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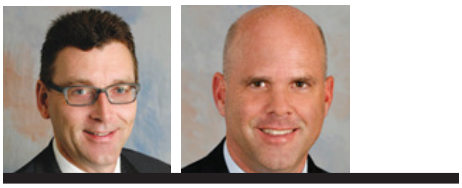
Forecasting Forthcoming 'Biosimilar' Drug Regulations



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Traditional pharmaceuticals (small molecule drugs) have long been subject to widespread generic competition under the generic competition provisions of the Drug Price Competition and Patent Term Restoration Act, aka Hatch-Waxman Act. By contrast, biologics, referred to here as "biosimilars," are large molecule drugs typically made by recombinant DNA techniques, and have not been subject to such widespread generic competition.

To improve access to more affordable therapeutic biologics, such as monoclonal antibodies, vaccines and genetically engineered recombinant proteins, Congress passed the Biologics Price Competition and Innovation Act (BPCIA) of 2009, an amendment to §351 of the Public Health Service Act (PHSA). This created a framework for the U.S. Food and Drug Administration to approve, through an abbreviated approval process, biological products that are "biosimilar" to or "interchangeable" with an already approved product.

As expected, this amendment was heralded with great enthusiasm by the generic drug industry, hoping to enter the lucrative "biosimilars" market. The U.S. Generic Pharmaceutical Association estimates that over the next seven to eight years, $31.1 billion worth of brand name biologics will lose patent protection.

According to the BPCIA, "biosimilar" or "biosimilarity" means that (i) the later-developed biological product is highly similar to the original reference product, notwithstanding minor differences in clinically inactive components, and (ii) there are no clinically meaningful differences between the later-developed biological product and the original reference product in terms of the safety, purity and potency. A showing of biosimilarity must be based on data obtained from analytical studies, animal testing and one or more clinical studies (PHSA; §351(k)(2)(A)(i)(I)).

One and a half years later, the biotechnology and pharmaceutical industry is still waiting for guidance from the FDA concerning details of the approval pathway for biosimilars. With the aim of eliminating unnecessary and unethical testing of biosimilars in animals and humans, the guidelines will permit utilizing data already established for a reference product. But how similar is similar enough and how much animal or clinical testing will still be required?

While the FDA officially has been silent on those issues, four high-level FDA officials (Steven Kozlowski, M.D., Janet Woodcock, M.D., Rachel Behrman Sherman, M.D., M.P.H. (directors at the FDA Center for Drug Evaluation and Research), and Karen Midthun, M.D. (director at the FDA Center for Biologics Evaluation and Research)) published an article in August in the New England Journal of Medicine entitled "Developing the Nation's Biosimilars Program." In the article, the authors shed some light on the FDA's current views and what to expect from the FDA's substantive guidelines, which are intended to be issued by the end of 2011.

It is widely expected that in developing scientific criteria to assess how similar a biosimilar must be to a reference product, the FDA will reflect on and draw considerably from the criteria already established by the European Medicines Agency. EMA published a number of guidelines relevant to biosimilars, such as the Guideline on Similar Biological Medicinal Products in 2005 and the Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies in 2010, and approved its first biosimilar product in 2006.

The EMA guidelines cover a range of issues — including manufacturing processes, measuring comparability, physicochemical and biological analyses — and require clinical testing of biosimilars to demonstrate safety and efficacy prior to market authorization, followed by tailored pharmacovigilance plans to monitor potential immunogenicity. Essentially, EMA's approach to the approval of a biosimilar product is to deal with it on a case-by-case basis.

"TOTALITY OF THE EVIDENCE" AND A "NEW PARADIGM"

Traditional "small" molecule drugs, such as Aspirin, with a defined molecular weight often between 100 and 1,000 daltons, are typically made by a well-defined chemical process. A generic "small" molecule drug essentially has the same active ingredient as a reference product. Because the safety and efficacy of such "small" molecule drugs have already been established in clinical trials by the original applicant, the generic manufacturer essentially need only show that it makes the same chemical compound

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through acceptable manufacturing processes for FDA approval.

By contrast, biologics are large, complex and heterogeneous proteins, even mixtures of proteins, with more variable molecular weights, commonly ranging from 18,000 to 145,000 daltons, but can be significantly higher. Further, the production of biologics in living cells can make the final biologic product very sensitive to changes in production conditions. As such, a "biosimilar" will not be the same as the original biologic reference product.

