

‘Follow-On Biologics’: Ensuring Continued Innovation In The Biotechnology Industry

New protein products will likely need more market protection than what is provided to new drug products.

by **Bruce S. Manheim Jr., Patricia Granahan, and Kenneth J. Dow**

PROLOGUE: The world of pharmaceuticals and patent law can be exceedingly complex. Or, to twist Gertrude Stein’s words, it is not correct that a drug is a drug is a drug. Nowhere is this more true than with “follow-on protein products,” the term the U.S. Food and Drug Administration (FDA) adopted in 2004 for proteins intended as similar versions of already approved protein pharmaceutical products.

In a bit more detail (as explained by PrimeZone), follow-on protein products “are ‘copies’ of recombinant DNA-derived protein products made by companies other than the innovator [company] and using an abbreviated approval path. These products are generally more difficult to make than small-molecule generic drugs due to their greater complexity.” Follow-on protein products are also sometimes referred to as generic biologics.

An ongoing discussion in the United States is whether protein products and “regular” drugs differ substantially from one another, and, if so, if they should have periods of market protection that differ. In this paper, lawyer Bruce Manheim and his colleagues lay out the costly, lengthy nature of creating original protein products as part of their case for why Congress should consider legislation that extends the period of time in which the FDA is barred from approving a follow-on product. This is often referred to as “statutory exclusivity.”

Not all pharmaceutical companies—or their lawyers—concur with this idea. Instead, how to handle patents on biosimilar medicines is a hot pharma-versus-pharma issue, with positions usually determined by whether a drug company makes the original protein product or the follow-on protein product. The lobbying is on, with both sides hoping for something beyond a regular generic victory.

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ABSTRACT: Congress adopted legislation in 1984 to encourage pharmaceutical companies to develop new drugs, while simultaneously allowing competitors to bring cheaper generic versions to market. More than twenty years later, Congress may be faced with a similar balancing act for biologics. When Congress takes up this issue, it must focus on the substantial differences that exist between biologics and drugs. It should also evaluate the patent law, which is yielding increasingly narrow patents. If additional measures are not adopted in light of the intersection of these factors, then any legislation allowing for “follow-on” biologics could stifle development of new medicines from biotechnology. [*Health Affairs* 25, no. 2 (2006): 394–404; 10.1377/hlthaff.25.2.394]

WITH SALES IN THE THERAPEUTIC PROTEIN MARKET expected to top \$57 billion by 2010, there is increasing discussion in the United States of allowing “generic biologics” or “follow-on protein products” to be approved by the Food and Drug Administration (FDA).¹ New legislation is required because the FDA is not authorized to approve follow-on versions of protein products.² Those pressing for such legislation might now increase the pressure for congressional action, since the FDA recently indicated that it would not issue further guidance on this subject in the near future.³ Although the impetus for such action will be to control rising drug costs, Congress will also need to create a regulatory mechanism that assures the safety and efficacy of follow-on protein products. At the same time, Congress must establish a statutory scheme that provides market protection for new protein products and thereby creates incentives for investment and innovation in the biotechnology industry.

To achieve this latter objective, Congress cannot overlook the possibility that a new statutory scheme for follow-on protein products could undercut innovator companies’ ability to secure effective market protection of their products through the patent system. Although legislation governing approval of generic drugs works in tandem with the patent system to afford some protection to an innovator’s investment, the same might not be true of a scheme governing protein products, where the follow-on version need only be “similar” to the innovator’s product. Because therapeutic proteins are complex, macromolecular products, a follow-on manufacturer might be able to design around an innovator’s patents and still secure regulatory approval of its product under the new regime. When one considers the increasing array of new protein products entering the market, the possible loss of market protection in this manner presents a major concern. In this paper we explore that possibility and describe new trends in the patent law that Congress should seriously consider as it evaluates legislative proposals that would allow for the marketing of follow-on protein products.

