

E-ALERT | Health Care

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HEALTH CARE REFORM: BIOSIMILARS LICENSING AND REIMBURSEMENT

On March 23, 2010, President Obama signed into law Pub. L. No. 111-148, the Patient Protection and Affordable Care Act (PPACA). Shortly afterwards, on March 30, 2010, President Obama signed into law Pub. L. No. 111-152, the Health Care and Education Affordability Reconciliation Act of 2010 (Reconciliation Amendments), amending PPACA. PPACA, as now amended by the Reconciliation Amendments (collectively the Act), will have far-reaching effects for the entire health care sector.

This e-alert, part of a series explaining the impact of the Act on life sciences companies, will summarize the provisions of the Act relating to biosimilars. These provisions are found in sections 3139 and 7001 to 7003 of PPACA. Sections 7001 to 7003 are the “Biologics Price Competition and Innovation Act of 2009” (BPCIA).

EXECUTIVE SUMMARY

- Among other things, the BPCIA adds sections 351(k), 351(l), and 351(m) to the Public Health Service Act (PHSA). These sections will permit licensure of biological products shown to be biosimilar to previously licensed reference biological products and will permit litigation of patent infringement cases between patent owners and biosimilar manufacturers prior to biosimilar market entry.
- A biological product is “biosimilar” to a 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 products in terms of the safety, purity, and potency. A biosimilar may be approved on the basis of an application that contains analytical, preclinical, and clinical data showing biosimilarity. The Food and Drug Administration (FDA) will have discretion to waive any data requirements that the agency determines are “unnecessary.”
- The BPCIA preserves a 12-year period of data exclusivity for reference biological products, during which approval of a biosimilar application relying on that reference product cannot be made effective.
- The BPCIA describes a showing that may be made to establish the interchangeability of a biosimilar biological product with its reference product. It also provides that the first interchangeable biosimilar is entitled to a period of “exclusivity” during which no other biosimilar may be deemed interchangeable with the same reference product.
- The Medicare Part B payment amount for a biosimilar product must be based on the sum of its own average sales price (ASP), plus 6 percent of the ASP of the reference product as calculated for a single source biologic product.

BIOSIMILAR APPLICATION REQUIREMENTS

- An application submitted under section 351(k) of the PHSA must include information demonstrating that: (1) the biological product that is the subject of the application is “biosimilar” to a single reference product; (2) the biological product and reference product use the same mechanism(s) of action for the condition(s) of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism(s) of action are known for the reference product; (3) the condition(s) of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product; (4) the biological product has the same route of administration, dosage form, and strength as the reference product; and (5) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

STANDARD OF APPROVAL

- FDA must license a biosimilar biological product if: (1) the agency determines that the information in the application is sufficient to show that the biological product is biosimilar to (or, if desired by the applicant, interchangeable with) the reference product; and (2) the applicant (or other appropriate person) consents to inspection of the facility that is the subject of the application.
- The showing of biosimilarity is to be made on the basis of data from (1) analytical studies showing that the products are “highly similar” notwithstanding minor differences in clinically inactive components, (2) animal studies, including an assessment of toxicity, and (3) a clinical study or studies (including an assessment of immunogenicity and pharmacokinetics or pharmacodynamics) sufficient to show the safety, purity, and potency of the proposed product for one or more “appropriate” conditions of use for which licensure is sought and for which the reference product is licensed. As noted above, however, FDA may waive any of these application requirements if it determines they are unnecessary for it to find the products are biosimilar.

INTERCHANGEABILITY

- In its initial application or a later supplement, a biosimilar manufacturer may seek an interchangeability determination from FDA. The agency must find interchangeability if it determines that the information submitted in the application shows that: (1) the biological product is biosimilar to the reference product, and (2) the biological product can be expected to produce the same clinical result as the reference product in any given patient. If the product will be administered more than once to an individual, FDA must also find the risk in terms of safety or diminished efficacy of alternating or switching between the two products is not greater than the risk of exclusively using the reference product.
- The first biological product determined to be interchangeable with a particular reference product for any condition of use receives a period of data protection, during which no other product may be deemed interchangeable to that reference product for any condition of use. The data protection period terminates on the earlier of: (1) one year after the first commercial marketing of the first interchangeable product; (2) 18 months after either a final court decision on all patents in suit, or the dismissal with or without prejudice of an action brought by the reference product sponsor against the biosimilar applicant under new section 351(l)(6) of the PHSA; (3) 42 months after approval of the first interchangeable biosimilar biological product, if an expedited

patent action was commenced against the applicant under section 351(l)(6) and the litigation is still ongoing; or (4) 18 months after approval of the first interchangeable product, if the reference product sponsor did not sue the applicant under section 351(l)(6).

