ALERTS AND UPDATES

FDA Proposes Pre-marketing User Fees for Biosimilar Product Manufacturers Comparable to Fees for Branded Manufacturers

May 11, 2011

In its next step toward implementing a pathway for biosimilar product approval under the Biologics Price Competition and Innovation Act of 2009 ("BPCI Act"), the U.S. Food and Drug Administration (FDA) released a Notice and Request for Comments on "Biologics Price Competition and Innovation Act of 2009; Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Year 2013 Through 2017," ("User Fee Notice")—published in the *Federal Register* on May 10, 2011.[1] In the User Fee Notice, FDA seeks comment on proposed user fees for manufacturers of biosimilar and interchangeable biologic products, including up-front and annual fees comparable to pre-marketing fees imposed on branded biologic drug manufacturers.

Signed into law in March 2010 as a provision of the Affordable Care Act, the BPCI Act created an abbreviated approval pathway under section 351(k) of the Public Health Service Act ("PHS Act") for biological products shown to be highly similar (biosimilar) to, or interchangeable with, an FDA-licensed biological product. FDA sought public comment on specific issues and challenges associated with implementing the biosimilar approval pathway in its October 5, 2010, Notice on "Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments." FDA also held a two-day public hearing in November 2010 to obtain additional input from stakeholders in the industry.

The User Fee Notice is FDA's first published notice on the biosimilar pathway since the hearings last November, and FDA is anticipated to issue further guidance on the biosimilar pathway in 2011. The BPCI Act requires FDA to consult with a range of groups and to provide the U.S. Congress with FDA's recommendations on user fee programs under the abbreviated section 351(k) approval pathway by January 15, 2012, for Congress' authorization by October 2012. Meanwhile, the fee for a biologics license application (BLA) remains the same for applications submitted under the new section 351(k) approval pathway and for applications submitted under the preexisting section 351(a) BLA pathway.

In the User Fee Notice, FDA proposes and seeks comments on:

1. FDA's principles for developing the biosimilar user fee program;
2. FDA's proposed structure for the program;
3. Proposed performance goals for FDA to review applications under 351(k); and
4. Specific questions in connection with performance goals for reviewing applications for which FDA cannot grant approval for at least two to eight years under the "exclusivity" provisions of the BPCI Act.

FDA's proposed principles set forth in the Notice recognize key health benefits flowing from both biosimilar products that provide life-saving or life-altering benefits at reduced costs, and from branded biologic products, which offer life-saving or life-altering therapies to treat previously unmet medical needs. FDA further recognizes the need to prevent unnecessary delays in the development and approval of biosimilar and interchangeable biologic products under 351(k), while also ensuring adequate resources for review of applications for innovator biologic products filed under 351(a). In addition, the 351(k) user fees "should provide funding to support activities that occur early in the biosimilar and interchangeable product development cycle."

In a move that may surprise manufacturers of biosimilar or interchangeable products, FDA proposes that, at least for the period of 2013–2017, user fees for biosimilar and interchangeable biologics should remain comparable to fees for branded biologic product applications under section 351(a). FDA notes that, at least initially, its review to determine biosimilarity or interchangeability of a proposed product in a 351(k) application will be as "complex, technically demanding, and resource-intensive" as its review of an application under 351(a). In addition, FDA anticipates that given the nascent state of the biosimilar approval pathway, FDA services will be most vital to manufacturers of biosimilar products during the investigational stage prior to submission of a marketing application.

Thus, FDA's proposed fee structure imposes payment of an up-front and annual biosimilar product development fee of around $150,000, to be paid upon submission of an investigational new drug application (IND) and annually thereafter, for a

biosimilar or interchangeable product to be submitted in a 351(k) marketing application. Credit for the biosimilar product development fee would then be subtracted from a marketing fee comparable to the marketing fee under 351(a), to yield the 351(k) marketing application fee. FDA further proposes setting establishment and product fees for marketed 351(k) products at rates equal to the comparable rates for products licensed under 351(a).

With respect to FDA performance goals, the User Fee Notice further anticipates two different categories of 351(k) applications. "In the first category are applications that are submitted 10 or more years after the date of first licensure of the reference product," which "would be eligible for approval in 2 years or less, depending on the relevant filing dates." The second category of applications are those submitted between four and 10 years after the date of first licensure of the reference product. Because the second category of applications would be two to eight years from approval, FDA proposes performance goals for reviewing only the first category of applications, but seeks input for performance goals relating to the second category of applications. Questions on which FDA solicits comment include:

1. What factors should FDA consider in determining performance goals, such as technological developments, facility changes and other issues arising in the period between application and approval?
2. How should FDA take into account readiness for inspection?
3. What other factors relating to the unique characteristics of the 351(k) approval pathway should FDA consider when setting performance goals?

