

# Follow-on Biologics and Patent Reform:

## Will They Discourage Venture Capital Investment in the Biotechnology Industry?

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According to a study by PricewaterhouseCoopers and the National Venture Capital Association, venture capital (VC) investing hit a five-year high in 2006, with \$25.5 billion invested. Notably, the Life Sciences sector, which includes biotechnology and medical devices, accounted for 28% of VC money invested, the largest investment sector in 2006.

As Life Sciences venture capital investing has risen, the biotechnology industry has become increasingly dependent on such funding. This is particularly true for start-up companies that cannot rely on revenue from marketed biologics to fund their research and development pipeline. To cover the nearly \$1 billion capital investment required to bring a biologic drug to market (from discovery through clinical trials and FDA approval), early-stage companies rely on VC investing. Investing in emerging companies, however, is risky for a venture capitalist: only 1 in 10 drugs discovered actually makes it to market, and despite the more than \$50 billion spent on biotech drugs in 2006, the great majority of early-stage companies never reach the point of net profitability.

Given the high failure rates and enormous costs of bringing a biologic to market, companies (and their investors) look to successful drugs to reap sufficient revenue to compensate for both the research and development costs of the successful drug and

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the expense of failed biologics. In this landscape, intellectual property protection is critical to the start-up biotech company and to its VC investors — without assurance that there exists adequate market exclusivity to allow a successful biologic product to earn adequate profits, VC investors have no guarantee of a return on investment, and will be hesitant to direct their funds to the Life Sciences sector.

Unfortunately, recent proposals in Congress to create an abbreviated pathway for approval of “biosimilar drugs,” in tandem with attempts to reform the patent system, may weaken intellectual property protection for emerging biologics companies to the extent that venture capitalists may be less willing to risk capital investment in the industry. For many early-stage companies, intellectual property is the only asset of value. Weakened intellectual property protection may stifle innovation and ultimately hinder patient access to life-saving new biological medicines.

## **Follow-on Biologics: Market Exclusivity Is Essential to Protecting VC Investment**

Under current law, most biologics are licensed for marketing by the Food and Drug Administration (FDA) under the Public Health Service Act. By contrast, small-molecule drugs are approved for marketing under the Federal Food and Cosmetic Act. The 1984 landmark Hatch-Waxman Act created an abbreviated pathway for approval,

which allowed generic versions of brand drugs to be approved without clinical studies. If the generic company could show its product was bioequivalent to the brand compound, it could rely on approval of the brand drug as evidence that the generic drug was safe and effective and therefore could also be FDA approved.

There is no such pathway available under the Public Health Service Act for biosimilar products, but several pending proposals in Congress would create such an abbreviated pathway for biosimilars, also known as Follow-on Biologics (FOBs). In the Senate, bipartisan legislation introduced by Senators Clinton, Enzi, Hatch, and Kennedy (S. 1695) appears to be the most viable, although it may change considerably before passage. In its current form, the Biologics Price Competition and Innovation Act (BPCIA) is a compromise worked out painstakingly in the Senate HELP Committee. The bill represents a considerable improvement over the original legislation introduced in the House by Congressman Waxman in February 2007, the Access to Life-Saving Medicine Act, H.R. 1038. The BPCIA was marked up in committee in June 2007, but has not been voted on by the full Senate. In the House, Representatives Eshoo and Barton recently introduced the Pathway

for Biosimilars Act, H.R. 5629, which is also an improvement over the Access to Life-Saving Medicine Act.

One of the issues of greatest importance involves the number of years of data exclusivity provided for a licensed biological product. “Data exclusivity” refers to a period of time during which an FOB applicant is precluded from relying on clinical data from the innovator product as evidence of safety and effectiveness. Too short an exclusivity period could serve as a serious deterrent for VC investors if they believe the risk of early market entry of a biosimilar product will reduce the profitability of the branded compound. The loss of VC funding would seriously hinder, if not destroy, biotechnology innovation. On the other hand, too generous an exclusivity period may inappropriately stifle competition.

The appropriate length of this exclusivity period has been the subject of much debate in Congress and among stakeholders. The original Waxman bill provided innovators with no period of data exclusivity. BPCIA and the Pathway for Biosimilars Act both provide 12 years. The Pathway for Biosimilars Act goes further by affording an additional two years of exclusivity for approval of a supplemental application for a “medically significant” indication. A third bill, the Patent Protection and Innovative Biologics Medicine Act (H.R. 1956) introduced in the House, provides 14 years of exclusivity, a period designed to match protection provided for small molecules through the patent term extension provisions under Hatch-Waxman. Data exclusivity is necessary to ensure an adequate, risk-adjusted return on investment for the branded compound and to provide security for VC investors in the emerging biotech company.

