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A Brave New World: The U.S. Food and Drug Administration's Newfound Authority for Regulation of Follow-on Biologics

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On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act bringing to conclusion Congress's much-awaited health care reform efforts.[1] While much of the publicity surrounding the approximately 900-page law relates to the sweeping modifications to the health care system as a whole, the law's many provisions also bring important changes to specific aspects of the highly-regulated pharmaceuticals industry.

Of particular interest to companies that develop and market therapeutic products, is the law's creation of a novel pathway for follow-on biologic pharmaceuticals called "biosimilars." Just as the Drug Price Competition and Patent Term Restoration Act of 1984[2] (or "Hatch-Waxman Act") and the Medicare Prescription Drug Improvement and Modernization Act of 2003[3] ("MMA") forever impacted the world of brand and generic drug products, the Biologics Price Competition and Innovation Act of 2009[4] ("BPCIA") within the Patient Protection and Affordable Care Act is sure to rearrange the landscape for biologic product innovators and companies seeking to market follow-on biologic products. Like the Hatch-Waxman Act, the new law attempts to balance the interests of innovators in recouping their huge investment in research, testing, and regulatory approval of innovative biologic products, with the public's interest in faster market entry and reduced prices for competing follow-on biologics.

Not surprisingly, the biosimilars legislation was intensely debated in the months leading up to enactment and a number of different approaches were proposed and considered. Only time will tell if the balance created by the new law is proper, sustainable, and successful at achieving its competing goals. In the meantime, however, the biologics industry must understand and prepare to operate within the framework and mechanics established for this new pathway. Additionally, the industry must keep abreast of the U.S. Food and Drug Administration's ("FDA's" or "Agency's") implementation activities as the Agency takes steps to fill the gaps in the new law. These details are likely to be developed through the issuance of general or product-specific guidance on the biosimilar approval process.[5] The following

review of the key provisions of the law is intended to serve as a guide for sponsors of both innovator products and competing "biosimilars."

What is a Biosimilar?: The Distinction between Biosimilars and Generic Drugs

Title VII of the Patient Protection and Affordable Care Act, the BPCIA, amends the Public Health Service Act[6] ("PHSA") to create a new approval pathway for follow-on biological products. New section 351(k) of the PHSA[7] permits submission of applications for licensure of biological products that are "biosimilar" to, or "interchangeable" with, a reference, branded biological product.[8] Like the Hatch-Waxman Act, which created a pathway for generic drugs to reach the market more quickly and with fewer regulatory hurdles, the BPCIA creates an abbreviated pathway for approval of biologic products that meet the law's approval standards. However, important differences in the source, biochemistry, properties, and approval pathway for biologics and drugs give rise to important distinctions between the pathway to approval of bioequivalent generic drugs and that enacted for biosimilar biologics.

Unlike non-biologic drug products, biologics are large, complex molecules for which demonstrating "sameness" is difficult, if not impossible. Small modifications in the manufacture of a biologic product can produce enormous changes to the product's biochemical identity, therapeutic action, and effect. Consequently, the standard of bioequivalence that the Hatch- Waxman Act applies to follow-on generic drugs is inappropriate for follow-on biologics. Instead, under the new pathway created by the BPCIA, a follow-on biologic product may only be approved if it is demonstrated to be "biosimilar to" *or* "interchangeable with" the reference innovator product, and the applicant consents to the inspection of the facility that is the subject of the application.[9]

Under the new law, a "biosimilar" product is defined as one that is "highly similar to the reference product notwithstanding minor differences in clinically active components" and for which "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[10] A biosimilar product is "interchangeable" when it "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[11] The standard for "interchangeability" is met when a product is biosimilar to *and* expected to produce the same clinical result as the reference product.[12] Where a biologic product is intended to be administered more than once to an individual, a follow-on product is only deemed "interchangeable" where the risk – in terms of safety or diminished efficacy – of

alternating or switching between the reference product and the biosimilar is no greater than the risk of using the reference product alone.[13]

A product that is biosimilar to, but not interchangeable with, the reference product is deemed to have a new active ingredient under section 505B of the Federal Food, Drug, and Cosmetic Act[14] ("FDCA").[15] A biosimilar product that is interchangeable with the reference product, is not considered to have a new active ingredient.[16]

Application for a Biosimilar

An application for a biosimilar product must include: (i) a showing of biosimilarity through data derived from analytical studies, animal studies, and clinical studies; (ii) information demonstrating that the proposed biosimilar and reference products utilize the same mechanism(s) of action, to the extent such mechanisms are known for the reference product; (iii) information confirming that the reference product has been approved for the conditions of use that will be prescribed, recommended, or suggested in the proposed labeling for the biosimilar product; (iv) a showing that the route of administration, dosage form, and strength of the biosimilar are the same as those of the reference product; and (v) support that the manufacturing facility meets standards designed to assure that the product continues to be safe, pure, and potent.[17] Biosimilar applications must also reference publicly-available information regarding the previous determination of safety, purity, and potency of the reference biological product, and may include any additional information in support of the application, including information demonstrating that the product meets the standard of "interchangeability."[18] Importantly, the law permits the Secretary of the Department of Health and Human Services ("HHS") to determine that certain analytical studies, animal studies, or clinical studies are unnecessary.[19] Thus, FDA may approve a biosimilar application even where the sponsor conducts no additional preclinical or clinical studies despite the fact that a biosimilar will not necessarily act in exactly the same way as the reference product.