The Hatch-Waxman Scheme And Drug Patent Protection

The Hatch-Waxman Amendments of 1984 amended the Federal Food, Drug, and Cosmetic Act (FDCA) to allow a party that wishes to market a generic version of a brand-name drug (a so-called innovator drug) to submit an Abbreviated New

Drug Application (ANDA) to the FDA.⁴ In an ANDA, a generic manufacturer may rely on the prior approval of the innovator drug if it can demonstrate that the generic version is the same as, and bioequivalent to, the innovator product. While creating this simpler pathway for approval of generic drugs, however, Congress barred the FDA from approving any generic product until five years from the date on which the FDA approved the corresponding innovator product. Furthermore, recognizing that this five-year period of statutory or nonpatent exclusivity might not be enough to encourage innovation, Congress included three additional provisions in the Hatch-Waxman Amendments that allow manufacturers of innovator products to bolster patent protection for their drug products.

First, Congress sought to ensure that the active ingredient in any product approved through the simplified ANDA process is the “same” as the active ingredient in the innovator drug.⁵ This requirement is critical because if there are differences, the generic manufacturer cannot rely on clinical data developed for the innovator product to demonstrate the safety and efficacy of the generic product. Although this requirement was originally designed to ensure the safety and efficacy of the generic product, it has had the additional effect of supporting effective patent protection for innovator drugs. That is because to be the “same,” the active ingredient in the generic product invariably must fall within the scope of the patent that the innovator holds for that compound. Thus, a generic drug manufacturer cannot have it both ways—it cannot gain FDA approval of its product by arguing “sameness” of the two products in an ANDA and then claim in the patent context that its product is different from the innovator’s drug.

Second, the Hatch-Waxman Amendments established a “patent certification” requirement that allows an innovator to bring a patent infringement action against a generic manufacturer before its product reaches the market.⁶ When the FDA approves an innovator’s application, it must list the innovator’s patents in a publication known as the *Orange Book*. When a patent is so listed, the generic company must notify the innovator in advance of its plan to market the generic product if it intends to do so during the life of the innovator’s patent. In the event that the innovator acts on that notice by bringing a patent infringement action against the generic company, the statute automatically requires the FDA to stay approval of the generic product for up to thirty months or until a court decides that the innovator’s patent is not infringed.⁷ Thus, this scheme provides the innovator with an opportunity to protect its intellectual property rights before the FDA allows a generic version of the drug on the market.⁸

Third, Congress recognized the broader patent issues associated with the development of new products in the pharmaceutical industry, and it created a mechanism allowing for “patent-term extensions”—that is, an extension of the patent term to reflect the period of regulatory review covering the product.⁹ In contrast to most products, drugs and biologics must undergo lengthy study, review, and approval by a government agency (the FDA) before they can be marketed. Yet be-

cause it is usually advisable to file a patent application soon after discovery of a compound, and the term of a patent starts to run from an application's filing date, the patent period is greatly shortened by the time such products have been reviewed, approved, and put on the market. To address this issue, Congress provided for an extension of the patent terms for drugs and biologics following FDA approval. That restored term is based on a formula that extends the patent by up to half of the time spent on human clinical trials, and for the full amount of time spent by the FDA in its review of the application. Although such extensions are limited in certain ways, this provision, coupled with the others set forth above, help ensure that the patent system maintains some incentive for the development of drug products regulated by the FDA.

The Similarity Standard

The provisions of the Hatch-Waxman legislation governing drugs cannot simply be incorporated into a regulatory scheme allowing for approval of follow-on protein products, because fundamental differences exist between drugs and protein products. Drugs are typically small organic molecules with well-defined structures, whereas protein products are complex molecules that may have various folding structures and that may be further modified by the addition of carbohydrate groups (such as glycosylation) or other forms of post-translational modifications. Moreover, while drugs are routinely produced in a laboratory through chemical synthesis, protein products are derived from living organisms. In addition, drugs have physical and chemical characteristics that can be defined and clearly described; protein products are more complex and variable and, therefore, more difficult to define.

These differences lead to a fundamental regulatory distinction: A generic manufacturer can generally demonstrate that its product is the “same” as an innovator drug through the use of analytical methodologies. In contrast, it is virtually impossible for a follow-on company to show that its product is identical to an innovator's product. This is especially true since it is the manufacturing process used to produce a protein product that determines the unique characteristics of each product. For example, the process for a recombinant product generally makes use of carefully selected and controlled materials and conditions, such as proprietary cell lines, production processes, and purification methods. Any changes in the manufacturing process—even seemingly minor ones—can have a major impact on the product. Accordingly, the identity of a protein product is clearly dependent on the process used to manufacture the product. And, because that information is properly protected as trade-secret data, a manufacturer would have great difficulty producing a follow-on protein that is identical to the innovator product.