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Adequate exclusivity periods are particularly important for the biotech industry. Under Hatch-Waxman, a small-molecule generic drug must be the same as the brand innovator drug to obtain approval. Because the active ingredient of the generic and brand compound is identical, innovator patents generally protect the brand drug from generic infringers until expiration of the patent. By contrast, due to the complexity of large protein molecules and the manufacturing process for biologics, the standard for approval of FOBs under all pending legislative proposals, including the BPCIA and the Pathway for Biosimilars Act, is “similar,” not identical. A biosimilar product that is “similar” to the innovator reference product might be similar enough under regulatory standards to obtain approval as an FOB, but different enough under intellectual property law to avoid infringing issued patents on the innovator product. Because of this, the 14 years of protection provided to small-molecule drugs under Hatch-Waxman through the patent system could be eliminated entirely in the case of FOBs.

In the absence of assured market exclusivity for the innovative biologic, FOB manufacturers will be encouraged to design around innovator patents, while still maintaining sufficient similarity to obtain FDA approval. This would be particularly worrisome for VC investors if “similar” FOBs could be substituted for the innovator biologic, yet, due to clever patent design, did not infringe the innovator’s patents. In this scenario, the FOB applicant achieves maximum market penetration with minimum cost, to the disadvantage of the emerging biotech company and its VC investors. The message here is that for VC investors, a sufficient period of data exclusivity is critical to support the capital invested in emerging biotechnology companies. VC investors should pay

careful attention to Congress as Members struggle to achieve the optimal exclusivity period.

## Follow-on Biologics: Potential Weakening of Patent Protection and Discouragement of VC Investment

The nexus between market exclusivity and patent protection is clear: if exclusivity periods are inadequate for innovator biologics, this puts pressure on the patent system to protect capital investment in biotechnology. There are, however, several provisions in the BPCIA which should be modified, lest they weaken, or even eliminate, intellectual property protection for biologic patent holders. The Pathway for Biosimilars Act includes improved intellectual property provisions, but even that legislation is not perfect. If not corrected, these provisions could reduce VC investment in start-up companies and stifle innovation.

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### Limited Pre-Market Litigation of Patents

The BPCIA confers an advantage on FOB applicants by permitting them to dictate which of the innovator's patents will be litigated before the FOB is commercially marketed. If the FOB applicant and the innovator company do not agree on which patents will be litigated in advance of market launch, each party is given authority under the BPCIA to list the patents it wishes to litigate. The FOB applicant is given a distinct advantage because the innovator may not list for early judicial resolution more patents than the FOB applicant lists (unless the FOB applicant lists no patents, in which case the innovator may choose to litigate just one patent). From the innovator's viewpoint, this gives the FOB applicant the ability to limit litigation to what it regards as the weakest patents, in hope of achieving early judicial success. It also permits the FOB applicant to force an innovator company to bring suit on patents it does not wish to defend and to defer suit on patents it wishes to enforce. These provisions weaken the value of the intellectual property portfolio of innovator biotechs and could deter VC investment in early-stage companies.

The Pathway for Biosimilars Act, in contrast, attempts to level the playing field for innovators and FOB applicants. After the innovator is notified of an FOB application and receives a confidential copy of the application, the innovator has 60 days to identify relevant patents, with no limitation on the number of patents that can be listed. The FOB applicant then has a 45-day window within which to provide a statement asserting that listed patents are invalid or will not be infringed. The innovator then has 60 days to bring suit on any of the listed patents. The Pathway for Biosimilars Act thus allows timely identification of potentially infringed patents through

confidential access to the FOB application, and does not provide the FOB applicant an undue advantage in litigating contested patents.

### Potential for At-Risk Launch of Infringing FOB

If the patent provisions in the BPCIA are enacted, rather than those of the Pathway for Biosimilars Act, only a subset of relevant patents will be litigated in advance of the FOB applicant's market launch of the potentially infringing product. Furthermore, under the BPCIA, the FOB applicant can provide as little as 180 days' notice to the innovator company before commercially marketing the FOB. Only then can the innovator sue on patents that were not listed for pre-market litigation. Six months is insufficient time to permit final resolution of all relevant patents or to obtain a preliminary injunction against marketing the FOB pending such resolution. This could allow the FOB applicant to launch its potentially infringing product at risk, before patent conflicts are resolved, possibly flooding the market with lower-priced competing products and adversely impacting the market before the innovator's patents can be enforced. The Pathway for Biosimilars Act attempts to minimize this risk by providing means to resolve all patent challenges prior to FOB market launch.

