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Update — United States Enacts Approval Pathway for Biosimilars

This is the first installment of a series of client alerts by Foley's Life Sciences Industry Team highlighting the provisions of the Patient Protection and Affordable Care Act that will likely have significant implications for life sciences companies.

On March 23, 2010, President Obama signed the Patient Protection and Affordable Care Act (The Act). The health reform bill included the Biologics Price Competition and Innovation Act of 2009. The Act amended the Public Health Service Act (PHS Act) to create a new pathway for the approval of applications for biological products shown to be biosimilar to a licensed reference product.

Biosimilar Products. The Act defines a biosimilar product to mean a biological product that is both "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 the safety, purity, and potency of the product." Companies have the option to demonstrate the interchangeability of the biosimilar product to a licensed reference product. An interchangeable biosimilar product is defined to mean a biological product that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."

Exclusivity Provisions. The Act also establishes a 12-year period of market exclusivity from the date of licensure for the licensed reference product, which may be extended by six months of pediatric exclusivity. The first four years (or 4.5 years with pediatric exclusivity) is a period of data exclusivity during which time an application for a biosimilar or interchangeable version of the reference licensed product may not be accepted by the FDA. The 12-year exclusivity period is not available for the approval of a supplement or subsequent application filed by the sponsor of the reference biological product for certain changes or modifications. The licensure of a biosimilar or interchangeable version of a reference product that was designated and approved as an orphan drug may only occur after the later of the expiration of any applicable seven-year orphan drug exclusivity or the 12-year market exclusivity period (or 7.5 years and 12.5 years with pediatric exclusivity).

The first interchangeable biosimilar product also is afforded a period of market exclusivity that expires on the earlier of: (1) one year after first commercial marketing of the interchangeable product; (2) 18 months after the resolution of patent litigation; (3) 42 months after initial approval of the interchangeable product if patent infringement litigation is ongoing; or (4) 18 months after approval of the first interchangeable biosimilar if that applicant has not been sued.

Patent Dispute Procedures. The legislation also establishes a new, complex procedure for resolving patent disputes based on a biosimilar application, and defines an applicant's challenge to patents as an act of infringement. These procedures are discussed in more detail below.

Other Provisions. The legislation amends the FDC Act to make user fees under the Prescription Drug User provisions applicable to biosimilar and interchangeable biological products, but does not do so until 2012. The legislation also includes a placeholder in the Medicare reimbursement provisions to provide for payment for biosimilar products, once approved by the FDA.

What the Future Holds. With the enactment of this legislation, the FDA now has the authority to accept, review, and ultimately approve license applications for biosimilar products. The FDA will have to establish procedures and create an organization to review the applications, and user fees for biosimilar products will eventually serve as a source of funding these efforts.

Many issues will need to be addressed for biosimilar products. Will the FDA begin accepting applications immediately? Can the applications be submitted before user fees are established for these types of products? What will be the data requirements to establish that a product is highly similar to the reference product? How will applicants demonstrate that 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?

The complex procedure for resolving patent disputes after a biosimilar applicant files a licensure application also will give rise to many issues. Like its earlier counterpart, the Drug Price Competition and Patent Term Restoration Act of 1984, when the FDA starts to implement the Biologics Price Competition and Innovation Act of 2009, many issues will surface that will need to be addressed during the execution and operation of The Act. While these issues will likely prove to be challenging and complex, the pathway for biosimilars has

finally been created and companies can soon seek approval for biosimilar products.

We will keep you appraised of continuing developments in this area.

Details of the Patent Dispute Procedures.

The new legislation establishes a complicated procedure for resolving patent disputes after a biosimilar applicant files an abbreviated application for FDA approval. This process involves several exchanges between the BLA holder and the biosimilar applicant, including: (i) the biosimilar applicant's manufacturing process, (ii) lists (from both parties) of the BLA holder's patents alleged or likely to be infringed, and (iii) factual and legal basis (from both parties) for non-infringement/invalidity or infringement/validity of the patents. The legislation provides that the parties will negotiate which patents will be litigated, with the biosimilar applicant having some control over the number of patents included in this litigation. The legislation also requires, however, that the biosimilar applicant provide notice to the BLA holder 180 days before market entry, at which time the BLA holder may seek a preliminary injunction pending the outcome of a second litigation of any patents that are not included in the first litigation.