In light of the characteristics of protein products, a regulatory scheme allowing for approval of follow-on versions will almost certainly not require the follow-on manufacturer to demonstrate that its product is the same as the innovator prod-

uct. Rather, the focus would be on what is necessary to establish sufficient “similarity” between the two. At a September 2004 public workshop on this question, the FDA indicated that it was developing scientifically relevant criteria to evaluate “two similar protein-based therapeutics.”¹⁰ Along the same lines, the European Medicines Agency (EMA) has focused on the similarity of follow-on and innovator protein products.¹¹ Sen. Orrin Hatch (R-UT)—a key legislator on this issue—has suggested that legislation for follow-on protein products could closely mirror existing European Union (EU) policy.¹² Consequently, legislation allowing for follow-on versions of protein products would rely on a “similarity” standard that falls short of the “identical” standards in place for generic drugs.

The Potential To Work Around Patents

Although a similarity standard for follow-on protein products has not yet been defined, such a provision could have a major impact on innovator companies’ ability to protect their investment in a protein product. The Hatch-Waxman scheme allows an innovator to assert some patent protection for its drug product because the active ingredient in the generic version must be the same as the active ingredient in the innovator’s product. On the other hand, to the extent that a follow-on protein product is not required to be the same as an innovator product, a follow-on manufacturer might be able to avoid the patents that an innovator holds on its product and still produce a sufficiently similar product for the purposes of regulatory approval. Thus, while Hatch-Waxman works in concert with the patent system to provide an additional degree of market protection to innovator drug products, the same might not be true for follow-on protein products.

The potential for this to occur is heightened by the fact that biologic products are large macromolecular products, and patents for such products may be narrowly tailored.¹³ One example of this comes from Synagis (palivizumab), a monoclonal antibody indicated for the prevention of serious lower respiratory tract disease in children. The narrow patent claim for this product requires an infringing antibody to bind to the same specific binding site, or epitope, as the Synagis antibody.¹⁴ Still another example is the patent covering Rituxan (rituximab), a monoclonal antibody approved for the treatment of non-Hodgkins lymphoma. The claim covering this product relates to the use of a particular deposited cell line.¹⁵

To be sure, the nature and scope of patent protection will vary from product to product. Early innovators, for example, received broad patents to cover their products. Yet as the biotech industry matures and more products are developed, it seems unlikely that broad patents for recombinant protein products will issue. In fact, because the number and types of biotech patents issued through the 1990s grew explosively, the scope of claims in patents covering recombinant protein products has generally become more narrowly drawn. Accordingly, as the industry continues to mature, follow-on manufacturers might have an easier time designing around an innovator’s patents covering a protein product.¹⁶ This may be

especially true in light of sweeping developments in patent law that are driving the system toward the issuance of narrower patent claims for all products.

Tightening The Specification Requirements

Under the Patent Act, the “specification” in a U.S. patent must provide “a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains...to make and use the same.”¹⁷ This provision has resulted in two basic disclosure requirements for a patent: the “written description” and “enablement” requirements. To satisfy the former, an inventor must provide a detailed description of the claimed invention. To comply with the latter, he or she must disclose how a person having ordinary skill in the art could make and use the claimed invention without “undue experimentation.”¹⁸ Taken together, these disclosure provisions will correspond closely to the working examples and detailed description set forth in the patent application. Those in turn will affect the scope of the claims in a patent. Consequently, to the extent that these disclosure requirements are tightened, so too will the scope of the claims in a patent.