Importantly, the law authorizes FDA to issue general or product class-specific guidance on the biosimilar approval process, but the issuance or non-issuance of guidance will not preclude FDA's review of or action on a particular biosimilar application.[20] However, if FDA issues product class-specific guidance, it must include the criteria FDA will use to assess whether a product is "highly similar" to the reference product in that class, and what criteria FDA will use to assess whether a product meets the interchangeability standard.[21] Additionally, FDA may issue product class-specific guidance to explain its basis for concluding that "the science and experience, as of the date of such guidance … does not

allow approval" of a biosimilar application for that particular product class.[22] Thus, close attention to, and participation in, the FDA process for development and issuance of biosimilar guidance will be crucial for the biologics industry.

Exclusivity for First Interchangeable Biosimilar

Follow-on biologics may be approved on a showing that they are only biosimilar to the reference product. However, the first follow-on product that also demonstrates interchangeability with the reference product is eligible for market exclusivity with respect to other follow-on products.[23] Thus, FDA is prohibited from approving a second, interchangeable follow-on product for any condition of use for a period of time that runs from the earlier of: one (1) year after first commercial marketing of the first interchangeable product; eighteen (18) months after a final court decision in a patent litigation against the applicant, or dismissal of such litigation; forty-two (42) months after approval of the interchangeable biosimilar if patent litigation is still ongoing; or eighteen (18) months after approval, if there is no patent litigation at all.[24] The resolution of any potential patent litigation determines the effective date of the first interchangeable biosimilar's exclusivity period.

Exclusivity for Reference Product

To encourage biologics innovation, the law also creates a non-patent exclusivity period for sponsors of reference biologic products. Specifically, the law prohibits approval of a biosimilar application until twelve (12) years after the reference product was first licensed.[25] Furthermore, a biosimilar applicant may not even submit its application (i.e., such an application will not be accepted for filing) until four (4) years after the reference product was first licensed (or, approved) by FDA.[26] The new law includes provisions to discourage innovators from evergreening, or stockpiling of exclusivity by making changes to their product in order to trigger successive exclusivity periods. Thus, the law does not permit a new period of exclusivity following approval of a supplement to the application for the reference product. Nor can the reference product sponsor extend its exclusivity by obtaining approval of a new application for a change in the indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, strength, or other change to the structure of the product that does not result in a change to the safety, purity, or potency of the biologic.[27] In order to extend its exclusivity period, the reference product sponsors must obtain approval of a product modification that results in a change in the safety, purity, or potency of its product.

The reference product sponsor's exclusivity period is also extended if it satisfies the requirements for pediatric exclusivity.[28] Thus, when a reference product sponsor conducts pediatric studies in response to an FDA request pursuant to the pediatric exclusivity provisions of the FDCA, it may receive an additional six (6) months of exclusivity. This additional exclusivity period provides reference product sponsor with a total of twelve (12) years and six (6) months of exclusivity and prohibits FDA from accepting a biosimilar application for four (4) years and six (6) months.[29] The pediatric exclusivity period would also extend by six (6) months the seven (7) year period of orphan drug exclusivity for a reference product that is designated under section 526 of the FDCA for a rare disease or condition.[30]

Patent Implications

A reference biologic product's protection from competition derives not only from the twelve (12) years of non-patent exclusivity, but also from the protection of its patents. Just as the Hatch-Waxman Act gave rise to extensive litigation surrounding the innovator drug sponsor's patent rights, so too will the BPCIA alter the landscape of patent litigation for this new class of FDA-regulated products.