- Under an amendment to section 351(j) of the PHSA, “interchangeable” — with respect to a biosimilar biological product — means that the product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

GUIDANCE DOCUMENTS

- FDA may issue general or specific guidance on the licensure of biological products under section 351(k). If the agency issues guidance, it must follow the requirements of section 701(h) of the Federal Food, Drug, and Cosmetic Act (FDCA), except that the public must have an opportunity to comment on any proposed guidance document before that document is adopted in final form. Further, FDA must establish a process through which the public may provide input on priorities for issuing guidance. The issuance or non-issuance of guidance does not preclude the review of, or action on, an application submitted under section 351(k).
- If FDA issues a product class-specific guidance, that guidance must describe the criteria FDA will use to determine whether a biological product is “highly similar” to a reference product in that product class, as well as the criteria “if available” that will be used to determine whether a biological product in that class is interchangeable with a reference product. FDA may indicate in a product class-specific guidance that current science and experience do not allow approval of section 351(k) applications with respect to a particular product or product class, except for recombinant proteins. FDA may modify or reverse such a decision in a subsequent guidance.

DATA PROTECTION

- An application may not be submitted under section 351(k) until four years after the date on which the reference product was first licensed under section 351(a). Approval of an application submitted under section 351(k) may not be made effective until 12 years after the date on which the reference product was first licensed.
- The date on which a reference product was first licensed does not include the date of approval of a supplement to the reference product application, nor does it include the date of approval of a subsequent application for (1) a change to the reference product, other than a structural change, that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength, or (2) a structural modification to the reference product that does not result in a change in safety, purity, or potency.
- If certain pediatric testing requirements are satisfied, section 351(l) extends the 4-year period and 12-year period by six months and adds six months to any orphan exclusivity in place. Section 351(l) also incorporates by cross-reference many of the provisions in section 505A of the FDCA, which governs pediatric exclusivity for new drugs.

USER FEES

- The prescription drug user fee system that applies to applications submitted under section 351(a) of the PHSa will apply to applications submitted under section 351(k). FDA must audit the costs of reviewing biosimilar applications and, if necessary, alter the user fee to appropriately account for the cost of their review.
- Beginning October 1, 2010, and using a public process, FDA must develop recommended performance goals for review of biosimilar applications in the years 2012 to 2017. The agency must submit these recommendations to Congress by January 15, 2012, and it is expected that biosimilar applications will be included in the 2012 round of user fee reauthorization.

PATENT PROVISIONS

- There is no patent listing process comparable to listing under the Hatch-Waxman amendments to the FDCA. Instead, under section 351(l) of the PHSa, the reference product sponsor and biosimilar applicant privately exchange information about relevant patents. The statute provides a default mechanism for this exchange, and the parties may agree to an alternative scheme.
- Under the provided scheme, within 20 days after FDA notifies the biosimilar applicant that its application has been accepted for review, this applicant must send the reference product sponsor a copy of the application and information concerning its manufacturing process. Outside counsel and one in-house counsel for the reference product sponsor are entitled to “confidential access” to the application.
 - Within 60 days after receiving this information, the reference product sponsor must provide the biosimilar applicant with a list of patents as to which it believes it (or a patent owner that has granted it an exclusive license) could reasonably assert a claim of patent infringement. The sponsor must also identify which patents it would be prepared to license to the applicant.
 - Within 60 days of receiving the reference product sponsor’s initial list, the biosimilar applicant may provide to the reference product sponsor its own list of patents as to which it believes the reference product sponsor (or a patent owner has granted it an exclusive license) could reasonably assert a claim of patent infringement. It must also provide — for each patent listed by the reference sponsor or itself — either: (1) a detailed statement describing, on a claim-by-claim basis, the factual and legal basis for its opinion that the patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the biosimilar product; or (2) a statement that it does not intend to begin commercial marketing of its product until after expiry of the patent. The biosimilar applicant must also respond to any offer by the reference product sponsor to license patents.
 - Within another 60 days, the reference product sponsor must provide: (1) as to each patent that the biosimilar applicant claims to be not infringed, its own detailed statement describing on a claim-by-claim basis why the patent will be infringed, and (2) as to each patent that the biosimilar applicant claims to be invalid and not enforceable, a response to the biosimilar applicant’s assertion.
- After exchanging these lists and statements, the parties must engage in good faith negotiations to identify patents that will be litigated pursuant to an expedited litigation procedure. If the parties do not agree on the list of patents within 15 days, the parties will exchange lists of patents each believes should be asserted. (The biosimilar applicant may choose as many as it

