Guardians at the gate
Biosimilar and patent reform legislation could fundamentally change the guards for therapeutic monoclonal antibodies—Part 2

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Patent protection and FDA exclusivity are the two principal forms of protection available to companies that develop therapeutic monoclonal antibodies. Proposed changes to both forms of protection are currently being debated in the United States Congress. Specifically, Congress is presently debating both biosimilar and patent reform legislation. Although no bill has yet passed, it is expected that patent reform legislation should pass this year. It is less likely that a biosimilar bill will pass this year. However, when legislations are enacted, the changes will significantly impact the business of therapeutic monoclonal antibodies.

Introduction
Part one of this series explored the basic principals for patenting of monoclonal antibodies. Part two explains how the proposed patent reform and biogenerics/biosimilars legislation will affect the business of therapeutic monoclonal antibodies. The forthcoming third part will explore how patent strategies should evolve to keep current with the new and up-coming legal framework for protecting these products.

As is true for any therapeutic, monoclonal antibodies are regulated products. Before these products can be sold in the United States, the Food and Drug Administration (FDA) must review the product to ensure that it is safe, efficacious, and of appropriate quality. The clinical trials required to demonstrate that a product is both safe and efficacious are extremely time consuming and expensive. Current estimates are that it can cost well over a billion dollars to evaluate a product using the current clinical trial process involving Phase 1, 2 and 3 studies. At present, there is no process by which a biological product intended for use by the general public can be approved other than to proceed with costly clinical trials.

Biosimilar legislation that was introduced at the beginning of 2009 would provide an expedited procedure wherein a biosimilar, which is defined as “a biological product [that has] no clinically meaningful differences between the biological product and the reference product… in terms of the safety, purity and potency if treatment were to be initiated with the biological product instead of the reference product,” could be approved with less regulatory review. The proposed bills provide different provisions for expediting approval. The debate over the biosimilar legislation is largely focused on the exclusivity provisions. Passage of the biosimilar legislation would obviously change the market dynamic for those approved therapeutic antibodies.

Multiple proposed patent reforms are also presently pending before the U.S. Congress. Although some of these reforms are generally favored by the biotechnology industry, e.g., the move to the first-to-file system, other reforms, most notably the changes to the damages provisions, greatly concern the biotechnology industry. As patent protection provides the second form of protection for therapeutic monoclonal antibody products, changes to the patent system could also change the market dynamic for those approved products.
### Biosimilar Legislation

On March 11, 2009, Rep. Henry Waxman (D-CA) introduced H.R. 1427 into the US House of Representatives. This bill, entitled the “Promoting Innovation and Access to Life-Saving Medicine Act”, is intended “to provide for the licensing of biosimilar and biogeneric biological products...” On March 26, 2009, Sen. Charles E. Schumer (D-NY) introduced the companion Senate bill, S. 726. The Senate bill contains the same title and text as H.R. 1427. Therefore, these bills will be referred to herein as “the Waxman bill” (H.R. 1427).

Rep. Anna G. Eshoo (D-CA) introduced, on March 17, 2009, another biosimilar bill: “to establish a pathway for the licensure of biosimilar biological products.” This bill, H.R. 1548, is entitled the “Pathway for Biosimilars Act” and will be referred to in this article as “the Eshoo bill” (H.R. 1548).

The Waxman bill and the Eshoo bill represent the beginning of the legislative process to provide a mechanism for the review and licensing by the FDA of biosimilar biotherapeutic products (also sometimes referred to in the biopharmaceutical industry and by the interest groups following that industry as “biogenerics” or “follow-on biologics,” but referred to herein as “biosimilars”). However, these two competing House bills set out to achieve this common goal in very different ways, setting up drastically different regulatory schemes for the approval of biosimilars. The debate over these rival bills promises to intensify the concerns various groups have regarding the issue of biosimilars regulation.

### The Key Provisions: A Comparison

The Waxman and Eshoo bills differ in many key provisions. Table 1 highlights several of these differences, and compares these provisions to those in the Hatch-Waxman Act, i.e., the generic small molecule therapeutics act, which enabled approval of generic versions of drugs approved under the Food, Drug and Cosmetic Act. The FDA refers to these drugs as new chemical entities (NCEs). Typically, but not always, these products are small molecule drugs.

The exclusivity period provided by each bill defines the key difference in the bills. This provision provides for the length of time after initial introduction of a new biologic product, a new formulation containing the biologic product, or a new indication (i.e., use) of the biologic product, during which the FDA could not approve a biosimilar drug for marketing in the U.S. if it contained the same biologic, was contained in the same or a similar formulation, or was indicated for the same medical or therapeutic use.