Exchange of Biosimilar Manufacturing Process and First Patent Lists. Within 20 days after the FDA has accepted its abbreviated application, a biosimilar applicant must provide the reference product sponsor (BLA holder): (i) a copy of the application and (ii) other information describing the process(es) for manufacturing the biosimilar product. The BLA holder must keep the application and information confidential, and may only used such material to evaluate infringement.

Within 60 days of receiving the above information, the BLA holder must provide the biosimilar applicant with a list (first BLA list) of all patents that the BLA holder reasonably believes are infringed, as could be asserted by either the BLA holder or by a patent owner that has granted exclusive rights to the BLA holder regarding the product. The BLA holder also must identify any patents on the list that it would be willing to license to the biosimilar applicant.

Within 60 days of receiving the first BLA list, the biosimilar applicant may provide to the BLA holder a list (first biosimilar list) of patents that the biosimilar applicant believes could be subject to a claim of patent infringement. As such, the biosimilar applicant may choose to list no patents, a subset of patents listed in the first BLA list, or additional other patents that it hopes to litigate.

Both Parties Provide Factual and Legal Basis. Within the same 60 days of receiving the first BLA list, regarding any patents listed in the first BLA list or the first biosimilar list, the biosimilar applicant must also provide: (I) a statement describing, on a claim by claim basis, a factual and legal basis for an opinion that a patent is invalid, unenforceable, or not infringed; or (II) a statement that the biosimilar applicant does not intend to market until the patent expires. The biosimilar applicant must also provide a response to the BLA holder's offer to license patents.

Within 60 days of receiving that material, the BLA holder must provide, regarding each patent described in (I) above, a reciprocal statement describing, on a claim by claim basis, a factual and legal basis for an opinion that a patent will be infringed as well as a response to the (I) statement regarding validity and enforceability.

Negotiations, Exchange of Second Patent Lists, and Patent Litigation. After the biosimilar applicant receives this material from the BLA holder, both parties must engage in good faith negotiations to identify which patents (if any) should be subject to a patent infringement lawsuit. Notably, the legislation does not set out a deadline for when the parties must begin these negotiations. Presumably, one expects it to happen quickly, but the current legislation does not expressly require it.

In any event, if both parties agree during these negotiations, the BLA holder may sue the biosimilar applicant within 30 days of such an agreement.

If both parties do not agree within 15 days of starting negotiations, the biosimilar applicant must notify the BLA holder the number of patents it will provide in a second list of patents, as discussed below. Within five days of this notice, the parties must simultaneously exchange: (1) a list of patents that the biosimilar applicant believes should be subject to a patent infringement suit (second biosimilar list); and (2) a list of patents that the BLA holder believes should be subject to a patent infringement suit (second BLA list). Notably, the number of patents in the second BLA list cannot exceed the number of patents in the second biosimilar list. If the second biosimilar list includes no patents, however, the second BLA list may list one patent. At this point, the BLA holder may sue the biosimilar applicant within 30 days of exchanging the two second lists.

Thus, it appears that the biosimilar applicant determines the number of patents that may be litigated, but the BLA holder always has discretion to sue regarding at least one patent.

Within 30 days after a complaint is served, the biosimilar applicant must provide the FDA notice and a copy of the complaint. The FDA will publish a notice of that complaint in the Federal Register.

If a new patent issues or is exclusively licensed to the BLA holder after it has provided its first BLA list, the BLA holder has 30 days to provide a supplemental first list to the biosimilar applicant. After receiving this supplemental first BLA list, the biosimilar applicant has 30 days to provide a statement (I) (factual and legal basis) or (II) (that it will not market until the patent expires). It is not clear if such patents are then subject to the rest of the process described above, but the legislation does state that these new patents will be subject to the notice provisions described below.

180 Days Notice Before Biosimilar Marketing. No later than 180 days before going to market with a biosimilar product, the biosimilar applicant must provide notice to the BLA holder. After receiving such notice, the BLA holder may seek a preliminary injunction prohibiting market entry until a court decides patent validity, enforcement, and infringement with regard to those patents listed in the first BLA or first biosimilar list, but not including those agreed upon by both parties to be subject to a patent infringement suit, or presented in second BLA and biosimilar lists.

In other words, the BLA holder may only seek a preliminary injunction regarding patents that are not subject to a patent litigation via the process described above. Consequently, the preliminary injunction provision may affect biosimilar applicants when determining whether to list certain patents (or not) in its second biosimilar list, or otherwise agree to litigation regarding certain patents. If a biosimilar applicant lists no patents in its second list, for example, it runs the risk of being subject to a preliminary junction regarding unlisted patents until patent cases are litigated and decided at a later date, or being unable to market until those patents expire.

