

## INNstight article by Siegfried J.W. Ruppert – August 2011

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### **A Look Ahead: FDA's Approach to Biosimilars - Totality of the Evidence and Risk-Based**

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 of 2009, in which it provided for an abbreviated approval process for biological products that are "biosimilar" to or "interchangeable" with an already-approved product. One and a half years later, biotechnology and pharmaceutical companies, hoping to enter the lucrative "biosimilars" market, are still waiting for guidance from the U.S. Food and Drug Administration ("FDA") concerning details of the approval pathway. It is to be hoped that the guidelines will permit utilizing data established for a reference product to eliminate unnecessary and unethical testing of biosimilars in animals and humans. But, how similar is similar enough and how much testing will still be necessary?

At the beginning of August, four high-level FDA officials published an article in the New England Journal of Medicine ("NEJM") entitled "Developing the Nation's Biosimilars Program," describing the agency's current views and what to expect from the FDA's substantive guidelines 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 already-established criteria by the European Medicines Agency ("EMA"), which published guidelines on similar biological products in 2005 and guidelines on similar biological medicinal products containing monoclonal antibodies in 2010. The EMA approved its first biosimilar product in 2006.

#### **"Totality of the Evidence" and a "New Paradigm"**

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, i.e., creating different standards for different product categories. It appears very unlikely that the agency will develop guidelines for biosimilarity assessment in a "one size fits all" format. The FDA rather 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" to an approved reference product. A totality of the evidence approach makes use of multiple and complementary methods that allow evaluating more attributes of a product at greater sensitivity. "Fingerprint"-like identification of protein structures using highly sensitive analytical techniques, although helpful, will certainly not be sufficient by itself for biosimilarity assessment. The agency, however, hinted that more "fingerprint" data might reduce the scope and extent of animal and clinical studies, which will be 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 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. 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. As the industry is painfully aware since the Eprex® case, even a relatively minor formulation change, such as the replacement of a stabilizer, can significantly affect safety and efficacy of a biological product. Thus, not too surprisingly, 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.

If a manufacturer demonstrates that a biosimilar product 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, the biosimilar product is considered to be "interchangeable" with the reference product. A pharmacist can then make substitutions between the reference product and the "interchangeable" product without the treating physician's intervention. Apparently, the FDA will articulate a regulatory standard for additional data requirements to satisfy this heightened "interchangeability" designation. The agency will also develop standards to ensure that a "biosimilar" product is not inadvertently substituted for an "interchangeable" product.

### **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, which may drive costs for developing and approval of a biosimilar too high for some. As products eventually are approved, some of the uncertainty will vanish and predictability of the approval process might be achieved.

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