FOLEY HOAG LLP

Patient Protection and Affordable Care Act (H.R. 3590)—Approval Pathway for Biosimilar Biological Products

On December 24, 2009, the U.S. Senate passed the Patient Protection and Affordable Care Act (H.R. 3590), its version of comprehensive healthcare reform legislation. On March 21, 2010, the U.S. House of Representatives also passed this legislation; and it was signed into law by the President on March 23, 2010. Included therein is a provision (Section 7002) amending the Public Health Service Act to permit approval of biosimilar biological products through an abbreviated biological license application (ABLA) submitted to the Food and Drug Administration (FDA).

	Patient Protection and Affordable Care Act (H.R. 3590)
Approval Pathway	Amends section 351 of the Public Health Service Act (PHSA) to create an abbreviated biological product application (aBPA) for **"highly similar"** biological products. Permits an FOB to be evaluated against only **one reference listed product.** ▪ Note: this allows only a single biological product to serve as a reference biological product. A "biosimilar" product is a product that is "**highly similar"** to the reference product **"notwithstanding minor differences in clinically inactive components,"** and for which there are **"no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product."**
Clinical Standards	Permits the Secretary, at his **discretion,** to issue **guidance documents,** with opportunity for public comment, on the process for submission of an aBPA. Guidance documents may be general or product specific. The Secretary must provide a process through which the public can provide input on priorities for issuing guidance. Issuance of guidance is not a prerequisite for approval of an FOB, and the Secretary may determine that the science does not allow for safe approval of an FOB for a certain product or product class in a guidance document. The Secretary must license an aBPA if the Secretary determines the information submitted is sufficient to show the FOB is **"biosimilar"** to the innovator product or **"interchangeable"** with the innovator product and if the applicant consents to inspection of the manufacturing facility. To support approval of the aBPA, the FOB must show that the biological product: ▪ **is "biosimilar to the reference product,"** based upon data from: (1) analytical studies to show the FOB is **"highly similar"** to the reference product, "notwithstanding minor differences in clinically inactive components"; (2) animal studies; and (3) a **clinical study** or studies (including assessment of immunogenicity) to demonstrate "safety, purity, and potency" for one or more appropriate conditions of use for which the innovator product is licensed. ▪ utilizes the **same mechanism(s) of action** for the condition(s) of use listed in the labeling, to the extent the mechanism of action is known for the innovator product; ▪ has **the same condition(s) of use** listed in the labeling as have been previously approved for the innovator product; ▪ has the **same route of administration, dosage form and strength** as the innovator product; ▪ the FOB **manufacturing facility meets appropriate standards** to ensure the product is safe, pure and potent; and

	Patient Protection and Affordable Care Act (H.R. 3590)
	▪ **additional information at the option of the FOB** applicant, including information demonstrating that the FOB is interchangeable with the innovator product. The Secretary, at his discretion, may waive any of these requirements on a case-by-case basis. The FOB may only be reviewed and approved for indications for which the reference product is already approved. Requires the Secretary to approve all biological products under section 351 of the PHS, unless: (1) the biological product is in a product class for which a biological product in such product class is the subject of an application approved under section 505 of the FFDCA not later than the date of enactment of this Act; and (2) the FOB application has been submitted to the FDA before the date of enactment of this Act or not later than 10 years after the date of enactment of this Act; and (3) there is no section 351 licensed biological product which could serve as a reference product. Requires FDA review of the FOB application by the division that reviewed the reference product.
Safety and Immunogenicity	**Requires clinical studies** to assess immunogenicity, pharmacokinetics and pharmacodynamics, but such studies **may be waived** by the Secretary at his discretion. Applies the **REMS requirement** to FOBs in the same manner it is applied to innovator biologics licensed under the PHS.
Interchangeability and Substitution	If the conditions for interchangeability are met, requires the Secretary to determine the FOB to be interchangeable with the reference product at the time of approval. Defines an **interchangeable** FOB as a product that is: ▪ **"biosimilar**" to the reference product; ▪ can be **"expected to produce the same clinical result"** as the reference product in **"any given patient"**; and ▪ the **risk of safety or diminished efficacy** of alternating or switching between the FOB and innovator product is **not greater than the risk of using the innovator product with no switch**, if the biologic is intended for use by more than one patient. No guidance provision specific to interchangeability, but see above guidance requirements. If a product is "interchangeable" it may be substituted for the reference product "without the intervention of the health care provider who prescribed the reference product."
Naming	No naming provisions.
Postmarket Requirements	Applies the **REMS requirement** to FOBs in the same manner it is applied to innovator biologics licensed under the PHS.
Other	Provides for a **public process** with all stakeholders, including industry, scientific and academic