Comparing ANDA to Biosimilar System. The following chart compares certain patent law implications relating to the filing an abbreviated new drug application (ANDA) under the Hatch Waxman Act, and the filing of an abbreviated new biologic application under the current legislation. The chart highlights certain differences and similarities between the two schemes.

ANDA — Hatch-Waxman Act (1984)	**Biosimilar Application — New Legislation**
Orange Book listing by NDA holder	**No Orange Book equivalent**
§271(e)(2)(A), (B) Submitting ANDA = infringement ▪ With respect to patents listed in Orange Book	§271(e)(2)(C) Submitting biosimilar application = infringement ▪ With respect to patents identified on provided lists, or ▪ If biosimilar applicant fails to provide application and manufacturing info, with respect to patents that could have been listed in BLA first list
In Orange Book, the NDA holder may only list patents relating to the chemical entity, formulation or methods of use, not methods of making. Patents having only “methods of making” claims may not be subject to ANDA litigation.	The BLA holder assesses patent infringement and sues based on biosimilar application and information about methods of making. Patents having “methods of making” claims may be subject to biosimilar litigation.
In ANDA, the filer must certify regarding all patents listed in Orange Book for product: (I): patent not listed in Orange Book (II): patent has expired (III): date patent will expire (and generic will not market until this date) (IV): patent is invalid, unenforceable or not infringed	**No certification required in biosimilar application.**
Within 20 days after ANDA with P(IV) is accepted for filing, the generic must provide to the NDA holder: ▪ Notice that ANDA has been accepted for filing ▪ Statement of factual and legal basis of opinion that patent(s) is/are invalid, unenforceable, or not infringed	Within 20 days after biosimilar application is accepted for filing, the generic must provide to the BLA holder: ▪ Copy of biosimilar application ▪ Other information describing process(es) used to manufacture product

	Within 120 days later, regarding patents in first BLA list, the biosimilar applicant must provide to the BLA holder a statement of: ▪ (I): factual and legal basis for opinion that patent is invalid, unenforceable or not infringed; or ▪ (II): it will not market before patent expires
The NDA holder not required to provide factual and legal basis regarding infringement, nor response concerning validity and enforceability.	In response to (I) above, the BLA holder must provide factual and legal basis for opinion that patent is infringed, and response concerning validity and enforceability.
Within 45 of receiving notice, the NDA holder may bring suit regarding P(IV) patents.	Within 30 days of party agreement on patent lists, or within 30 days after exchange of second lists, the BLA holder can sue regarding patents agreed upon, or on second lists If the BLA holder does not bring suit within 30 days, exclusive remedy is reasonable royalties regarding those patents
If the NDA holder sues within 45 days, the FDA will approve ANDA: ▪ After **30 month stay** ▪ When district court or appeals court decides patent is invalid or not infringed (or date of settlement stating similar)	**No 30-month stay** ▪ After receiving 180-day notice, possible preliminary injunction until court decision regarding patents asserted by the BLA holder, but not agreed upon by the biosimilar applicant to be subject to patent litigation ▪ Permanent injunction until patent expiration if final court decision decides patent is infringed and the biosimilar product has not yet been approved because of §351(k)(7) of the PHS Act, 35 USC §271(e)(2)(D) ▪ The FDA is not required to stay approval based on pending litigation — applicants could market "at risk"
The generic may file declaratory judgment (DJ) action if ANDA has P(IV) certification and NDA holder has not sued within 45 days. The NDA holder cannot file a DJ action, except as normally available after generic commercially markets.	If the biosimilar applicant provides application and manufacturing information to the BLA holder, neither party may sue for DJ before the biosimilar applicant provides 180-day notice of marketing. If the biosimilar applicant fails to do any required actions, the BLA holder may bring DJ action for any patent listed in first BLA list (or supplemental first BLA list).

This article is an update to our "Biosimilars Provision Included in House Health Care Reform Bill – The Time Has Finally Come" Legal News Alert from November 2, 2009.

Legal News Alert is part of our ongoing commitment to providing up-to-the-minute information about pressing concerns or industry issues affecting our clients and colleagues. If you have any questions about this alert or would like to discuss the topic further, please contact your Foley attorney or the following:

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