EPSTEIN BECKER GREEN | HEALTH CARE & LIFE SCIENCES CLIENT ALERT

Thought Leaders in Health Law®

The Proposed Approval Pathway for 'Biosimilars' and its Potential Implications for Various Stakeholders

by Alaap B. Shah, Benjamin S. Martin and Lee H. Rosebush

November 2009

The principal federal health reform bills currently being considered by Congress propose to create a pathway by which the Food and Drug Administration ("FDA") would approve biologics that are "biosimilar" to previously approved biologics. Based on our comparison of these bills–H.R. 3962, the "Affordable Health Care for America Act," which was passed on November 7, 2009, by the House of Representatives, and S. 3590,[1] the "Patient Protection and Affordable Care Act," which was introduced on November 18, 2009, for consideration by the Senate[2]–it appears that a consensus has emerged as to the likely mechanics of that pathway, in the event that health reform legislation is enacted.

Described below are 10 areas concerning "biosimilars" that may be of interest to stakeholders in the biologics market at this critical juncture. (These areas correspond to the 10 key issues described in the December 2009 EpsteinBeckerGreen companion EBG newsletter "Top Ten Key Issues Concerning 'Biosimilars.'") Although the specific issues discussed within each area may evolve as the bills progress through the legislative process, these areas of interest likely will remain relevant for stakeholders in the event that any approval pathway is established for biosimilars. EpsteinBeckerGreen will continue to provide additional information about these areas as further developments warrant.

1. The Proposed Approval Pathway

Currently, a Biologics License Application ("BLA") is submitted to the FDA pursuant to Section 351(a) of the Public Health Service Act ("PHSA") (42 U.S.C. § 262) for evaluation to determine whether the information contained therein demonstrates that a biologic is safe and effective for its intended uses. Both H.R. 3962 and S. 3590 would amend Section 351 (by adding subsection (k)) to allow for the licensure of biologics that are "biosimilar" to "reference products" approved under the existing Section 351(a) pathway. The provisions in each bill concerning the creation of this pathway are nearly

identical.

- ***'Biosimilar' defined***

  Under the proposed pathway, a Section 351(k) BLA would include certain information prescribed by statute, and the FDA would approve that BLA upon a determination of the subject product's biosimilarity to the reference product identified therein. The subject product would be biosimilar to the reference product if it "is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and if "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product." Such a determination by the FDA would substitute for a demonstration of the subject product's efficacy, which would have been established by the reference product.

- ***'Interchangeable' defined***

  Also, under the proposed pathway, a Section 351(k) BLA could include, at the election of the sponsor, information that the FDA would evaluate to determine whether the subject product is "interchangeable" with the reference product (*i.e.*, that the subject product "can be expected to produce the same clinical result as the reference product" and that, "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch"). Notably, the FDA previously has expressed concerns that, because current analytical technology is insufficient to establish that two biologics are molecularly identical, interchangeability would have to be established through clinical trials; accordingly, "[t]he design and ethical considerations for such studies will require careful consideration."[3]

  Both H.R. 3962 and S. 3590 would authorize the FDA to develop guidance documents relating to the licensure of biosimilars, consistent with existing statutory procedural requirements, with the additional requirement that the public be given an opportunity to comment on the proposed guidance before it is finalized. If the FDA develops product class-specific guidance, such guidance would describe the criteria the FDA will use to evaluate whether a product is biosimilar to and interchangeable with a reference product. Importantly, both bills state that the issuance or non-issuance of guidance would not preclude the FDA from accepting and reviewing Section 351(k) applications.

Biotechnology companies should begin familiarizing themselves with the concepts of "biosimilarity" and "interchangeability", given that they are different than the concepts associated with generic drugs.[4] These companies also should monitor the FDA's activities regarding the development of guidance documents that flesh out the meaning of these concepts, both generally and with respect to specific product classes. Additionally, biotechnology companies and other stakeholders, including patient

advocates, should pay particular attention to the development of standards used to determine "interchangeability."