wishes for this expedited litigation; the reference product sponsor may choose at least one but in any case no more than chosen by the biosimilar applicant.) The reference product sponsor must bring suit for infringement of the listed patents within 30 days of the agreement or exchange, whichever is appropriate. Failure to do so will limit the company to recovery of a reasonable royalty for patent infringement in any subsequent suit.

- If a reference product sponsor should have included a patent in its initial list but failed to do so within the designated time frame, the patent owner may not bring a patent infringement action with respect to the biosimilar in question.
- The applicant must provide notice to the reference product sponsor 180 days before launching the biosimilar product. The reference product sponsor then may seek a preliminary injunction as to patents that were in its initial list but are not subject to expedited litigation under section 351(l)(6).

TRANSITION

- The BPCIA amended the definition of biological product in section 351(i) to include proteins, but not synthetic polypeptides. Under a provision of the BPCIA that will not be codified, applications for biological products, including proteins, must now be submitted under section 351 of the PHSa and not under section 505 of the FDCA.
- There is one exception. An application for a biological product may be submitted under the FDCA if the product is in a product class for which there is already an approved new drug application (NDA) and if the application is submitted before March 23, 2020. That said, an application may not be submitted under section 505 of the FDCA if there is another biological product licensed under section 351(a) of the PHSa that could serve as its reference product.
- On March 23, 2020, any approved NDA for a biological product will be deemed a licensed approved under section 351 of the PHSa.

MEDICARE PART B PAYMENT FOR BIOSIMILARS

- The Medicare Part B payment amount for a biosimilar product licensed under the BPCIA will be based on the sum of its own ASP, plus 6 percent of the ASP of the reference product as calculated for a single source biologic product. The reference product will continue to be paid at 106 percent of its own ASP. This provision, section 3139(b) of PPACA, takes effect on July 1, 2010. The biosimilar licensure provisions discussed above take effect immediately.

OUTSTANDING ISSUES AND IMPLEMENTATION CHALLENGES

- If the 1984 Hatch-Waxman amendments to the FDCA are any guide, FDA and the courts will face substantial challenges interpreting and implementing the new biosimilar licensure provisions. The legislation does not require FDA to engage in rulemaking or issue guidance documents, it leaves key concepts undefined, and it gives — or appears to give — the agency considerable latitude in its implementation of key provisions. Although FDA has signaled its views on biosimilar approval issues repeatedly in the past, including in a detailed September 2008 letter to Congressman Pallone, whether it adheres to these previously stated views remains to be seen.
- Fundamental concepts that will need to be explored include: what it means to say that there are no “clinically meaningful differences” between two products “in terms of safety, purity, and

potency”; whether and when analytical, preclinical, and clinical data might be “unnecessary” in a particular biosimilar application; and how one would show that one biological product can be “expected to produce the same clinical result” as another in “any given patient.”

- One key question for all stakeholders is how the agency will determine the data that are necessary, and unnecessary, in biosimilar applications. In 2008, the agency signaled that it envisioned a public and product class-based approach to defining data requirements. The legislation suggests, but does not require, such a process. It does, however, require the agency to solicit public input on guidance priorities, and this may be a mechanism for stakeholders to propose or request a class-based approach, as has been followed in Europe. European regulators have completed guidelines for granulocyte-colony stimulating factor (GCSF), recombinant erythropoietin, and recombinant interferon alpha, for example, and they are currently examining monoclonal antibodies.
- Another key question is how the agency envisions handling concerns about immunogenicity both prior to, and following, biosimilar licensure. The agency signaled in 2008 that there would be few circumstances where assessment of immunogenicity would not be critical, and it actually endorsed a statutory requirement of premarket immunogenicity studies. European regulators have devoted considerable attention to this issue and generally require both substantial premarket immunogenicity data and a postmarket pharmacovigilance plan that includes systematic attention to possible signals of immunogenicity. Concerns about immunogenicity could affect, among other things, how FDA thinks about both risk management plans and product labeling.

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There are many detailed changes in the Act. We would be pleased to discuss these changes and their potential impact on your industry, company, or customers.

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