During the past decade, the Court of Appeals for the Federal Circuit—the appeals court that hears all patent appeals—has handed down several landmark decisions that have imposed stringent disclosure standards, especially in the field of biotechnology products.¹⁹ In particular, the Federal Circuit has raised the bar for the written-description requirement through a series of cases involving important biotechnology products. In *Fiers v. Revel*, the court considered patent applications claiming the human DNA sequence that produces the protein fibroblast beta-interferon.²⁰ Subsequently, the Federal Circuit reviewed a patent covering a microorganism carrying the DNA sequence coding for human insulin.²¹ In both cases, the court held that disclosing a method for obtaining a DNA molecule or even describing the protein that the DNA molecule encodes is inadequate for a claim to the DNA molecule itself without a detailed written description of the structure of the molecule. The court also found that a functional description of what the molecule does without structural information is inadequate.²² Accordingly, the written-description requirement effectively limits the ability of a patentee of a biotechnology invention to obtain claims with a literal scope that extends beyond the description of the molecules contained in the patent application.

At the same time, the Federal Circuit has also maintained a stringent standard for the enablement requirement. In *Amgen v. Chugai*, the patentee claimed nucleic acid sequences coding for the protein erythropoietin (EPO) or for other proteins with the same biological function.²³ The court found that the examples as disclosed in the patent were insufficient for the enablement of the myriad DNA sequences encoding the EPO analogs. Similarly, the Federal Circuit’s holding in *Genentech v. Novo Nordisk A/S* suggests that the scope of claims may be limited to the embodiments disclosed in an applicant’s working examples.²⁴ After considering a

claimed method for producing human growth hormone, the court declared that “where, as here, the claimed invention is the application of an unpredictable technology in the early stages of development, an enabling description in the specification must provide those skilled in the art with a specific and useful teaching.” This approach suggests that the more innovative the technology, the more detail will be required to meet the enablement standard.

New Restrictions On The ‘Doctrine Of Equivalents’

Recent restrictions on a rule of patent law known as the “doctrine of equivalents” could also lead to more narrow construction of claims in patents. That rule provides that where a product or process at issue does not literally infringe patent claims but nonetheless performs much the same function in much the same way to achieve much the same result as the claimed invention, the product or process infringes as an “equivalent” to the claimed invention. The purpose underlying the doctrine is to prevent would-be infringers from avoiding liability simply by making minor changes to their product or process, which might not have been anticipated by the patent owner.

Until recently, the doctrine of equivalents was relatively forgiving to patent owners who filed amendments to add limitations to their claims. That is, a patent applicant could argue with some force that the doctrine expanded the claim coverage despite the earlier narrowing amendments. In late 2000, however, the Federal Circuit greatly reduced the availability of this doctrine by holding that it could not be used to give any equivalence to an element of a claim that had been narrowed by an amendment during the patent application process (*Festo I*).²⁵ The U.S. Supreme Court subsequently rejected the absolute bar as applied by the Federal Circuit but did establish a presumption against use of the doctrine that could only be overcome under certain circumstances (*Festo II*).²⁶

In the wake of these decisions, most commentators believe that patent applicants will seek to avoid amendments by drafting their original patent claims much more narrowly than before, thereby minimizing the possible limitations needed before the patent issues. For example, one judge with the Federal Circuit (Randall Rader) has indicated that the approach to drafting of claims has historically been to start with the broadest claim possible.²⁷ He suggests that after *Festo I*, however, narrower claims will be filed because “any narrowing amendment or disclaiming argument to overcome [a] rejection will endanger a patent’s coverage.” Still other commentators have declared that “the literal scope of biotechnology patents will be quite narrow: patent claims are confined to the DNA sequences actually generated and disclosed, rather than those enabled by the patentee. While that scope may be broadened by the doctrine of equivalents, the recent trend to limit the scope of the doctrine of equivalents may mean that the biotechnology industry will be characterized by large numbers of narrow patents.”²⁸

An Incentive To Spur New Biotech Development

Given these trends in the patent law, Congress will need to evaluate the impact of any scheme allowing for marketing of follow-on protein products on innovators' ability to protect their investment through the patent system. Indeed, as the standard for approval of follow-on protein products widens from sameness to similarity, the patent system is generally moving toward the issuance of increasingly narrow claims. Thus, under a statutory scheme allowing for approval of follow-on protein products, a follow-on version could be similar enough to an innovator product for the purposes of regulatory approval but different enough to avoid patent infringement. The combined effect of these developments could, therefore, be to reduce effective market protection for innovator protein products. That, in turn, could stifle the development of new medicines from biotechnology.

