical factors related to reference product exclusivity;
- Scientific and technical factors that may inform the FDA's interpretation of "product class" as it relates to available regulatory pathways for certain protein products during the 10-year transition period following enactment of the BPCI Act; and
- The establishment of a user fee program for biosimilar and interchangeable biological products.

See 75 Fed. Reg. 61497-61501 (Oct. 10, 2010). Interested stakeholders included representatives from patient groups for whom biologic drugs are or may in the future be critical (*e.g.*, arthritis, immune disorders, cancer); doctors with experience researching, prescribing, and running clinical trials for biologic drugs; companies with biologic drugs already on the market; companies intending to bring new and/or follow-on biologics to market; companies with analytical technologies capable of comparing large, complex biomolecules; and various other lawyers, consultants, and scientists with experience – either in the United States, Europe, or elsewhere – in the field of biologics.

While no firm conclusions can be drawn from the hearings, and the FDA is still accepting public comment until the end of the year, the following themes emerged from the hearings.

Clinical Data Set Requirements for Biosimilars

Unlike the Hatch-Waxman Act for small molecule generic drugs, the BPCI Act contemplates that the follow-on applicant submit clinical data to support the similarity of its drug vis-à-vis the reference product. But the Act does not specify how much clinical data is required, or under what circumstances,

[1] Edwards Angell Palmer & Dodge has previously reported on the debate leading up to the passage of the Act (*see* EAPD June 2009 Client Advisory) as well as the specific provisions of the Act as passed (*see* EAPD March 2010 Client Advisory).

and it even contemplates the possibility of the FDA waiving such clinical requirements entirely. Thus, this issue was a primary focus at the FDA hearing.

Many of the declared follow-on companies argued that if the clinical requirements under the BPCI Act were not reduced in practice, then the allegedly "abbreviated" § 351(k) pathway established by the Act would make little sense relative to the filing of a full-blown Biologics Licensing Application. These companies suggested that the FDA follow a pyramid-type structure, with analytical characterization and comparison of the follow-on and reference products at the base of the pyramid. Their point was that if a given biologic could be characterized as similar to the reference product from a chemical and biochemical standpoint (at least within the same variability of attributes as the reference product itself), then the scope and number of clinical trials – the "top" of the pyramid – could be accordingly reduced, even to the point of no clinical trials being required at all in an appropriate case. These companies contended that if a follow-on product was the same as the reference product across all "relevant" structural attributes, then the FDA should not be concerned with differences across the "irrelevant" attributes.

The counterargument from many of the reference product sponsors was that in the complex arena of biologics, even very subtle structural differences that might not normally be deemed "relevant" can often result in significant clinical differences. The only way to account for such unpredictability, they argued, is to require fairly substantial pre-market clinical trials in all cases.

Use of Clinical Data from Biosimilar Products Previously Approved Elsewhere

In addition to asking that the FDA allow them to come forward with a reduced clinical data set if a strong analytical comparison base could be established, many follow-on companies requested that the FDA consider comparative clinical studies data from other countries in which the same (or similar) biosimilars have already been approved for use. Such data exists in the European Union, which first approved a biosimilar in 2006, as well as in developing countries, particularly India and China.

The arguments in favor of this global data sharing approach sound in efficiency, cost, and ethics (*i.e.*, reduced human and animal testing). A significant argument against this approach, however, is that biosimilars still do not have much market penetration in the European Union. And in countries such as India, where market penetration is far greater, the regulatory regimes are not as stringent as in the U.S. or European Union. Thus, the FDA may wish to see more extensive post-market data on biosimilars before drawing on clinical data from other countries.

Regardless of the scope of clinical trials that the FDA will require for follow-on biologics, there also remains considerable debate over how the trials should be structured. The FDA may have to issue at least general guidance on how many patients are necessary, how many "switches" are required (*i.e.*, from reference product to biosimilar, and vice versa), and how long each switch should last.

Extrapolating Clinical Data from One Indication to Another

This issue is likely to become of greater importance as more and more biologics drugs come to market and are used for different indications. If, for example, a follow-on company has provided the FDA with clinical data sufficient to support "biosimilarity" or "interchangeability" vis-à-vis a reference product used for one indication, and if the reference product is then subsequently approved for a new indication, does the follow-on company need to submit additional clinical data? The answer will likely revolve around whether or not the biologic has the same mechanism of action for both indications. If it does, and if that mechanism is well characterized, then the follow-on companies advocated that additional clinical trials not be required of the follow-on applicant.

Balancing Clinical Trials with Post-Market Studies

Many of the follow-on companies suggested that the way to mitigate the potential downside of reduced clinical data at the application stage is with increased post-market studies. This, they suggested, is what they have done in both the European Union and in developing countries, to good effect. The counterargument is that in the case of

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certain biologics, it has only been through *pre*-market clinical testing that serious adverse consequences were first revealed. These are classic risk-benefit arguments that the FDA will have to debate and resolve.

Biosimilarity vs. Interchangeability

The BPCI Act provides for a distinction between follow-on biologics designated as "biosimilar" and those designated as "interchangeable." On one end of the spectrum are those stakeholders that think this distinction should be recognized, and that interchangeability status should be extremely difficult to achieve. On the other end are those that contend that if a biologic is approved as biosimilar, it should *necessarily* be interchangeable as well. One interesting question is whether the FDA will (1) require follow-on companies to select either the "biosimilar" or "interchangeable" tracks at the outset of the application process; or (2) make that determination itself after reviewing the application; or (3) wait to make the determination until after a certain amount of post-market data has been collected.

Class-by-Class Guidance

Many speakers suggested that the FDA first issue guidance with respect to the class of smaller, less complicated, and better characterized protein-based biologics. Then, only after some experience is gained by the FDA with follow-on applications for the less complicated products, should it issue guidance on more complex products, such as monoclonal antibodies (mAbs). One problem with monoclonal antibodies, for example, is that they often have a different mechanism of action for each different indication, making cross-indication extrapolation of clinical data particularly difficult.

Naming Conventions

A concern was raised that because biosimilars are by definition not identical (*i.e.*, not "generic"), a follow-on biologic should have a different International Non-Proprietary Name (INN) and number, and not just a different brand name, from the reference product. It is imperative, these stakeholders argued, that the two biologics be distinguishable. On the flip side, many companies urged that the INN names for biosimilars be the same as for their reference product counterparts, as this would reduce patient confusion and more readily promote substitutability. These companies felt that in the case of any adverse events resulting from a given follow-on product, the product would still be traceable based on the lot number and manufacturer information included on the drug label or container.

In sum, the recent hearings have given the FDA a tremendous amount to think about with respect to the implementation of the BPCI Act. Edwards Angell Palmer & Dodge will continue to report on developments as the FDA's actual guidance begins to take shape.

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