As noted in Table 1, the Hatch-Waxman Act prohibits approval of generic pharmaceuticals by the FDA during the first five years after approval of an NCE, and during the first three years after approval of either a new formulation containing a previously approved and marketed NCE, or a new medical/therapeutic use for a previously approved and marketed NCE; the Act also provides for a six-month additional period of market exclusivity if the approval-holder undertakes pediatric studies to determine the safety and efficacy of the approved drug in pediatric populations. In enacting Hatch-Waxman, Congress balanced these periods of market exclusivity to provide the brand name pharmaceutical companies with incentives to research and develop new pharmaceutical products, and yet provide an expedited process for the approval of generic versions of approved drugs at the expiration of those periods of exclusivity.

The Waxman biosimilars bill largely tracks with the exclusivity periods in the Hatch-Waxman Act: exclusivity periods of five years for NCEs, three years for new indications, and the same six-month pediatric extension. The Eshoo bill provides 12 years of market exclusivity for a new biologic product and up to 14 years

### Table 1. A comparison of some key provisions of biosimilars bills and the hatch-waxman act

| Provision | Waxman bill (HR 1427) | Eshoo bill (HR 1548) | Hatch-Waxman act |
|-----------|-----------------------|----------------------|------------------|
| **Exclusivity** | New Product: 5 yrs. | New Product: 12 yrs. | New Product: 5 yrs. |
|            | New Indication: 3 yrs. | New Indication: 14 yrs. | New Indication: 3 yrs. |
|            | Pediatric Applications: additional 6 months | Pediatric Applications: additional 6 months | Pediatric Applications: additional 6 months |
| **New Clinical Trials Required?** | No | Yes | No |
| **Interchangeability with branded drug?** | Yes | No, except in limited circumstances | Yes |
| **Patent Notification** | No listing requirement by approval holder. Rather approval holder is to provide a schedule of patents that are relevant to the approved product within 60 days of a written request by the Biosimilar applicant or prospective applicant | Patents covering product or use must be listed by approval holder in “Orange Book” |

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1 Measured from date of first approval of new product using a given biologic. 2 Measured from date of first approval of new indication. 3 Added to the end of exclusivity period provided for new product or indication.
for a previously approved biologic product if, during the first eight years after its approval, the biologic is approved for a new indication. Thus, under the Waxman bill, a new biologic product could receive a maximum of 5½ years of market exclusivity before a biosimilar could be approved, while the Eshoo bill would provide for up to 14½ years of market exclusivity for a new biologic product.

Another key difference between the bills is the requirement for new clinical trials on the part of the biosimilar applicant. The Eshoo bill requires biosimilar applicants to conduct clinical trials comparing the immunogenicity of the biosimilar product to that of the previously approved biologic product. The FDA could waive the requirement for such trials, but only after it had published regulatory guidance on this issue. In contrast, the Waxman bill does not require new clinical trials. Rather, the biosimilar applicant could rely upon the safety and efficacy data of the previously approved drug, provided that the biosimilar application contains information demonstrating that: (1) the biosimilar product and the reference biologic product have highly similar molecular structural features; (2) no clinically meaningful differences would be expected between the biosimilar and the reference product in terms of safety, purity and potency; (3) the biosimilar and the reference biologic product have the same mechanism or mechanisms of action; and (4) the biosimilar and the reference biologic product are used and administered in the same way, and that the dosage form and strength of the biosimilar are the same as those of the reference product.

Other differences between the Waxman and Eshoo bills exist. For example, the Waxman bill would permit complete interchangeability of an approved biosimilar drug for the reference drug. In contrast, the Eshoo bill only permits such substitution in a certain limited set of situations and only after the FDA has issued guidelines explaining when interchangeability would be permitted.

Finally, the two bills significantly differ in the mechanism for permitting challenges to patents that may protect biologics or their methods of use or manufacture. Neither of the biosimilar bills uses the “Orange Book” system set forth in the small molecule generic pharmaceuticals Hatch-Waxman Act.

The Waxman bill permits a biosimilar applicant (or someone even just contemplating filing a biosimilar application) to request information from the approval holder on the reference biologic drug regarding any patents that the approval holder believes will cover the approved biologic, its use, or its manufacture. Upon receipt of such a request, the approval holder has 60 days to provide the requestor the patent information.

Under the Eshoo bill, the FDA would provide a copy of a biosimilar application to the reference product approval holder, who would then be required to (1) provide the biosimilar applicant with a list of patents that purport to cover the product or its use, and (2) explain in writing to the biosimilar applicant why the reference product approval holder believes the biosimilar product would infringe one or more patents on that list. Thus, the Eshoo bill shifts the burden of patent certification from the biosimilar applicant to the reference product approval holder.