2. Regulatory Jurisdiction for Protein-Based Products

Both H.R. 3962 and S. 3590 would revise the definition of a "biological product" to include non-chemically synthesized proteins. (Historically, some protein-based products have been approved as "drugs.") Accordingly, applications for all products within this revised definition would be submitted under Section 351 of the PHSA and, thus, evaluated by the FDA's Center for Biologics Evaluation and Research ("CBER"), unless such a product is in a class that includes a product already approved as a "drug" under Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 355). (In such a case, the product presumably also would be subject to approval through the Section 505 pathway.) However, both bills include a provision that would convert all approved Section 505 applications for products that fall within the definition of "biological product" (as revised) to BLAs 10 years after enactment. Thus, manufacturers of protein-based products currently regulated as drugs by the Center for Drug Evaluation and Research should begin considering the potential impact of this jurisdictional transfer.

3. User Fees

Both H.R. 3962 and S. 3590 would amend Section 735(1)(B) of the FDCA to subject Section 351(k) BLA sponsors to user fees already charged to sponsors of New Drug Applications ("NDAs") and Section 351(a) BLAs. However, the Senate bill would require the FDA to collect and evaluate data on the costs associated with reviewing applications for biosimilars, compare those costs to the costs of reviewing Section 351(a) BLAs (relative to the user fees charged), and adjust the user fees charged to biosimilar application sponsors if the difference between the ratios exceeds 5 percent.

Given that Abbreviated New Drug Applications ("ANDAs") currently are not subject to user fees, generic drug companies considering entering the biosimilars market may find it helpful to begin acquainting themselves with the FDA's processes and guidance regarding user fees.

4. Market Exclusivity

Both H.R. 3962 and S. 3590 would prohibit the FDA from approving a Section 351(k) BLA until 12 years after the date on which the reference product identified therein was approved, and the FDA could not accept such an application for review during the first four of those 12 years. This period of exclusivity would appear to be distinct from any additional patent protection that the reference product may enjoy.

Both H.R. 3962 and S. 3590 would grant a period of exclusivity to the first biosimilar that the FDA determines is also interchangeable with the reference product. The FDA would be prohibited from determining that a second product is interchangeable with the same reference product until the earlier of: (a) one year after the date on which the first

interchangeable biologic was commercially marketed; (b) 18 months after the date on which any patent infringement litigation against the first interchangeable biologic's sponsor is dismissed or resolved by final court decision; (c) 42 months after the date on which the first interchangeable biologic's application was approved, if the applicant was sued for patent infringement; or (d) 18 months after the date on which the first interchangeable biologic's application was approved, if the applicant was not sued for patent infringement. Presumably, the FDA would not be prohibited from approving the second product's Section 351(k) application on the basis of established biosimilarity.

Biotechnology companies should consider how the various potential exclusivity periods for reference products and interchangeable biologics intersect with one another and with the patent infringement litigation process discussed below. These issues may affect strategies for developing and submitting applications for interchangeable biosimilars.

5. Role of Patent Protections

Because of the unique composition of biological and biosimilar products, innovative strategies may be available to biotechnoly companies that wish to protect their intellectual property. For example, a biological product, unlike a chemical compound, could be protected by a patent on a specific gene, amino acid, or protein sequence or by pathway and method of treatment patents. Conceivably, such patent terms could extend years beyond the 12-year exclusivity period that would be granted to reference products under both H.R. 3962 and S. 3590.

However, these patent strategies could be greatly affected by the decision in *Bilski v. Kappos*, which is currently pending before the U.S. Supreme Court. The question before the Court is whether a "process" described in a method patent must either be tied to a particular machine or an apparatus or transform a particular article into a different state or thing, in order to be eligible for a patent (*i.e.,* whether to follow the "machine-or-transformation" test, as formulated by the U.S. Court of Appeals for the Federal Circuit). The Court's holding in *Bilski* could have a far-reaching effect on the patent protection of biological products.

In addition, biologics are eligible under the Hatch-Waxman Act for patent term restoration, which may restore up to five years to the term of an unexpired patent. However, the restoration cannot result in a patent term that exceeds 14 years from the date on which the product's application was approved. Therefore, it appears that any resulting restored patent term would exceed the 12-year exclusivity period that would be granted to reference products under both H.R. 3962 and S. 3590 by only two years.

When considering whether to seek patent term restoration, biotechnology companies or other owners of patents that relate to reference product biologics should weigh the advantages of potentially gaining an incremental two years of patent-conferred exclusivity against the costs associated with the restoration process. More generally, biotechnology companies should consider the benefits of various patent prosecution and restoration strategies when seeking the best protection for their biologics.

