

## The Generic Biologics Debate: *Industry's Unintended Admission that Biotech Patents Fail Enablement*

GREGORY N. MANDEL<sup>†</sup>

### ABSTRACT

*This Article reveals that many already issued and actively enforced medical biotechnology patents may be invalid. Biologics, medical therapeutics derived through biotechnology techniques, are the fastest growing and most promising pharmaceutical sector. They represent a \$45 billion a year industry that is anticipated to double in five years and that already provides novel treatments for cancer, diabetes, and heart disease. Due to unforeseen consequences of past decisions, manufacturers currently are significantly limited in their ability to sell generic copies of biologics even after the pioneer biologic patents expire. As early biologics are starting to go off-patent, this regulatory mix-up is having a notable impact on the availability of biologics and raising the cost of health care.*

*The generic biologics debate has dramatically heated-up recently due to proposed legislation to create a new regulatory process for generic biologics, the biotechnology and pharmaceutical industry defending the status quo, and the Food and Drug Administration struggling to handle the situation. This Article exposes for the first time that industry's own arguments have an unintended, striking consequence—many of their biologic patents fail enablement, and therefore are not valid in the first instance.*

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<sup>†</sup> Associate Dean for Research and Scholarship and Professor of Law, Albany Law School. I would like to thank Kelly Marks for her outstanding research assistance.

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## I. INTRODUCTION

¶1 Many already issued and actively enforced medical biotechnology patents are actually not valid under existing law. The patent owners proclaim facts demonstrating their own patents' invalidity, yet government officials and the biotechnology industry appear blind to the problem. This remarkable set of circumstances is made evident in the growing debate over generic biologics.

¶2 "Biologics" are a class of medical therapeutics derived through the manipulation of living sources, such as recombinant DNA techniques. The rapidly growing medical biologic industry includes products such as insulin for diabetes, human growth hormone, treatments for cancer and heart disease, and a variety of other breakthroughs. Biologics are widely considered one of the greatest hopes for future advances in medicine.

¶3 Inventors of new biologics routinely obtain patents on their inventions, allowing the owner to exclude others from making or selling the patented invention for a limited time. The first biologic patents have recently expired and many more will expire over the next few years. At the expiration of the patent term, society cashes in on its part of the patent bargain as the subject matter enters the public domain and anyone can make and sell the invention. Patent expiration is the source of traditional low-cost generic drugs, which are copies of pioneer drugs whose patents have expired. This is how patent law is supposed to function; actual practice for biologics, however, is a different matter.

¶4 The sale of a drug in the United States requires regulatory approval from the Food and Drug Administration (FDA), a process that is lengthy and expensive. An entity that desires to manufacture a generic version of a medical biologic at the expiration of the biologic's patent term cannot even begin the regulatory process until the patent expires.

Making the biologic earlier in order to obtain regulatory approval would infringe the patent.

¶5 Conventional (i.e., non-biologic) pharmaceuticals do not face this dilemma. Pursuant to a statute enacted twenty-three years ago, manufacturers of conventional pharmaceuticals may seek FDA approval for a generic version of a pioneer drug prior to expiration of the pioneer drug's patent term. Furthermore, generic manufacturers may rely on the prior FDA approval of the pioneer drug to expedite the generic drug's approval process, avoiding the time and expense of clinical trials. As a result, conventional generics can go on sale the date a patent expires at a substantially lower price than the pioneer brand-name drug, resulting in vast savings for government and consumers.

¶6 Due to decisions that predate the biotechnology industry, however, medical biologics are regulated by the FDA under a different statutory scheme than conventional pharmaceuticals, despite the fact that the approval process is now markedly similar. An (apparently) unintended consequence of this difference is that the expedited approval process for conventional generics is not available for biologic generics. This result is highly suspect—it allows biologic patent owners to effectively extend their patent monopolies far beyond the term provided in the Patent Act, dramatically impacting the availability of biologics and raising the cost of health care.

¶7 The pioneer biotechnology and pharmaceutical industries, unsurprisingly, strongly defend this status quo. Pioneer industry raises both legal and scientific arguments. Though the legal arguments generally lack merit, as discussed in detail below, the scientific concerns deserve greater attention.

