Sponsored article

An Overview and Update on Biosimilars

By Stephen Paul Mahinka and Kathleen M. Sanzo of Morgan, Lewis & Bockius.

The Patient Protection and Affordable Care Act of 2010 ("PPACA" or "the Act") will significantly affect biopharma growth and investment. A major element of this healthcare reform law is the Biologics Price Competition and Innovation Act ("BPCIA").

The BPCIA provides the approval of biological products as biosimilar or interchangeable (BPCIA § 351(k)). As part of the FDA's approval process, biosimilar products would need to produce the same clinical effect and, if a multi-dose product, not present any greater safety or efficacy risk to patients in switching from the reference product. In essence, there would have to be no "clinically meaningful differences" between the pioneer biologic reference product and the biosimilar product in order to gain FDA approval.

Congress granted the FDA substantial flexibility in determining approval standards for biosimilars, including whether and what type of clinical studies will be required and what differences in approval process from the biologics license applications ("BLA") process are appropriate. FDA approval would grant 12 years of data exclusivity to pioneer manufacturers, barring FDA approval of a 351(k) application from "the date on which the reference product was first licensed." Furthermore, an application cannot be submitted to the FDA until four years after the date on which the BLA for the reference product was first granted. Such exclusivity periods are provided for against the first approved biosimilar which is commercially marketed. Supplemental BLAs or "slight modifications", which is an undefined term in BPCIA, are not included in the exclusivity period and do not extend such a period.

The FDA will set its own approval requirements, which should include, unless the FDA waives them: analytical studies demonstrating the biosimilar is highly similar to the reference product; animal studies; a clinical study sufficient to demonstrate safety, purity, and potency; and other information showing that the biosimilar uses the same mechanism of action, route of administration, dosage form, and strength.

It is important to note that the BPCIA's patent challenge provisions are significantly different from those under Hatch-Waxman Act for generic drugs, in that they require "negotiation" of patent disputes and exchanges of patent information between the parties prior to instituting patent litigation. Also mandated under the BPCIA, risk evaluation and mitigation strategy ("REMS") requirements shall apply to biosimilars as they do to the reference pioneer biologic. Reimbursement for biosimilars is set at Average Sales Price (ASP) plus 6% of the amount determined for the reference pioneer biologic. The BPCIA allows for imposition of user fees to review biosimilars.

The biopharma industry faces several questions as its members decide whether to submit Section 351(k) applications, including: What is a biosimilar, and how similar to the reference product must a biosimilar be, to be approved and considered interchangeable; What scope of data is necessary, if any, to show biosimilarity; The scope of innovator modifications to a product that can provide a basis for additional exclusivity; and how important the manufacturing process is to showing biosimilarity.

Moreover, there are issues surrounding the naming of biosimilars, and what effect the FDA's generic versus unique or proprietary naming requirements will have on drug safety reporting and/or recalls, as well as on reimbursement. Also unanswered is whether a biosimilar applicant needs to provide data in connection with all approved indications of the reference product, and whether a biosimilar can be better than the reference product (i.e., "biobetters"), and if so, in what way (e.g., safety or efficacy).

On Feb. 9, 2012, the FDA issued three draft guidance documents intended to facilitate the submission of marketing applications for biosimilars: (1) "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" ("Biosimilars Q&A"); (2) "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product" ("Biosimilars Scientific Guidance"); and (3) "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product" ("Biosimilars Quality Guidance").

First, the Biosimilars Q&A provides general guidance on the content to be included in 351(k) applications, recommends that sponsors meet early with the FDA to discuss their proposed plans for biosimilar development programs and anticipated clinical studies, and responds to some of industry's preliminary exclusivity questions. Finally, the guidance sets out the FDA's current view that comparative animal or clinical data developed using a non-US-licensed product can provide evidence that proposed product is biosimilar to a US-licensed reference product.

Second, the Biosimilars Scientific Guidance sets out three approaches on demonstrating biosimilarity. The first is a "stepwise approach," which can include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics ("PK") and pharmacodynamics ("PD"), clinical immunogenicity, and clinical safety and effectiveness. The FDA's second discussed approach is the "totality-of-the-evidence" approach that the agency will use to review applications for biosimilar products. Finally, the third approach is one of "general scientific principles" in conducting comparative structural and functional analysis, animal testing, human PK and PD studies, clinical immunogenicity assessment, and

clinical safety and effectiveness studies (including clinical study design issues).