	Patient Protection and Affordable Care Act (H.R. 3590)
	experts, Congress, patient representatives and healthcare professionals, **to develop appropriate user fee**s and FDA performance and safety goals for FOBs, to be implemented October 1, 2012. The public process must be started no later than October 1, 2010. Provides for data collection on the cost of reviewing aBPA applications from the date of enactment of this Act through October 1, 2010. Requires a biennial audit, beginning two years after the first aBPA user fees is collected and ending October 1, 2013, comparing user fees collected with actual cost of reviewing the aBPA. Directs aBPA user fees to be adjusted accordingly after review of the audit. Deems a biological product with an approved section 505 application to be a license for the biological product under section 351 of the PHS 10 years after enactment of this Act Establishes within the Treasury the "Biologic Product Savings Fund" to be used for "activities authorized under the Public Health Service Act." The BPSF is funded by annual appropriations in the amount equal to the amount that is saved by the Federal government as a result of this Act. Funds are available without fiscal year limitation. Requires a GAO study and report to Congress not later than 3 years after enactment of BPCIA regarding the extent to which pediatric studies for biological products are being required under the FFDCA and any pediatric needs that are unmet under existing authority. Clarifies that if a reference product has orphan drug status, an FOB application for a biosimilar product for the same indication may not be approved for the later of 12 years exclusivity period under BPCIA or the 7 year exclusivity period granted for orphan drugs.

Exclusivity Provisions

	Patient Protection and Affordable Care Act (H.R. 3590)
Innovator Market and Data Exclusivity	**42 U.S.C. § 262(l) (Public Health Service Act § 351(l))** Includes provisions for innovator product data and market exclusivity. ▪ The FOB applicant may not submit an application for approval for **4 years** after the reference product was first approved. ▪ FDA may not approve an FOB application until **12 years** after the reference product is first licensed. No new exclusivity is granted for BLA supplements or subsequent applications for a new indication, route of administration, dosage form, or strength of a previously licensed biologic.
FOB Market Exclusivity	Provides **one year** of exclusivity for the first approved interchangeable FOB for a reference product. If an FOB is approved as interchangeable, the Secretary may approve other FOBs relying on the same reference product, but may not determine that such an FOB is interchangeable with the reference product until the earlier of one year after the first commercial marketing of the first interchangeable FOB or 18 or 42 two months depending on patent certification and litigation.

Intellectual Property Provisions

	Patient Protection and Affordable Care Act (H.R. 3590)
Notification & Actions for Infringement	***Confidential Access to aBPA for Patent Identification and Litigation Purposes.*** **PHS § 351 (l)(1), (2).** Requires the FOB applicant to within 20 days of FDA notice that the aBPA was accepted for filing, to provide the reference product sponsor "confidential access" to a copy of the aBPA and other information that describes the manufacturing process. The FOB applicant may provide other information requested by the reference product sponsor. Such "confidential information" must be supplied to: ▪ Outside counsel, defined as attorneys designated by the reference product sponsor, but not employed by the reference product sponsor and who do not engage in patent prosecution for the reference product. ▪ In-house counsel, defined as one attorney employed by the reference product sponsor who does not engage in patent prosecution for the reference product. ▪ A representative of a third party owner of a patent exclusively licensed to a reference product sponsor, provided: 1) that the third party patent owner has retained a right to assert the patent or participate in litigation concerning the patent; and 2) that the representative informs the product sponsor and the FOB applicant of his/her agreement to be subject to confidentiality provisions. Those privy to confidential information may not disclose the information to anyone without prior written consent of the FOB applicant, which may not be "unreasonably withheld." Confidential information may be used for the "sole and exclusive purpose" of determining whether a claim of patent infringement could be "reasonably asserted" with respect to each patent assigned to or exclusively licensed to the reference product sponsor. Ownership of the confidential information remains with the FOB applicant. If the reference product sponsor files a patent infringement suit, the use of confidential information is governed by this section (i.e., the information may not be shared or publicly revealed without prior written consent) until the court enters a protective order. ***Rule of construction:*** Nothing in this subsection shall be construed "as an admission by the [FOB applicant] regarding the validity, enforceability, or infringement of any patent; or an agreement or admission by the [FOB applicant] with respect to the competency, relevance, or materiality of any confidential information." Disclosure of any confidential information in violation of this section is considered to cause irreparable harm for which no legal remedy is sufficient (i.e, no monetary damages will adequately compensate the FOB applicant). Immediate injunctive relief is the appropriate remedy. ***Procedure for Patent Identification*** **351(l)(3).** Within 60 days of receiving the confidential information, the reference product sponsor must provide to the FOB applicant: ▪ a list of patents for which the reference product sponsor believes a claim of patent infringement could "reasonably be asserted" (by the sponsor or patent owner); and ▪ an identification of the patents on the list the reference product sponsor would be willing to license to the FOB applicant.