As one might expect, the biotechnology and pharmaceutical industries generally favor the Eshoo bill, particularly because of its provision of longer exclusivity periods for newly approved biologics. In contrast (as would be expected), the generic pharmaceutical industry views the Eshoo bill as “the wrong road for patients looking for safe and affordable biogeneric medicines, particularly during these difficult economic times.” The generics industry favors the Waxman bill, arguing that it would “achieve the much-needed balance between pharmaceutical competition and innovation for the benefit of consumers, payers and state and federal governments.”

Thus, a vigorous debate on the biosimilars legislation has begun between the biotechnology industry and its advocates on one side, and the generic pharmaceuticals industry and its advocates on the other. Because this debate is still in its early stages, and because there is at yet a wide gulf in their respective positions, it is not expected that the biosimilars legislation will pass this year. However, the outcome of this debate will shape future proposed legislation, and even the present legislation if a compromise is reached to permit its passage.

**Patent Reform Legislation**

Currently pending before Congress are a series of bills for reforming the patent system. H.R. 1260 was introduced by Rep. John Conyers (D-MI) into the US House of Representatives on March 3, 2009. This bill, entitled the “Patent Reform Act of 2009,” is intended “to amend title 35, United States Code, to provide for patent reform.” On April 2, 2009, Sen. Patrick Leahy (D-NY) introduced the companion Senate bill, S. 515. The Senate bill, which contains the same title, and, until recently, the same text as H.R. 1260, recently passed out of the committee with a marked-up bill. These bills are intended to fundamentally overhaul the patent system and introduce several sweeping changes. Some of these changes are less controversial, but one is highly controversial. Table 2 provides the key differences between the two bills.

Generally, the first-to-file system of both bills is favorably viewed by the biopharmaceutical industry. This would harmonize the United States patent laws with much of the rest of the world, which follows a first-to-file system. In giving up the current system, which awards the patent right to the first-to-invent, the biopharmaceutical industry would gain greater certainty over their rights to their respective inventions. Indeed, under the proposed system, once a company’s own patent application had published that company should know with far greater certainty what other people are working in the field and what its relative patent rights are with regards to those competitors. This is because the company would know whether it was the first-to-file, and thus in the dominant position, for that technology. In disposing of the first-to-invent system, the bills dispose of patent interferences, which are costly and complicated proceedings and replace them with two types of challenges: post-grant oppositions and derivation proceedings.

The post-grant opposition provision establishes an “all-issues” post-grant review proceeding in which parties may seek cancellation of patents. A petition
Table 2. A comparison of some key provisions of the patent reform bills

| Provision                        | H.R. 1260                                                                 | S. 515 (as amended April 2, 2009)                                                                 |
|----------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| First-Inventor-to-File           | The provision moves the U.S. to a first-inventor-to-file system.          | Language substantially the same as House bill                                                  |
| Derivation proceedings           | Provision establishes derivation proceedings before the Patent Trial and Appeal Board to determine the right of the applicant to a patent, replacing interference proceedings. | Includes provision similar to House text                                                       |
| Damages                          | Court determines the method for determining reasonable royalty based on the facts of the case and identifies the relevant factors. Only those factors may be considered. Paragraph (A) provides that the court may employ the entire market value rule when the court determines that the “claimed invention’s specific contribution over the prior art is the predominant basis for the market demand” for the product. Paragraph (B) provides that a royalty may be based on the terms of an existing license when the patent has been the subject of a nonexclusive license secured before suit and sufficient enough to “indicate a general marketplace recognition of the reasonableness of the licensing terms” and when the infringer’s use is substantially similar to that of the licensees. Additionally, the invention must be shown to have “sufficiently similar noninfringing substitutes in the relevant market” which have also been subject to such nonexclusive licenses. Alternatively, paragraph (C) provides that the court may base a reasonable royalty by applying the “portion of economic value of the infringing product or process properly attributable to the claimed invention’s specific contribution over the prior art.” For “combination inventions,” this may include the “value of the additional function resulting from the combination, as well as the enhanced value” of the prior art elements to the combination. | Court shall identify the methodologies and factors that are relevant to the determination of damages, and the court or jury, shall consider only those methodologies and factors relevant to making such determination. |
| Post Grant Opposition            | Establishes an “all-issues” post-grant review proceeding in which parties may seek cancellation of patents. A petition must be filed within 12 months after the patent is issued unless the patent owner consents. | Language substantially similar to House language.                                              |
| Patent Trial and Appeal Board    | Establishes a Patent Trial and Appeals Board to consist of administrative patent judges to hear appeals of examiners’ decisions, to hear appeals from reexaminations proceedings, to conduct derivation proceedings and to conduct postgrant opposition proceedings. | Includes provision substantially similar to House text.                                       |

must be filed within 12 months after the patent is issued. It is an “all issues” review because, unlike reexaminations that limit the review to solely prior art, a postgrant opposition can challenge a patent for written description and enablement issues. The patents would be reviewed by the Patent Trial and Appeals Board, which would largely be composed of former Administrative Law Judges from the Board of Appeals and Interferences.