### Truncated Period within Which to Bring Suit

A third problem under the BPCIA is the limited time frame afforded to innovator companies to bring suit. After lists are exchanged, identifying relevant patents on the innovator product, and some form of agreement is reached regarding which patents will be litigated in advance of market entry, innovator biotech companies are given a mere 30 days to bring a patent infringement suit. Thirty days is an unreasonably short time frame within which to expect

the company to file a complaint (contrast the 45-day period under Hatch-Waxman and the 60-day window under the Pathway for Biosimilars Act). This is especially true because innovator companies face a unique problem that rarely arises during litigation involving small molecule drugs. In the biotech world, due in part to the opportunities provided under the Bayh-Dole Act, many universities and other research institutions hold the underlying patents for the innovator biologic drug and must participate in litigation involving the patents, due to jurisdictional standing requirements. Typically, these institutions license the patents to emerging biotech companies that fund the clinical stages of research and development and eventually launch the product. An emerging biotech company simply cannot communicate with universities and other third-party patent holders to coordinate litigation on all relevant patents in 30 days. The process involves too many actors to move that quickly, particularly if more than one patent is designated for litigation. Yet, if the innovator does not bring suit within the designated 30 days, its damages are limited to a reasonable royalty — recovery of lost profits resulting from sales of the FOB is foreclosed. For VCs, this represents a decrease in the value of the emerging company’s patent and therefore lost return on investment. If not corrected, this weakens economic incentives to invest in emerging biotech companies.

*“[180 days’ notice] could allow the FOB applicant to launch its potentially infringing product at risk, before patent conflicts are resolved, possibly flooding the market with lower-priced competing products.”*

In contrast to the BPCIA, the Pathway for Biosimilars Act explicitly recognizes the interests of third-party patent owners such as universities. It provides that interested third parties themselves may notify the FOB applicant of their rights in one or more relevant patents. The FOB applicant must then provide the third party with a copy of the FOB application and other relevant information about the composition and method of manufacturing the FOB. The third party then has 90 days to identify the relevant patents in which it has an interest. If the FOB applicant issues a patent challenge, the third party has 60 days to bring an infringement action that, if successful, will postpone approval of the FOB application until after expiration of all of the third party’s patents found to have been infringed.

### **Limitations on Patent Enforcement**

Finally, under the BPCIA, innovator companies are prohibited from enforcing any patents that are not identified in the original exchange of lists between the innovator company and FOB applicant. Although the same holds true under Hatch-Waxman, given the prevalence of third-party patent holders in the biotech industry, it is critical that legislative proposals provide an effective mechanism for the FOB applicant to notify these third-party patent holders in order to identify potentially infringed patents. Unfortunately, several of the current legislative proposals do not adequately address notification of third-party patent holders.

Although the BPCIA and the newly introduced Pathway for Biosimilars Act do provide for third-party access to the FOB application for patent identification purposes, the notification provisions are inadequate. For example, none of the current

proposals requires that the FOB applicant provide a sample of its product to the patent holder, which likely will be needed in order to evaluate the question of infringement.

Although the patent provisions of the BPCIA have improved over prior draft versions of the bill, and the Pathway for Biosimilars Act signifies even more progress, problems still exist that must be addressed, particularly with respect to third-party notification. Strong patent protection is essential to incentivizing VC funding of emerging biotech companies, the foundation of innovative biologic product research and development. The Hatch-Waxman Act has succeeded because it effectively balances patient access to affordable generic drugs with incentives for innovator companies to continue to invest in research and development of new drugs. To be equally beneficial, follow-on-biologics legislation must effectively protect the intellectual property and market exclusivity of emerging

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companies to foster continued VC investment in the biotech industry.

To put this in context, according to a recent Health Affairs article, of the 8,259 generic applications filed between 1984 and 2000, only 6 percent (478) raised patent challenges. The absence of intellectual property conflicts between brand and generic drug companies signals that the Hatch-Waxman regime efficiently balances price competition with stimulation of innovation. There is no data to predict the number of patent conflicts that will arise between branded biologics and biosimilar products. However, we can surmise that if Congress does not achieve the optimal balance between competition and innovation through appropriate market exclusivity and intellectual property protection, VC investment in emerging biotech companies will become higher risk.

## Patent Reform: Potential Weakening of IP Protection and Discouragement of VC Investment

Intellectual property protection for the biotech industry may be further weakened by pending patent reform legislation, creating additional disincentives for VC investment in the life sciences sector.

The House and Senate are both considering legislation — the Patent Reform Act of 2007 — that would significantly alter the current patent system. The House passed its measure in early



September and is waiting for the Senate to vote on the companion bill. VC investors should keep a close eye on the progress of these bills, as passage of the legislation would have important implications for VC investment in all sectors. Patent reform is of particular importance to the biotech industry because the industry relies heavily on intellectual property to support returns on investment. In particular, currently proposed provisions governing the reasonable royalty measure of damages, post-grant review, and inequitable conduct could seriously weaken intellectual property protection for emerging biotechnology companies and discourage VC investment in the industry.