The law delineates the steps a biosimilar applicant must take to notify the patent owner of the reference product, and sets forth specific requirements and limitations on the patent owner's ability to sue.[31] First, the biosimilar applicant must, within 20 days of FDA's acceptance of a biosimilar application for review, provide notice of the application to the patent owner(s)' outside and in-house counsel – neither of whom may be engaged in patent prosecution relevant or related to the reference product.[32] The notification must provide the reference product sponsor or patent holder with confidential access to the application, and any other information that describes the process(es) used to manufacture the product[33] for the limited purpose of determining whether a claim of patent infringement can reasonably be asserted.[34]

Within 60 days after receipt of the notification, the reference product sponsor must provide the biosimilar applicant a list of patents believed to be potentially infringed and identify those that the reference product sponsor would consider licensing.[35] Within 60 days of receipt of the abovementioned list, the biosimilar applicant must identify those patents it believes would not be infringed and provide a detailed statement describing, for each claim, its factual and legal bases for asserting that the patent is invalid, unenforceable, or will not be infringed, or a statement that it will not begin to market the product before the patent expires.[36] The reference product sponsor must, again within 60 days, reply with a detailed

statement describing, for each patent and claim, its bases for asserting that the patent will be infringed and responding to claims challenging the validity and enforceability of such patents.[37]

If, following these mandated communications, the biosimilar applicant and reference product sponsor fail to agree on the patent infringement issues, the law mandates negotiations to determine which, if any, of the patents shall be the subject of litigation.[38] If the parties fail to reach agreement within 15 days,[39] the biosimilar applicant must specify the number of patents that it believes to be properly the subject of patent litigation.[40] Within five (5) days thereafter the parties must exchange a list of patents that each believes should be the subject of patent infringement litigation.[41] The number of patents on the reference product sponsor's list must not exceed the number of patents listed by the biosimilar applicant,[42] except that, if the biosimilar applicant lists no patents, the reference product sponsor may identify one patent only.[43]

Where both parties agree on the patents that will be the subject of litigation, the reference product sponsor must bring an action for infringement within 30 days of the agreement.[44] Where the parties cannot reach agreement, the reference product sponsor must bring an infringement action within 30 days against the biosimilar applicant with respect to each patent included on the lists exchanged by both parties.[45] The biosimilar applicant must notify HHS of the lawsuit and HHS will publish a notice of the complaint in the Federal Register.[46]

Where a patent infringement suit is filed, the confidential information disclosed by the biosimilar applicant must remain confidential until the court overseeing the litigation enters a protective order.[47] If the reference product sponsor does not file suit within the specified deadlines, it must return or destroy the confidential information, in accordance with the wishes of the biosimilar applicant.[48] The law presumes that the disclosure of any confidential information in violation of the law subjects the biosimilar applicant to irreparable harm for which immediate injunctive relief is required from the courts.[49]

In addition to the pre-litigation procedure described above, the biosimilar applicant must also provide notice to the reference product sponsor within 180 days of commercial marketing of the biosimilar.[50] The reference product sponsor may then seek a preliminary injunction to prohibit the manufacture or sale of the product until the court decides the issue of validity, enforcement, and infringement of any patent, regardless of whether such patent is included on the lists exchanged by the parties in the pre-litigation procedure.[51] The reference product sponsor may also seek a declaratory judgment on the patent issues

where the biosimilar applicant does not comply with its pre-litigation notification and negotiation mandates.[52]

The patent implications and pre-litigation procedures accompanying the new biosimilars pathway are extensive and complex. Thus, both the reference product sponsor and the biosimilar applicant must pay careful attention to the detailed requirements surrounding the patent litigation process to ensure compliance.

The newly created avenue for approval of biosimilars (including interchangeable biologics) is sure to have a tremendous impact on the biologics industry, and the health care system as a whole. Given that much of the development of this new regulatory scheme has yet to occur, as FDA is expected to issue general and product class-specific guidance, those most affected would be wise to follow the FDA activity in this arena to take advantage of any opportunities to participate in the process and to ensure that they understand, and comply with, this brand new world of regulatory review.

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1 H.R. 3590, 111th Cong. (2010) (enacted).

2 Pub. L. No. 98–417, 98 Stat. 1585 (1984).

3 Pub. L. No. 108–173, 117 Stat. 2006 (2003).

4 H.R. 3590, at Title VII, Subtitle A.

5 H.R. 3590, § 7002(a)(2) (adding 42 U.S.C. § 262(k)(8)) (authorizing FDA to issue guidance with respect to the licensure of a biological product under newly created subsection (k)). However, the non-issuance of guidance will not preclude the review of, or action on, a biosimilar application. *Id.* § 7002(a)(2) (adding 42 U.S.C. § 262(k)(8)(C)).

6 42 U.S.C. §§ 201 et. seq.

7 H.R. 3590, § 7002(a)(2) (adding 42 U.S.C. § 262(k)).

8 A "reference product" is a licensed biological product "against which a [biosimilar applicant's product] is evaluated." *Id.* § 7002(b)(3) (adding 42 U.S.C. § 262(i)(4)).

9 *Id.* § 7002(a)(2) (adding 42 U.S.C. § 262(k)(3)).

10 *Id.* § 7002(b)(3) (adding 42 U.S.C. § 262(i)(2)).

11 *Id.* (adding 42 U.S.C. § 262(i)(3)).