The most controversial provisions of either bill are the amendments to the damages provisions. At the heart of that debate is the fundamentally different business model between the electronics companies on the one hand and biotechnology companies on the other hand. These businesses view patents very differently.

On the one hand, the electronics industry is a constantly evolving, capital intensive market, where each product is covered by 100s to 1,000s of patents, and so the value of individual patents is hard to quantify. In contrast, the therapeutic antibody industry, which is also a capital intensive market, generally have only a few patents that cover products, and the products are generally sold for the full term of the patent and beyond. For that industry, each patent is tremendously valuable to protecting the product.

The main proponent of the patent reform legislation has been the “Coalition for Patent Fairness,” which is a coalition of major electronics companies. It has been determined that the members of the Coalition have paid about two billion dollars in patent infringement damages over the past ten years, which is an obvious motivator to have the damages provisions changed. One reason why the electronics
industry paid such damages is the prevalence of lawsuits by non-practicing entities, i.e., patent trolls, that largely do not exist in the biopharmaceutical industry.

Thus, the proponents for damages reform, which includes the Coalition for Patent Fairness, seek to fundamentally change the way damages are determined. Under current law, an infringer of a patent has to pay the patentee damages adequate to compensate for the infringement, which is generally no less than a “reasonable royalty” but could be the patentee’s “lost profits.” Currently, courts follow a flexible set of factors in assessing the “reasonable royalty,” including the 15 factors outlined in the seminal Georgia Pacific case. The reasonable royalty is that amount a willing licensor would have agreed to pay, and a willing licensor would have agreed to accept, for a patent that both parties agreed was valid, enforceable, and, absent a license, infringed.

H.R. 1260 would introduce a process for determining and applying reasonable royalty damages, wherein courts would “ensure that a reasonable royalty is applied only to that economic value properly attributable to the patent’s specific contribution over the prior art.” In other words, the court would be required to subtract from the infringed patent claim all elements that existed previously in the prior art. However, most inventions are, to some degree, built on the prior art, and many patented components are essential to the intended functionality of the overall infringing product—two facts that are particularly applicable to biotechnology patents.

Under this bill, the resulting royalties would likely be lower than the reasonable royalties calculated under current law. This could make infringement cheaper and thus discourage investment in technology. In an industry such as biotechnology, which as previously explained is a capital-intensive, long term industry, such devaluation of intellectual property rights could be especially damaging.

The Senate proposal is more palatable in that the judge operates as a “gatekeeper.” In that function, the court would assess what methodologies and factors are based on legally sufficient evidentiary basis. Therefore, unlike the House proposal, which pushes the damages calculation towards apportionment, the court under the Senate proposal would not apply apportionment until after a full evidentiary hearing on the merits. As the courts already presently do as much as in a proper Georgia Pacific analysis, the Senate bill may not represent much of a change in damages law. To the extent that the Senate bill gains traction and moves forward towards passage, the biopharmaceutical industry should remain vigilant as to what the legislative history says about the bill. As the major push by the Coalition for Patent Fairness for patent reform was damages reform, the biopharmaceutical industry should ensure that the legislative history remains properly balanced between the different concerns of the respective industries.

Conclusion

Given that therapeutic monoclonal antibody products have only two principal forms of protection, either the biosimilar legislation or the patent reform legislation could fundamentally affect the business model for this industry. The biosimilar legislation is not expected to pass this year. There is simply no consensus between the generics industry and the biopharmaceutical industry on the length of the exclusivity period. Until the two sides have had further opportunity to debate their respective positions, it is unlikely that a consensus will be found.

However, on the patent reform front, it is highly likely that the Senate proposal could pass this year. It is always extremely difficult to predict when legislation will pass; there are simply too many competing interests to reasonably predict when a bill will be given the floor time for a full vote. However, this bill reaches a reasonable compromise position over the most difficult of issues, the damages reforms, and thus should not have major opposition that would prevent it from reaching the floor. Therefore, this author predicts passage of this bill this year.

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