FDA's assessment of the biosimilar product development fee upon filing of an IND may suggest that future biosimilar guidelines would require clinical data to establish that a product is biosimilar to, or interchangeable with, a reference biologic drug—at least where "active development" is required to establish biosimilarity or interchangeability. FDA's statement that review of a 351(k) marketing application will be "comparably complex, technically demanding, and resource-intensive as review of a proposed 351(a) application," further suggests that significant analytical and clinical data may generally be required to establish biosimilarity or interchangeability. However, Rachel Behrman, associate director for medical policy in FDA's Center for Drug Evaluation and Research, has indicated that FDA will likely first evaluate analytical data before providing "advice on the extent to which animal or human testing will be necessary" to establish biosimilarity or interchangeability. Behrman also noted that duplicative testing is unethical, and stated that "What I think we've shown in our decision on generic enoxaparin, is we may be able to take the European experience [approving biosimilar products] and go one step further."[2]

The User Fee Notice also appeared to resolve controversy over the interpretation of the 12-year exclusivity provision of the BPCI Act. FDA avoided a second controversial reference to "a 12-year period of marketing exclusivity,"[3] and instead tracked the "exclusivity" language in section 351(k)(7) of the BPCI Act by stating that "a 351(k) application may not be submitted to the Secretary of Health and Human Services (the Secretary) until 4 years after the reference product was first licensed under section 351(a); however, the Secretary may not make approval of a 351(k) application effective until 12 years after the reference product was first licensed." By further observing that applications submitted 10 or more years after the date of first licensure "would be eligible for approval in 2 years or less, depending on the relevant filing dates," FDA appears to have resolved any remaining uncertainty over the "exclusivity" provisions of the BPCI Act in favor of the interpretation proffered by U.S. Senators Harkin, McCain, Schumer and Brown in a January 24, 2011, letter written to FDA Commissioner Margaret Hamburg, and against the "data exclusivity" interpretation proposed by Senators Hagan, Hatch, Enzi and Kerry in their January 7, 2011, letter to the FDA commissioner.[4]

FDA also cites unique challenges for establishing the user fee program due to the nascent state of the industry, the lack of approvals to-date of any products under 351(k), as well as challenges in identifying companies comprising the "regulated industry." Additionally, FDA plans to hold a series of industry-stakeholder meetings to seek further comment on the underlying principles, the proposed user fee program and performance goals set forth in the User Fee Notice. Comments in response to the User Fee Notice are due within 30 days of publication, by June 9, 2011.

For Further Information

If you have any questions about this *Alert*, please contact Vicki G. Norton, Ph.D., Lewis F. Gould, Jr., any member of the Intellectual Property Practice Group or the attorney in the firm with whom you are regularly in contact.

Notes

1. "Biologics Price Competition and Innovation Act of 2009; Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Year 2013 Through 2017," 76 Fed. Reg. 27062 (May 10, 2011).
2. See Interview with Dr. Rachel Behrman, Associate Director of Medical Policy, Center for Drug Evaluation and Research (May 1, 2011), http://www.biocenturytv.com/fullplayer.aspx#/BC%20Show%2033%3A%20Biosimilars%3A%20Will%20the%20U.S.%20Plan%20Work%3F/BioCentury%2005.01.11%20%2D%20%5B1%5D%20The%20Pathway/608459720001/923169085001/924495749001 (reporting Behrman's comments in connection with FDA's approval of Momenta's generic version of Lovenox® enoxaparin in July 2010 without requiring any clinical data, presumably based on clinical data submitted to the European Medicines Agency; which regulates heparin products such as enoxaparin as biologic drugs and requires clinical data to approve biosimilar versions of low-molecular-weight heparin products like enoxaparin).
3. "Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments." 75 Fed. Reg. 61497, 61500 (Oct. 5, 2010).
4. Section 351(k)(7) does not refer to "market" or "data" exclusivity, instead referring to:

> EXCLUSIVITY FOR REFERENCE PRODUCT.—
> (A) EFFECTIVE DATE OF BIOSIMILAR APPLICATION APPROVAL.—Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a).
> (B) FILING PERIOD.—An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a)."