BIOSIMILARS LEGISLATION UPDATE (Spring 2010)

On March 30, 2010, President Obama signed into law a reconciliation bill that finalizes Congress’s health care reform legislation, the Patient Protection and Affordable Care Act. In addition to the much-discussed provisions regarding health insurance, the Act creates a regulatory pathway for the approval of follow-on biologics (FOBs). The relevant statutory text is subtitled “Biologics Price Competition and Innovation Act” and is available here.

Key features of the Biologics Price Competition and Innovation Act include:

- Twelve years of market exclusivity (with a possible further six months of pediatric exclusivity) for pioneer products during which time FOB applications cannot be approved
- Two standards of FOB approval – biosimilarity and interchangeability – to be implemented by the Secretary of Health and Human Services
- Exclusivity for the first FOB product found to be interchangeable with the pioneer product
- Confidential, choreographed exchanges of highly detailed, substantive disclosures between the FOB applicant and the pioneer regarding the FOB product, pioneer patents and the parties’ respective contentions relating to the product and the patents
- Absence of a statutory stay of generic approval during the pendency of patent litigation

Impact on Patent Prosecution, the FDA and Litigation Practices

The new Act differs from the Hatch-Waxman Act in several significant procedural and substantive regards. Although some of the Act’s impact will not be clear until the FDA sets specific guidelines and requirements, several provisions of the Act will impact patent prosecution and litigation, as well as FDA practice. While presenting several challenges to those companies whose business relates to biologics, the Act presents an opportunity for the prepared to take steps now to potentially improve their future position. Areas of particular interest and opportunity are listed below.

Pioneer Exclusivity

The Act grants pioneers 12 years of marketing exclusivity from application approval (with a potential further six months for pediatric studies). In addition, during the first four years of such
exclusivity (or four years plus six months for pediatric studies), the FOB applicant cannot submit an FOB application. The Act does not include any additional exclusivity for pioneer products currently on the market, so a product approved four years ago has eight years of exclusivity remaining, but an FOB application against that product can be now be accepted. Pioneers who change the “biological structure” of their products are eligible for 12 years of marketing exclusivity for the new structure provided it also results in a change in indication(s), route of administration, dosing, delivery or strength, or a change in safety, potency or purity. Patent term extension would also appear to be available for approval of such new structures.

Actions to Consider: Pioneers should continue to maximize patent term extension and adjustment and to actively pursue secondary inventions that can be filed later during drug development. In addition to countries and regions like the United States and Europe, patent protection will be especially important in regions of the world that are active in biotech research and manufacturing, such as China, India, Israel, Russia and Brazil, among others.

Also, keep an eye on patent reform legislative developments, which may offer a “supplemental examination” proceeding in which patentees may disclose additional prior art to the Patent and Trademark Office. If enacted, pioneers may want to take advantage of such supplemental examination during the exclusivity period (particularly during the first four-year period before any FOB application could be accepted) to remove any potential invalidity or inequitable conduct challenges.

Biosimilarity and Interchangeability

The Act defines a “biosimilar” product as one that is “highly similar to the [pioneer] product notwithstanding minor differences in clinically inactive components” and one in which “there are no clinically meaningful differences . . . in terms of safety, purity, and potency of the product.” It also defines an “interchangeable” product as one that is both “biosimilar” and may be substituted for the pioneer product, without the intervention of a health care provider. These standards potentially permit some minor structural variation from the reference product, leaving opportunities for design-around by FOB applicants.

Actions to Consider: Patent prosecution strategies should focus on claims that are broad enough to limit design-around and protect production and manufacturing techniques. Since pioneers should anticipate being limited to litigating one patent against the FOB applicant under the new law (discussed infra), such strategies should be evaluated for all relevant patents.

Include claims directed to properties or structures of the biologic that an FOB applicant will have to prove to establish biosimilarity or interchangeability.
Also useful to include claims to methods that would be induced by instructions and statements that would need to appear on any FOB product’s drug label. See article on such patent strategies here.

**FOB Review Process**

The Act includes a mandate to the Secretary of Health and Human Services to implement a process of review of biosimilar biologic product applications, including setting an October 1, 2010, deadline for the Secretary to present to Congress a five-year plan for its proposed review process. The Act also provides that the Secretary may issue guidance documents for the review of a particular biologic product or class of products that may include the appropriate tests or criteria that would need to be met by FOB applicants to show biosimilarity or interchangeability. Further commentary regarding the issues facing the FDA in establishing a testing regime for FOB products can be accessed here.