Third, the Biosimilars Quality Guidance provides direction on analytical studies relevant to assessing whether the proposed biosimilar protein product and the reference product are "highly similar." The guidance also suggests there may be an opportunity for innovators to argue current technology does not permit for demonstration of "biosimilarity" of a potentially competitive product in a manner adequate to gain approval under 351(k), thus necessitating the filing of full BLA.

In recent comments to the FDA, members of the biotechnology, pharmaceutical research and manufacturing, and generic pharmaceutical industries raised concerns regarding both what was in, and what was absent from the guidance. The Biotechnology Industry Organization ("BIO") expressed concern that the guidance documents suggest that animal toxicity or safety data are only required in some cases. BIO also suggested that the agency should require each biosimilar to have a distinct, non-proprietary name to permit tracking adverse events. Finally, BIO questioned how quality comparisons between reference and biosimilar products should be conducted when quality attributes are unstable and/or change over time.

The Pharmaceutical Research and Manufacturers of America ("PhRMA") in its comments advocated that controllable differences between biosimilars and references should be minimized. PhRMA also urged the FDA to recognize the limits of state-of-the-art analytical technology in its drafting of biosimilars regulations, and suggested the agency require the abbreviated approach taken by each biosimilar applicant to be fully scientifically justified. Finally, PhRMA argued that any data from foreign product trials should be used only to corroborate pivotal data comparing biosimilars to US-approved reference products.

In contrast to PhRMA's and BIO's comments, the Generic Pharmaceutical Association ("GPhA") suggested in its comments that clinical trials should only be required "if and when the totality of the other evidence is insufficient to establish that the proposed biological product is highly similar to the reference product." GPhA also advocated that a biosimilar manufacturer should not be required to provide more data than the originator did, and that there should be regulatory consistency in the treatment of biosimilars and novel biologics. The association argued that any sponsor demonstrating biosimilar comparability, as a scientific matter, relative to a reference product should have the option of designating interchangeability at the time of initial approval. Finally, GPhA noted that the FDA may not need to require clinical immunogenicity studies because it is possible that an immunological response with a biosimilar is no more likely, and may be less likely, than with the reference product.

There are many outstanding practical issues regarding biosimilar marketing and development. For example, the effect on coverage and reimbursement of the pioneer biologic based on approval of a biosimilar, and of biosimilars itself is a question that could significantly affect biopharma investment. In fact, there is an absence of express treatment of biosimilars in the new act under Medicare Part B, Medicare Drug Pricing Program, Medicaid, 340B program. Finally, it will be important to determine whether biosimilars will constitute "multi-source drugs." There exists significant uncertainty under BPCIA's provisions in view of the substantial discretion provided to FDA regarding details and standards for submissions and approvals of biosimilars, and regarding the competitive market effects.

Gauging risk versus reward in the biosimilars market is also a challenge, as there is likely going to be substantially different competitive market dynamics for biosimilars from that of generic drugs market. Unlike the generic drugs market, the biosimilars market is likely to have a smaller number of entrants, significantly greater cost of applications and testing, less reduction in price from that of a pioneer biologic, and necessity of marketing staffing. There is a lack of certainty regarding what type and scope of sales/marketing approach and staffing will be needed for biosimilars, and what potential there will be for use of authorized biologic settlement agreements, deriving from the patent negotiation process.

It is also unclear what degree of cost reduction and difference with a pioneer biologic will be needed to drive purchasing. There exist potential purchaser/payor concerns regarding interchangeability and safety and efficacy (i.e., potency). In late 2010, Sandoz experienced purchaser resistance to Omnitrope (biosimilar somatropin), notwithstanding the price advantage. There is also concern over a potential biologics "evergreening" strategy through the use of pioneer biologics modifications to extend the exclusivity period.

Finally, there is uncertainty whether payors will require additional data regarding efficacy or safety for certain products, such as biosimilar monoclonal antibodies, and whether cooperation between the FDA and the European Medicines Agency ("EMA") will result in more expeditious approval of biosimilars in both jurisdictions. In June 2011, the EMA and FDA issued a joint report noting the interactions between the two agencies. Just last month, the first application for a biosimilar version of a monoclonal antibody (Remicade) was filed in the EU.

Despite these uncertainties, and notwithstanding that the FDA has not yet issued proposed biosimilars regulations, agency officials have noted that the agency has conducted 21 pre-IND meetings for proposed biosimilar development programs.

The regulatory pathway for biosimilars has obvious impact on biopharma research and development, mergers and acquisitions, and valuation of companies and products. Industry and its investors are uncertain whether and when biosimilars will be approved, as well as regarding sales and rate of return consequences of biosimilars on pioneer products.