6. Patent Infringement Litigation

Both H.R. 3962 and S. 3590 would establish an intricate process for conducting patent infringement litigation related to biosimilar products. This process would differ significantly from the process governing drugs approved under Section 505 of the FDCA (*i.e.,* litigation between NDA and ANDA sponsors). Most notably, whereas NDA sponsors are required to list all patents related to the subject drug with the FDA for publication in the Orange Book, Section 351(a) BLA sponsors would not have a similar requirement. Instead, a Section 351(k) applicant would provide a copy of its application to in-house and outside counsel designated by the sponsor of the reference product BLA, provided those attorneys have no role in prosecuting patents related to the reference product. The parties then would engage in a series of information exchanges designed to identify those patents that may be infringed by the biosimilar and that subsequently would be the subject of patent infringement litigation. Failure to adhere to the process could result in statutorily imposed disadvantages during the litigation.

7. Antitrust Scrutiny

In contrast to the approach taken in the pending bills, the Federal Trade Commission ("FTC") has taken the position that creating an abbreviated pathway for the approval of biosimilars that does not a include a long exclusivity period for reference products can increase competition without stifling innovation. In a June, 2009, report, the FTC interprets market data to suggest that competition between a biosimilar and its reference product would more closely resemble "brand-to-brand" rather than "brand-to-generic" competition. In this regard, the FTC concluded that a reference biologic likely would face competition from only three or less biosimilars, that biosimilars likely would offer discounts ranging from 10 percent to 30 percent, and that the reference product likely would retain 70 percent to 90 percent of its market share.

Based on these estimates, the FTC argues that traditional methods of competition, such as market pricing and patent protection, would be sufficient to protect reference biologics upon entry of biosimilars. Accordingly, in the FTC's view, a long exclusivity period for reference products, such as the 12-year period proposed in both H.R. 3962 and S. 3590, is unnecessary and could result in anticompetitive effects.

Given the tenor of the June, 2009, report, biotechnology companies should be prepared for continued scrutiny of allegedly anticompetitive activities, including pay-for-delay settlements of patent infringement litigation (discussed below), the misuse of the FDA citizen petition process to delay entry of biosimilars, and an anticompetitive market concentration through mergers or acquisitions involving competing biologics.

8. 'Pay-For-Delay' Settlements Involving Biosimilars

Currently, antitrust authorities strongly oppose "pay-for-delay" settlements in the pharmaceutical industry, but it remains uncertain if similar opposition will exist in the biologics industry. The FTC and U.S. Department of Justice ("DOJ") argue that reverse payments from patent holders to generic companies to settle patent infringement

disputes can constitute anticompetitive conduct if those settlements delay the entry of generics into the market.[5] Based on challenges in the pharmaceutical area, it appears the biologics industry may have little respite from FTC and DOJ scrutiny.

Although, to date, antitrust authorities have had limited success in the courts in challenges to pay-for-delay settlements, a split currently exists among the U.S. Courts of Appeal. The U.S. Supreme Court has not yet granted certiorari in any of these cases.

The limited success of the FTC and DOJ to persuade the courts that pay-for-delay settlements are anticompetitive has prompted them to seek legislative restrictions on such settlements. Currently, three bills are pending in Congress, but they all would regulate only settlements between New Drug Application and Abbreviated New Drug Application sponsors.

However, H.R. 3962 would facilitate review of potentially anticompetitive agreements involving biosimilars. H.R. 3962 would require agreements "regarding the manufacture, marketing, or sale of" biosimilar or reference products, or agreements "contingent upon, provid[ing] a contingent condition for, or otherwise relat[ing] to" such agreements, to be filed with the Assistant Attorney General and the FTC. Although this legislation would not presume that pay-for-delay settlements involving biosimilars generate unlawful anticompetitive effects, policy concerns similar to those in the pharmaceutical market may exist.

9. Medicare Part B Reimbursement For Biosimilars

Both H.R. 3962 and S. 3590 include provisions relating to the reimbursement of biosimilars under Medicare Part B, which covers certain drugs and biologics, including those administered by physicians in an outpatient setting. Under S. 3590, the reimbursement amount for any biosimilar product would equal the weighted Average Sales Price ("ASP") of all package sizes of the biosimilar within the applicable billing code, plus 6 percent of the weighted ASP of all package sizes of the reference product within the applicable billing code. Assuming that the weighted ASP for the reference product's billing code were higher than that of the biosimilar, the 6 percent of this relatively higher value would provide physicians with an incentive to administer biosimilars instead of reference products.