■ **Period of nonpatent exclusivity.** Congress could address this potential problem by establishing a period of nonpatent exclusivity for protein products.²⁹ But that time period would need to be longer than the five years now given to manufacturers of new drug products under Hatch-Waxman, which itself may be too short to spur development of new types of drug products. The following example helps illustrate this point. Assume that a patent on a protein product is filed in 1990 and expires in 2010, and the product is approved for marketing in 2001. Under current law, the patent on this product could be extended to 2015, and because there is no follow-on competitor, the product has effective market exclusivity for the maximum allowable period of fourteen years. In contrast, under a regime where it is assumed that the similarity standard effectively undercuts or weakens patent protection, the period of effective market exclusivity would be only five years, until 2006, or possibly until mid-2008 if the innovator can trigger the thirty-month bar through a patent certification scheme (if made available in any new regime).

On the other hand, if the period of nonpatent exclusivity were set at twelve years, then the innovator product would have market protection until 2013 if it could avail itself of a patent certification scheme similar to that governing drug products. A twelve-year market protection period would be commensurate with the maximum allowable time period for pharmaceutical products under current law. According to a 1998 Congressional Budget Office report, the average period of time for marketing a drug product with patent protection is eleven and a half years, and it takes an additional one to three months from the date of patent expiration for the FDA to approve a generic product.³⁰ It therefore seems reasonable to use this period for biotech products, because such products should receive at least the same level of protection as drug products. In fact, that may be particularly true since the costs and risks of developing such products, and other barriers to entry, appear to be higher for protein products than for drug products.³¹

A twelve-year period of nonpatent exclusivity for protein products also would appear to be appropriate on the basis of the length of patent protection available to them. Under the patent-term-extension provisions that apply to protein prod-

ucts, an innovator is entitled to up to fourteen years of patent protection beyond the date of FDA approval of its product. Although no recent studies appear to have evaluated the average length of time that an innovator's protein product has enjoyed patent protection, it is likely close to this period of time, given the absence of generic competition to date. In fact, in 1999 the Biotechnology Industry Organization (BIO) reported that the average length of protection of biologic patents was more than fifteen years. Also, because there is no regulatory pathway for a generic copy of an innovator protein product, the actual market exclusivity for such products effectively extends beyond the life of the patents. Accordingly, in light of the substantial costs necessary to develop protein products, sound public policy would dictate that any statutory formula that allows for follow-on protein products should at least retain existing market protection for innovator products provided through the patent system.

■ **Potential challenges.** Some parties will undoubtedly challenge the idea that Congress should establish a period of nonpatent exclusivity for protein products that goes beyond that now afforded to new drug products. To that end, they would likely characterize such action as an "extension" of the current level of market protection that will result in higher prices, burdened private and government health plans, and lack of access to the drug for some patients because of cost. Yet, based on the foregoing analysis, a twelve-year period of nonpatent exclusivity would not effectively change the status quo. Nor, in virtually all cases, would such action constitute an "extension" of protection for protein products. That is because the period of nonpatent exclusivity for a particular product runs concurrently with the patent term for the product. In most cases, that patent is likely to extend beyond twelve years. Thus, the nonpatent period would create actual market protection for the product only in those instances where the follow-on manufacturer is able to gain FDA approval of its product and, at the same time, work around the patents held by the innovator.

■ **Comparison with animal drugs.** Shortly following enactment of the Hatch Waxman Amendments in 1984, Congress focused on whether it should adopt a similar statutory scheme to govern animal drugs. Congress subsequently chose to do so in 1988 with enactment of provisions authorizing the FDA to approve generic versions of animal drugs.³² In this connection, however, Congress decided not to allow for generic versions of animal drugs derived from biotechnology, in response to concerns raised by the biotech industry that patents relating to biotech-derived drugs do not provide the same level of market protection as is available to chemically derived drugs. In fact, key legislators found that application of the Hatch-Waxman scheme to biotech-derived animal drugs could remove incentives for innovators to develop new products in this area.