**Actions to Consider Pre-Marketing:** Having passed the FDA review process for their own biologic products, pioneers are ideally suited to actively participate in shaping the FOB approval process. They are also capable of playing a key role in establishing FDA criteria for determining what it means to be “highly similar” and standards for interchangeability, both for specific products and classes of products. Such participation by pioneers begins during their own review process when they take positions as to which tests/trials are (or are not) necessary to show safety and efficacy. Extra care should be taken by pioneers in staking those positions now since they may be used against them during the FOB approval process.

**Actions to Consider Post-Marketing:** The post-marketing monitoring of safety and efficacy of pioneer biological products will be essential to any FOB product review process. Having faced these issues, pioneers will be uniquely positioned to advocate for any further testing that should be undertaken by FOB applicants during the FDA approval process.

**FOB Applicant Exclusivity**

FOB applicants are awarded exclusivity for being the first product determined to be “interchangeable” with the pioneer biologic. This contrasts with the Hatch-Waxman exclusivity

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1 The Act provides several scenarios pursuant to which exclusivity would be calculated, prohibiting a second or subsequent FOB product from being approved until the earlier of:
- One year after first commercial marketing of the first interchangeable FOB product;
- [Additional exceptions provided]
for the first generic to file a paragraph IV statement certifying to non-infringement, invalidity or unenforceability of an Orange Book-listed patent.

Actions to Consider: By keeping certain manufacturing and processing details as trade secrets, the pioneer may make it more difficult for the FOB applicant to replicate a product such that it could be deemed "interchangeable" or even "biosimilar."

Patent Notices and Pre-Litigation Disclosures

Unlike in the Hatch-Waxman context, in which pioneers provide notice of the patents that protect their product in a public forum – the Orange Book – the Act provides for private notices of such patents. The Act also provides for very detailed, confidential disclosures between the pioneer and the FOB applicant over an approximate 180-day period following the acceptance of the FOB application.

The level of analysis demanded in the FOB framework exceeds what companies may be accustomed to in the Hatch-Waxman context. Because the statute sets a fast pace for these exchanges (60 days between each exchange), inter-party negotiations (15 days) and subsequent filing of law suits (30 days), pioneers would benefit from substantial advance diligence so that they can identify and advance highly defensible positions from the outset.

Below are some of the key disclosures that must take place and some tips on complying with them.

- **Notice to Pioneer of Product/Process:** The FOB applicant must provide a copy of its application and a description of its manufacturing process to the pioneer within 20 days of acceptance of the application for review. Access to this confidential material will be provided to outside and in-house counsel for the pioneer and, if the product sponsor exclusively licenses a patent for the reference product, to a patent owner representative. Those granted access cannot engage, formally or informally, in patent prosecution relevant or related to the pioneer product. Such persons are also prohibited from disclosing the information they receive with any other person without prior written consent from the FOB applicant. If the FOB applicant fails to provide the application and

- Eighteen months after: (i) a final court decision, including appeal, against first approved interchangeable FOB; or (ii) dismissal with or without prejudice of the first approved interchangeable FOB; or
- Forty-two months after approval of the first approved interchangeable FOB if applicant sued and litigation still ongoing; or,
- Eighteen months after approval of the first approved interchangeable FOB if FOB not sued.
required information to the pioneer, the pioneer can bring an action against it for a declaration of infringement, validity or enforceability of any patent that claims the product or its use.

**Actions to Consider:** To minimize delay in getting a copy of the application from the FOB applicant, pioneers should identify outside counsel, in-house counsel, and, if applicable, a patent owner representative to receive such confidential material.

It is also important to note that the Act does not provide for any notice of third party patents other than those to which the pioneer has a license. This may result in having to negotiate separately for licenses to foundational patents owned by third parties.

- **Pioneers’ List of Relevant Patents:** Within 60 days of the production of the application and manufacturing process, the pioneer must identify the relevant patents it could assert, the patents to which it has an exclusive license, as well as the patents it is willing to license. If the pioneer fails to timely identify a patent it may be foreclosed from bringing an action for infringement of that patent. The Act allows the pioneer to amend its list to identify newly-issued or licensed patents within 30 days after such issuance or licensing.

  **Actions to Consider:** Pioneers should regularly audit their patent estate to ensure that they would be in a position to provide an FOB applicant with the required patent list within that time frame.