In contrast, H.R. 3962 distinguishes between interchangeable and non-interchangeable biosimilars. Whereas a non-interchangeable biosimilar would be reimbursed just as any biosimilar would be under S. 3590, the reimbursement amount for an interchangeable biosimilar under H.R. 3962 would equal the weighted ASP of all package sizes of all interchangeable biosimilars and the reference product within the applicable billing code, plus 6 percent of that amount. Accordingly, the "administration" portion of the reimbursement amount would be the same for either type of biosimilar, but the "ingredient" portion presumably would be higher for an interchangeable biosimilar.

10. Managed Care Contracting

Notwithstanding the FTC's conclusion that competition between a biosimilar and its reference product would more closely resemble "brand-to-brand" competition, it is not currently clear how interchangeable and non-interchangeable biosimilars would be treated under "generic substitution" requirements imposed by health plans and governed by state pharmacy laws. For example, would health plans utilize their formularies or implement other utilization management techniques to encourage the dispensing of all biosimilars, or only of interchangeable biosimilars (to the extent otherwise permitted by law)? Generally, when the first generic version of a prescription drug enters the market, the innovator drug may be excluded from coverage under a pharmaceutical benefit entirely. This may not be the case, however, for reference biologics or, at least, for reference biologics with no interchangeable alternative.

Given the uncertain treatment of biosimilars in the managed care setting, biotechnology companies should review the contracting strategies for their biologics and consider how those strategies may be affected by the availability of biosimilars under various possible treatments by health plans.

* * *

This Client Alert was authored by Alaap B. Shah, Benjamin S. Martin, and Lee H. Rosebush. The authors thank the following additional EpsteinBeckerGreen attorneys for their contributions: Constance A. Wilkinson, Patricia M. Wagner, and Kathleen A. Peterson. For additional information about the issues discussed in this Client Alert, please contact one of the authors or contributors or the EpsteinBeckerGreen attorney who regularly handles your legal matters.

The EpsteinBeckerGreen Client Alert is published by EBG's Health Care and Life Sciences practice to inform health care organizations of all types about significant new legal developments.

Lynn Shapiro Snyder, Esq.
EDITOR

If you would like to be added to our mailing list or need to update your contact information, please contact, Kristi Swanson, Kswanson@ebglaw.com or 202-861-4186.

Endnotes

[1] The actual number of the bill pending in the Senate is "H.R. 3590". Our understanding is that the Senate health reform legislation was added to an uncontroversial bill – H.R. 3590, the "Service Members Home Ownership Tax Act of 2009" – which was previously passed by the House of Representative as part of a parliamentary strategy to bring the legislation to the Senate floor. To avoid confusion, we refer to the Senate bill as "S. 3590."

[2] S. 3590 was synthesized from S. 1796, America's Healthy Future Act, which was approved by the Senate Finance Committee on October 13, 2009, and S. 1679, the Affordable Health Choices Act, which was approved by the Senate Health, Education, Labor, and Pensions Committee on July 15, 2009. The provisions in S. 3590 relating to the approval pathway for biosimilars originated in S. 1679, while the provisions relating to reimbursement for biosimilars under Medicare Part B originated in S. 1796.

[3] Letter from Frank M. Torti, M.D., M.P.H., Principal Deputy Commissioner and Chief Scientist, FDA, to the Hon. Frank Pallone, Jr., Chairman, Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, at 9 (Sept. 18, 2008) (on file with authors).

[4] For example, Abbreviated New Drug Application sponsors must demonstrate that their products are "pharmaceutically equivalent" and "bioequivalent," and thus "therapeutically equivalent," with their reference products.

[5] In a recent speech, Jon Leibowitz, Chairman of the FTC, advocated for "reverse payment reform," noting that eliminating reverse payments was one of the FTC's "highest priorities" because doing so could save consumers $35 billion over the next 10 years. In July, 2009, the DOJ argued in its supporting brief in In re Ciprofloxacin Hydrochloride Antitrust Litigation (on appeal to the U.S. Court of Appeals for the Second Circuit) that pay-for-delay settlements should be treated as presumptively unlawful.