[12] *Id.* § 7002(a)(2) (adding 42 U.S.C. § 262(k)(4)(A)).

[13] *Id.* (adding 42 U.S.C. § 262(k)(4)(B)).

[14] 21 U.S.C. §§ 301 et seq.

[15] H.R. 3590, § 7002(d)(2) (adding 21 U.S.C. § 355c(n)(1)).

[16] *Id.* (adding 21 U.S.C. § 355c(n)(2)).

[17] *Id.* § 7002(a)(2) (adding 42 U.S.C. § 262(k)(2)).

[18] *Id.* (adding 42 U.S.C. § 262(k)(2)(A)(iii)).

[19] *Id.* (adding 42 U.S.C. § 262(k)(2)(A)(ii)).

[20] *Id.* (adding 42 U.S.C. § 262(k)(8)(A)-(C)).

[21] *Id.* (adding 42 U.S.C. § 262(k)(8)(D)).

[22] *Id.* (adding 42 U.S.C. § 262(k)(8)(E)(i)). Subsequent guidance may be issued to modify or reverse a guidance document issued under that section.

[23] *Id.* (adding 42 U.S.C. § 262(k)(6)).

[24] *Id.*

[25] *Id.* (adding 42 U.S.C. § 262(k)(7)(A)).

[26] *Id.* (adding 42 U.S.C. § 262(k)(7)(B)).

[27] *Id.* (adding 42 U.S.C. § 262(k)(7)(C)).

[28] *Id.* § 7002(g)(1) (adding 42 U.S.C. § 262(m)).

[29] *Id.*

[30] *Id.* (adding 42 U.S.C. § 262(m)(4)); *id.* § 7002(h). The extension of exclusivity does not apply if the reference product has fewer than 9 months of biosimilar exclusivity remaining when the pediatric or orphan exclusivity determination is made (i.e., the product has already enjoyed 11 years and 3 months of exclusivity).

[31] *See id.* § 7002(a)(2) (adding 42 U.S.C. § 262(*l*)).

[32] *Id.* (adding 42 U.S.C. § 262(*l*)(1)(B)).

[33] *Id.* (adding 42 U.S.C. § 262(*l*)(2)(A)) The applicant may also provide additional information requested by the reference product sponsor. *Id.* (adding 42 U.S.C. § 262(*l*)(2)(B))

[34] *Id.* (adding 42 U.S.C. § 262(*l*)(1)(D)). This express limitation on the use of the confidential information provided by the biosimilar applicant appears to prohibit access to the information by those engaged in patent prosecution relevant or related to the reference product – thus making it difficult for those with the information to efficiently determine whether such a patent infringement claim is, in fact, "reasonable." Moreover, such inside and outside counsel are prohibited from further disclosing the confidential information to anyone else, including the reference product sponsor employees or consultants, without prior written consent of the biosimilar applicant. *Id.* (adding 42 U.S.C. § 262(*l*)(1)(B)(iii)).

[35] *Id.* (adding 42 U.S.C. § 262(*l*)(3)(A)). For later-issued or licensed patents for which the reference product sponsor believes a claim of patent infringement could reasonably be asserted, the reference product sponsor must notify the biosimilar applicant within 30 days of such issuance of licensure or the sponsor's intention to supplement this list. *Id.* (adding 42 U.S.C. § 262(*l*)(7)(A)-(B)).

[36] *Id.* (adding 42 U.S.C. § 262(*l*)(3)(B)).
[37] *Id.* (adding 42 U.S.C. § 262(*l*)(3)(C)).
[38] *Id.* (adding 42 U.S.C. § 262(*l*)(4)(A)).
[39] *Id.* (adding 42 U.S.C. § 262(*l*)(4)(B)).
[40] *Id.* (adding 42 U.S.C. § 262(*l*)(5)(A)).
[41] *Id.* (adding 42 U.S.C. § 262(*l*)(5)(B)).
[42] *Id.* (adding 42 U.S.C. § 262(*l*)(5)(B)(ii)).
[43] *Id.*.
[44] *Id.* (adding 42 U.S.C. § 262(*l*)(6)(A)).
[45] *Id.* (adding 42 U.S.C. § 262(*l*)(6)(B)).
[46] *Id.* (adding 42 U.S.C. § 262(*l*)(6)(C)).
[47] *Id.* (adding 42 U.S.C. § 262(*l*)(1)(F)).
[48] *Id.*.
[49] *Id.* (adding 42 U.S.C. § 262(*l*)(1)(H)).
[50] *Id.* (adding 42 U.S.C. § 262(*l*)(8)).
[51] *Id.* (adding 42 U.S.C. § 262(*l*)(8)(B)).
[52] *Id.* (adding 42 U.S.C. § 262(*l*)(9)).