- **FOB Applicant’s Contentions:** Within 60 days of the production of the list of patents by the pioneer, the FOB applicant shall provide a detailed (i.e., claim by claim) statement that describes the factual and legal basis for why each patent listed by the pioneer is not valid and enforceable or would not be infringed by commercial manufacture of the FOB product, or, in the alternative, state that the FOB applicant does not intend to commercially market any FOB product until the date one or more patents expire. The FOB applicant must also provide a “response” to each patent the pioneer has indicated is available for licensing. It may also provide the pioneer with a list of patents which it believes a claim of patent infringement could be asserted. Failure by the FOB applicant to make any of these disclosures may subject it to suit by the pioneer of any patent originally listed by the pioneer.

  **Actions to Consider:** Pioneers should continue to track the status of relevant patent applications and notify the FOB applicant should such patent applications issue.
• **Pioneer’s Contentions:** Within 60 days of receiving the FOB applicant’s contentions on infringement, validity and enforceability, the pioneer shall provide a detailed (i.e., claim by claim) response to such contentions.

*Actions to Consider:* Because the Act sets a fast pace for this exchange, pioneers would benefit from substantial advance diligence so that they can allege highly defensible positions from the outset. The Act provides no guidance as to how one goes about responding to such defenses and will likely be the subject of debate in ensuing litigation. For example, does a pioneer facing a charge of invalidity based on obviousness have to respond with evidence of commercial success?

Supplemental examination proceedings contained in the proposed patent reform legislation (discussed above), if enacted, may also prove to be advantageous to pioneers during the advanced diligence process.

**Determining Which Patents Will Be Litigated**

The Act also provides that the parties shall engage in good faith negotiations with a goal of agreeing on which, if any, patents should be litigated. The parties are given 15 days to resolve any differences. If they reach an agreement, the pioneer must file suit within 30 days for each patent in the agreement. If the parties cannot reach agreement, the Act requires further disclosures. The FOB applicant goes first by notifying the pioneer of the number of patents it believes should be litigated. Within five days of such notification, the parties simultaneously exchange their list of patents that each believes should be the subject(s) of an infringement action. Notably, the number of patents listed by the pioneer cannot exceed the number identified by the FOB applicant. If, however, the FOB identifies no patents, the pioneer can only list one patent to be litigated. The Act requires the pioneer to bring an action for infringement within 30 days after the exchange of lists.

*Actions to Consider:* Pioneers should anticipate being limited to litigating one patent against the FOB applicant and stress test their portfolio of relevant patents. Each and every patent should be crafted and prosecuted with the goal of having some latitude to prevent design-around.

**Limits on Staying FOB Approval**

The Act does not grant pioneers an automatic stay to prevent generic approval during the pendency of patent litigation. Rather, the Act requires that the FOB applicant provide the pioneer with 180 days’ notice of first commercial marketing so that the pioneer can seek a preliminary injunction from the Court where such litigation was instituted. It is important to note, however, that the Act precludes pioneers from obtaining injunctive relief for any patent that
the parties agreed should be litigated or, if the parties could not agree, any patent on either list of patents identified by the parties during the simultaneous exchange. It also precludes injunctive relief for untimely patent suits or timely filed suits dismissed without prejudice or prosecuted in bad faith – in which case the remedy for infringement is limited to a reasonable royalty. This reinforces the desirability of having multiple patents that can potentially be asserted against any FOB applicant.

**Actions to Consider:** Without an automatic stay on FOB approval, there is a potential that FOB applicants may commercially market their products before any resolution of the litigation (or “launch at risk”). Recognizing this risk, pioneers should prepare by gathering evidence they would need to support a motion for a preliminary injunction such as factors supporting irreparable harm.

**So...What Do We Do Today?**

Because the disclosure periods in the Act are very short, and far more analysis is demanded upfront than in the Hatch-Waxman setting, now is the time for pioneers to audit their portfolios of patents relating to biologic patents to identify and fix any potential issues. Stress test the patents for the validity and non-infringement positions FOB applicants are likely to take, and plan and refine your portfolios accordingly.

Consider the relevant people in your company (and on your outside counsel roster) who will be the recipient of confidential material from FOB applicants.

Identify potential design-arounds and continue to patent the additional aspects of your inventions.

Stay abreast of (or get involved in) the FDA guideline-setting process, especially those related to interchangeability.

If possible, acquire rights to platform patents along with the right to enforce same in litigation.

These are just a few of the new issues and challenges for pioneers manufacturing and developing biologics. For more information, please visit us at www.fr.com/biologics.