SURELY, IF CONGRESS CAN EXERCISE this level of caution to protect innovation in the animal drug industry, it must be doubly certain to do so for protein products intended for use in human beings. To that end, Congress should acknowledge that in light of the differences that distinguish drugs from protein products, any regulatory regime governing follow-on protein products will be different from the Hatch-Waxman provisions for drugs. Although one of those differences will involve the degree of sameness required for a follow-on protein product, another will stem from innovators' increased difficulty in securing effective patent protection. One way in which Congress could harmonize these differences and preserve incentives for the development of new medicines from biotech is by extending the period of nonpatent exclusivity for innovator products well beyond that now afforded to new drug products.

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NOTES

1. The FDA adopted the term "follow-on protein product" in August 2004 to refer to a protein that is intended to be a similar version of an already approved or licensed protein pharmaceutical product. See *Federal Register* 69, no. 50386 (16 August 2004): 50386–50388. Inasmuch as biologic products from different manufacturers cannot be identical, we use the FDA's term throughout this paper rather than the more oft-quoted term "generic biologics."
2. Although the FDA recognizes that it does not have legal authority to approve follow-on versions of products originally approved under Section 351 of the Public Health Service Act, it has taken the position that it does have authority to approve follow-on versions of complex protein products that happen to be treated as drugs under the Federal Food Drug and Cosmetic Act (FDCA). See "Follow-Ons Off? FDA Shelves Near-Term Plans for Biologics Documents," *Pink Sheet* 67, no. 41 (2005): 14. To date, the FDA has approved several complex protein products under the FDCA.
3. *Ibid.*
4. As an additional concession to the generic drug industry, Congress enacted the "Bolar exception," allowing generic drug manufacturers to develop information necessary for an ANDA without being subjected to a patent infringement action. See 35 U.S. Code, sec. 271(e)(1).
5. See, for example, 21 U.S. Code, Sec. 355(j)(2)(A).
6. *Ibid.*, Sec. 355(j)(2)(A)(vii)(IV); also see 35 U.S. Code, Sec. 271(e)(2).
7. 21 U.S. Code, Sec. 355(j)(5)(B)(iii).
8. Most generic manufacturers appear to be aware of the difficulty of litigating against innovators, since their products are required to be same and they therefore agree to wait to seek approval of their products until the patent for the innovator product expires. Of the 8,259 generic applications filed between 1984 and January 2001, only 6 percent raised a patent issue. Stated differently, during that period, 7,781 generic drug applications did not involve paragraph IV patent litigation. See Pharmaceutical Research and Manufacturers of America, "The Hatch-Waxman Perspective: Pharmaceutical Industry Context for the FTC's Generic Drug Study—FTC File No. V000014" (18 June 2002), 18.
9. See 35 U.S. Code, Sec. 156.
10. See U.S. Food and Drug Administration, "Public Workshop: Scientific Considerations Related to Developing Follow-On Protein Products, September 14–15, 2004," <http://www.fda.gov/cder/meeting/followOn/followOnPresentations.htm> (accessed 11 October 2005).
11. EMEA Committee for Proprietary Medicinal Products, "Note for Guidance on Development Pharmaceuticals," CPMP/QWP/155/96, 28 January 1998, <http://www.emea.eu.int/pdfs/human/qwp/015596en.pdf> (accessed 30 January 2006); and "Guideline on Comparability of Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues," CPMP/BWP/3207/00/Rev 1*, 11 December 2003, <http://www.emea.eu.int/pdfs/human/bwp/320700en.pdf> (accessed 30 January 2006).