### **Reasonable Royalty**

The award of damages for patent infringement is critical to patent enforcement. The threat of significant monetary liability is often a deterrent to keep a potential infringer from engaging in infringing behavior. If the patent is infringed, damages should adequately compensate the patent holder for the infringer's unlawful use of the invention. In the context of biotechnology, damages protect the patent holder as well as the VC investor who has funded the emerging biotech company. Under current patent law, damages are awarded to a successful patent owner in an infringement suit either based on the patent owner's lost profits or, more frequently, in the amount of a "reasonable royalty." A landmark case directs courts to consider a multitude of factors when calculating "reasonable royalty," to ensure that the patent holder is fairly, but not excessively, compensated in light of all relevant economic factors. The factors are broadly designed to estimate the financial terms of a reasonable license for the patent if both licensee and licensor had negotiated an agreement prior to the commencement of

infringement, based on the assumption that the patent was valid and infringed.

The pending patent reform legislation significantly alters the calculation of reasonable royalty, by limiting the court to three narrowly defined options for determining the figure. In general, courts are directed to determine reasonable royalty based upon "the economic value properly attributable to the patentee's specific contribution over the prior art." Courts are thus required to subtract the value of all prior art, as of the time of the invention, when calculating "reasonable royalty." This ignores the fact that for most inventions, including biologic drugs, the value of the product (and its patent) is generally greater than the economic sum of its parts and is based upon market conditions at the time of infringement. The proposed new method of calculating damages would compensate the patent holder only for a part of the value of the patent, making infringement cheaper and more attractive and thus discouraging VC investment in the biotech sector.

### **Post-Grant Review**

Another worrisome provision in the Senate Patent Reform Act allows virtually anyone to administratively challenge the validity of a patent during a "second window" for post-grant opposition proceedings after the patent is granted (the House version has no such "second window"). Under the proposed new law, a potential infringer who can reasonably show that the patent would cause it "significant economic harm" may, through a petition to the Patent and Trademark Office (PTO), challenge the validity of the patent at any time during the life of the patent, provided certain conditions are met. Such a challenger can raise the full panoply of invalidity defenses, not just an objective

presentation of prior-art patents and printed publications. Even worse, this “second window” would remain open indefinitely, even if other challenges have been rejected.

Allowing limitless challenges to the validity of biotechnology patents throughout the life of the patent creates uncertainty about the validity of the patent, diminishes the value of the patent, and discourages VC investment in emerging biotechnology companies, to the detriment of the public and at the expense of innovation.

### **Inequitable Conduct**

Finally, the proposed patent legislation worsens a difficult situation arising from judge-made doctrine that can deem valid patents unenforceable based on allegations of “inequitable conduct” in prosecuting the patent. At present, if a defendant alleges that the patentee misrepresented or failed to disclose material information to the patent examiner, a costly and time-consuming inquiry into the patent application process and the applicant’s intentions is required. If this subjective inquiry turns up culpable conduct relating to even one claim, the entire patent, or patent family, can be declared unenforceable, even if the claimed invention is found to be patentable and each of the claims is found to have been validly issued.

The present legislation would codify the current intent standard for inequitable conduct, but set the standard of materiality to merely a prima facie case of unpatentability. In addition, the Senate version of the Patent Reform Act allows a determination of unenforceability based upon conduct that bears no relevance to the merits of the patent being considered. These changes would encourage time-consuming and expensive litigation, further discouraging VC investment in emerging biotechnology companies.

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## **Conclusion**

Together, the pending follow-on biologics and patent reform legislation could weaken intellectual property protection for biotechnology companies, creating disincentives for VC investment in biotechnology. This would be particularly harmful to small, start-up biotechs who depend most heavily on VC funding. VCs should take immediate steps to communicate with their representatives in Congress to make sure that these proposals are revised to adequately protect VC investment in emerging biotech companies to foster continued life-saving biotechnology innovation.

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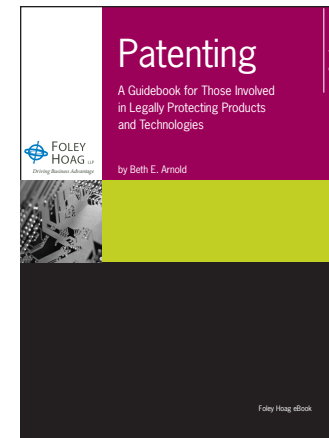
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