	Patient Protection and Affordable Care Act (H.R. 3590)
	Within 60 days of receipt of the reference product sponsors list, the FOB applicant may provide to the reference product sponsor a list of patents to which the FOB applicant believes a patent infringement claim could be "reasonably asserted." The FOB applicant must provide to reference product sponsor: ▪ A detailed "factual and legal" statement on a "claim by claim basis" as to why the patents listed by the reference product sponsor and the patents listed in turn by the FOB applicant are invalid, unenforceable or will not be infringed by the FOB product; ▪ A statement that the FOB applicant will not begin commercial marketing of the FOB before the patent expires; and ▪ A response to the reference product sponsor's offer to license specific patents. Within 60 days after receipt of the FOB applicant's response, the reference product sponsor must provide the FOB applicant a detailed "factual and legal" statement on a "claim by claim basis" for why the listed patents are infringed, and a response to the validity and enforceability statements provided by the FOB applicant. ***Good Faith Negotiations.*** **351(l)(4).** Requires the FOB applicant and reference product sponsor to engage in good faith negotiations to determine which (if any) listed patents will be the subject of infringement actions. If, within 15 days of the start of negotiations, no agreement is reached, the procedure for patent resolution (see below) must be followed. ***Patent Resolutions if No Agreement Reached During Negotiations.*** **351(l)(5).** If no agreement as to which patents will be litigated is reached, the FOB applicant and reference product sponsor must exchange a list of patents they believe should be the subject on an infringement suit. The reference product sponsor may not list more than the FOB applicant, unless the FOB applicant lists no patents (in which case the reference product sponsor may list 1 patent). **351(l)(7).** If the reference product sponsor is licensed a patent after the date that lists are exchanged, the reference product sponsor has 30 days to provide a supplemental list that include that patent, and the FOB applicant then has 30 days to respond with a statement as to why that patents is invalid, unenforceable or not infringed.
Suits for Infringement	**PHS § 351(l)(6).** Within 30 days after a negotiated list is agreed to, or after the exchange of lists occurs if negotiations fail, the reference product sponsor must bring an action for infringement for all patents in the lists. The FOB applicant is required to provide HHS with notice and a copy of the complaint. HHS must publish notice of the complaint in the Federal Register.
Preliminary Injunctions	**PHS § 351(l)(8).** The FOB applicant is required to notify the reference product sponsor no later than 180 days before the first commercial marketing of the FOB. After receiving such notice and before the first commercial marketing, the reference product sponsor may petition for a preliminary injunction prohibiting the FOB applicant from marketing the FOB for any patent that is identified in the list provided by the FOB applicant or reference product sponsor under 351(l)(3) ("listed patents") and which is not included (as applicable) in the lists relating to patent litigation (whether negotiated under 351(l)(4) or exchanged under 351(l)(5)).

	Patient Protection and Affordable Care Act (H.R. 3590)
	Requires "reasonable cooperation" between the reference product sponsor and the FOB applicant to "expedite such further discovery" as is needed to resolve the motion for a preliminary injunction.
Declaratory Judgment Actions	**PHS § 351(l)(9).** If the FOB applicant provides appropriate access to confidential information, the reference product sponsor and FOB applicant are prohibited from bringing action for a declaratory judgment of infringement, validity or enforceability of any patent listed by the FOB applicant or reference product sponsor. If the FOB applicant fails to: ▪ provide a detailed statement regarding invalidity, non-infringement or unenforceability regarding a listed patent; ▪ exchange a list of patents for litigation purposes under 351(l)(5) if discussions to negotiate a list break down, ▪ notify HHS after a complaint for patent infringement is served; or ▪ provide notice within 180 days of the first commercial marketing of the FOB, The reference product sponsor may bring an action for declaratory judgment for any listed patent If the FOB applicant fails to provide confidential access to the required information, the reference product sponsor may bring a declaratory judgment action for any patent that covers the biological product.
Transition Period	No transitional exclusivity.
Other	Amends **35 U.S.C. 271(e**): ▪ To deem an FOB application seeking approval of a product claimed in a patent or the use of which is claimed in a patent an act of infringement. ▪ To limit the remedies available in any litigation brought after the 30 day window to reasonable royalties. This provision has the effect of providing for compulsory licensing if an infringement suit is not brought within 30 days. ▪ To prohibit the owner of a patent that should have been identified in the patent lists from bringing an action for infringement; and ▪ To require the court to issue a permanent injunction prohibiting the FOB applicant from infringing a patent that is found to be infringed by a final court decision until the patent expires.

Payment

	Patient Protection and Affordable Care Act (H.R. 3590)
Payment	Provides for separate billing codes for Part B biosimilar products; statutorily mandates that reimbursement equal the ASP of the biosimilar plus six percent of the ASP of the reference product. (Sec. 3139)