12. See “Hatch Eyes Generic Biologics Bill Modeled on E.U. Approach,” *I.P. Law Bulletin* (11 October 2004).
13. The examples cited herein are meant to be illustrative only. We have not conducted extensive patent studies on each of these products, and the actual patent situation might differ from this analysis.
14. Claim 1 recites: “A neutralizing antibody against...respiratory syncytial virus binding to the same epitope as an antibody comprising three heavy-chain CDRs,” with specific amino acid sequences as set forth in the patent.
15. Claim 1 recites: “Immunologically active, chimeric anti-CD20 antibody produced from a transfectoma comprising anti-CD20 in TCAE 8, ATCC deposit number 69119.” U.S. Patent no. 5,736,137 (7 April 1998).
16. For example, Eli Lilly’s insulin product, HUMALOG, is covered by a patent with claims directed to only four possible amino acid substitutions at position B28 and two possible amino acid substitutions at position B29 of the human insulin protein. Novo Nordisk was able to avoid Lilly’s patent for its own insulin product, NOVOLOG, by substituting with a different amino acid at position B28 of the human protein. Similarly, Aventis’s insulin product, APIDRA, does not infringe on either of these patents since it, too, substitutes certain amino acids at different parts of the protein backbone.
17. 35 U.S. Code, Sec. 12.
18. See, for example, *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).
19. See, for example, A.A. Naini, “Convergent Technologies and Divergent Patent Validity Doctrines: Obviousness and Disclosure Analyses in Software and Biotechnology,” *Journal of the Patent and Trademark Office Society* 86, no. 7 (2004): 541–567; and J.A. Kopczyński, “A New Era for §112? Exploring Recent Developments in the Written Description Requirement as Applied to Biotechnology Inventions,” *Harvard Journal of Law and Technology* 16, no. 1 (2002): 229–264.
20. 984 F.2d 1164 (Fed. Cir. 1993).
21. 119 F.3d 1559 (Fed. Cir. 1997).
22. The court has continued to apply rigorous written description requirements in recent cases involving biotechnology and chemical patents. See, for example, *In re Wallach*, 378 F.3d 1330 (Fed. Cir. 2004); *Univ. of Rochester v. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004); and *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003).
23. 927 F.2d 1200 (Fed. Cir. 1991).
24. 108 F.3d 1361 (Fed. Cir. 1997).
25. See *Festo v. Shoketsu Kinzoku Kogyo Kabushiki*, 234 F.3d 558 (Fed. Cir. 2000) (*Festo I*).
26. See *Festo v. Shoketsu Kinzoku Kogyo Kabushiki*, 535 U.S. 722 (2002) (*Festo II*).
27. R.R. Rader, “Recent Patent Law Cases in the United States: *Festo*’s Effect on Patent Acquisition Practices,” http://www.softic.or.jp/symposium/open_materials/10th/en/rader-en.pdf (accessed 11 October 2005).
28. See D.L. Burk and M.A. Lemley, “Is Patent Law Technology-Specific?” *Berkeley Technology Law Journal* 17, no. 4 (2002): 1182. See also Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*, July 1998, <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> (accessed 24 January 2006); and M. Meadows, “Greater Access to Generic Drugs: New FDA Initiatives to Improve Drug Reviews and Reduce Legal Loopholes,” *FDA Consumer Magazine* 37, no. 5 (2003): 12–17.
29. Some might argue that changes in patent law could address this problem as well. However, such changes could only be effectuated by congressional or court actions. Such changes could also lead to technology-specific patent law in which patentability standards (and therefore scope of patent protection) vary among different technology areas. On balance, this would not be a desirable result.
30. CBO, “The Effects of the Hatch-Waxman Act on the Returns from Innovation,” in *How Increased Competition*, chap. 4.
31. Although no comprehensive studies have evaluated the comparative costs of bringing drugs and biologics to market, several studies have focused on certain facets of this question, including total development costs, total development times, development failure risks, and manufacturing costs. See, for example, Tufts Center for the Study of Drug Development, *Outlook 2004*, <http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2004.pdf> (accessed 24 January 2006), 1; J.M. Reichert, “Trends in Development and Approval Times for New Therapeutics in the United States,” *Nature Reviews: Drug Discovery* 2, no. 9 (2003): 695–702; and Biotechnology Industry Organization, “A Brief Primer on Manufacturing Therapeutic Proteins,” April 2003, <http://www.bio.org/healthcare/pmp/factsheet1.asp> (accessed 9 November 2005).
32. *Generic Animal Drug and Patent Term Restoration Act of 1988*, Public Law 100-670, 102 Stat. 3971 (1988) (codified at 21 U.S. Code, Secs. 301 note, 360b, 360b notes, 321, 353; 28 U.S. Code, Sec. 2201; and 35 U.S. Code, Secs. 156, 271).