Differences between a biosimilar claiming to be "highly similar" to an approved reference product have been a major concern for the industry, regulatory agencies and patient advocates worldwide. In recognizing the complexity of therapeutic biologics and building on EMA's experience with abbreviated approval pathways, the FDA likely will propose biosimilar product-specific requirements for structural, animal and clinical studies, thus creating different standards for different product categories.

In view of the FDA's New England Journal of Medicine article and EMA's guidelines, it appears unlikely that the FDA will develop guidelines for biosimilarity assessment in a "one size fits all" format. Rather, the FDA favors the integration of various types of information, referred to as "totality of the evidence," to provide an overall assessment of whether a biosimilar product is "biosimilar" enough to an approved reference product. While each individual assay may have its own inherent limitations, a totality of the evidence approach makes use of multiple and complementary assays that allow for evaluating more attributes of a product at greater sensitivity.

There might also be a need for the FDA to articulate standardized assays to enable comparison of results from different laboratories. However, fingerprint-like identification of protein structures, using highly sensitive analytical techniques, although helpful, will certainly not be sufficient by itself for biosimilarity assessment. The FDA, however, hinted that if more "fingerprint" data might be provided, it could reduce the scope and extent of animal and clinical studies, which the FDA currently sees as being required "for the foreseeable future."

In reference to the EMA monoclonal antibody guidelines, the FDA might include in its own guidelines for biosimilarity a requirement for studies using populations, pharmacodynamic markers, and end points addressing potential differences between reference and biosimilar products.

The authors of the NEJM article also advocate a more intense interaction between a sponsor of a biosimilar (i.e., generic companies) and the FDA (in the FDA's words, "a new paradigm") to provide helpful guidance on how much additional analytical data are needed and on the scope of animal and human studies involving the biosimilar. It appears the FDA expects to work with the sponsor on an elaborate case-by-case specific agenda. The FDA will have to structure those interactions and consider how they will affect the user-fee program that Congress has mandated for biosimilars and which the FDA has to present to Congress by January 2012.

RISK-BASED APPROACH, SAFETY MONITORING AND INTERCHANGEABILITY

The NEJM article's authors suggest the FDA apply a risk-based approach for the evaluation of biosimilarity, assessing the product's complexity, formulation, stability, manufacturing process, immunogenicity, clinical effects, and biochemical and functional characterization. The onset and incidence of immunogenicity of a biosimilar is unpredictable. The industry still is painfully aware of the Eprex case, where a relatively minor formulation change, the replacement of a stabilizer, significantly affected safety and efficacy of the biological product. Thus, the FDA likely will include a strong requirement in its guidelines for biosimilar product-specific safety monitoring, tracking adverse events associated with the use of a biosimilar product. Again, the industry should expect that the FDA's guidelines will take into account the recommendations of EMA's Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins, promulgated in 2008.

The BPCIA considers a biosimilar product "interchangeable" with a reference product when the manufacturer can demonstrate that it is expected to produce the same clinical result in any given patient and that the risk associated with alternating or switching between a reference and biosimilar product is not greater than the risk involved using the reference product alone. A pharmacist can then make substitutions between the reference product and the "interchangeable" biosimilar product without the prescribing physician's intervention. Apparently, the FDA will articulate a regulatory standard for additional data requirements to satisfy this heightened "interchangeability" designation. The FDA will also develop standards to ensure that a "biosimilar" product is not inadvertently substituted for an "interchangeable" product, by giving the "interchangeable" product a distinguishing non-proprietary name, at the very least.

CONCLUSION

The FDA's NEJM article, while not official agency policy, provides a glimpse of what to expect from the FDA guidelines on abbreviated approval pathways for biosimilars. The industry should not expect a simple "one size fits all" instruction manual and low-cost data demands, but rather complex product-specific guidelines. If the NEJM article reflects what to expect from the FDA guidelines, and there might be little doubt that it does, then there appears justifiable concern for the generic industry that the requirements for analytical and clinical testing may drive costs for developing and approval of a biosimilar too high for some. We expect, however, that when biosimilar products eventually are approved (to the authors' knowledge, currently no biosimilar application has been filed with the FDA), some of the uncertainty will vanish and predictability of the approval process might be achieved.