¶8 A traditional generic receives expedited approval when the manufacturer demonstrates to the FDA that the generic drug is equivalent to the pioneer drug. If equivalency is established, the generic manufacturer does not need to independently demonstrate the safety and efficacy of the generic drug, which can be accomplished only through expensive and time-consuming clinical trials.

¶9 Pioneer biologic industry contends that this equivalency cannot be established for biologics. Biologic products, pioneer industry argues, are so intricately dependent on their manufacturing processes that minor changes in temperature, timing, purification conditions, or other factors could produce a different product. Further, biologics are such complex molecules that any difference may not be identifiable, potentially resulting in a product that lacks safety and efficacy. While this contention has some merit for particular complex biologics, it is not scientifically justified for simpler biologics, which represent many of the biologic products on the market today. Numerous biologics either are not highly sensitive to their manufacturing process or can be characterized to the extent necessary to satisfy safety concerns.

¶10 What is most striking about pioneer industry's argument, however, is that it effectively concedes that the very biologic patents the argument is intended to protect actually are not valid. A central requirement of patent validity is that the application

adequately disclose the invention. This is the applicant's part of the patent bargain—society grants a patent in exchange for being taught the invention. A core element of adequate disclosure is “enablement,” that the patent discloses how to make the invention such that a person having ordinary skill in the art can make and practice it. By arguing that equivalence cannot be established for biologics, pioneer industry is stating (apparently without realizing it) that its biologic patents are not fully enabled. If pioneer industry's unachievable equivalence argument is correct, generic manufacturers are not able to make the biologic that the pioneer inventor contends is covered by patent. The patents therefore fail enablement and are invalid.

¶ 11 Part I of this Article introduces the reader to medical biologics and the biologic industry. Part II provides a primer on patent law and the FDA regulatory approval process for drugs, biologics, and generics. Part III analyzes the issues surrounding the extension of the expedited approval process to generic biologics, focusing on the revelation that pioneer industry's arguments against such extension indicate that many biologic patents are invalid. This revelation is particularly timely, as the generic biologics debate has dramatically heated up recently, with legislation recently having been introduced and the FDA struggling to come to grips with the situation.

## II. MEDICAL BIOLOGICS

¶ 12 Biotechnology in its broadest sense concerns the applied use of living organisms. More particularly, it refers to the use of genetic engineering and recombinant DNA technology to modify living organisms to produce useful products and processes. Medical therapeutic products produced through biotechnology processes represent one of the primary and fastest growing applications of biotechnology. Such products are commonly referred to as “biologics.”<sup>1</sup> Biologics include a wide variety of synthetic and recombinant versions of natural biological substances, such as proteins, antibodies, vaccines, and blood and tissue products.

¶ 13 The United States biologic market is booming. Sales of medical biologics already generate \$45 billion in revenue annually and are expected to double in several years.<sup>2</sup> Spending on specialty pharmaceuticals, like biologics, is growing at twice the rate of spending on traditional pharmaceuticals, and is expected to account for one quarter of expenditures on pharmaceuticals in the United States this year.<sup>3</sup> That is not bad for an industry that had no commercial products twenty-five years ago.

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1. Another therapeutic application of biotechnology is gene therapy. Gene therapy concerns attempting to cure diseases by modifying a patient's DNA in some manner in order to eliminate a genetic defect. Gene therapy has not yet been successfully achieved. *See, e.g., Rick Weiss, Boy's Cancer Prompts FDA to Halt Gene Therapy*, WASH. POST, Mar. 4, 2005, at A2.

2. Kenneth D. Brown, *Biosimilars Shake up the Biologics Market*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS, Dec. 1, 2005, available at <http://www.genengnews.com/articles/chitem.aspx?aid=1159>; *Cost Savings in Generic Biotech Drugs Detailed*, L.A. TIMES, Feb. 15, 2007; *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. (2004) [hereinafter *Biologic Hearings*] (statement of Sen. Orrin Hatch, Chairman, S. Comm. on the Judiciary).

3. Geeta Anand, *The Most Expensive Drugs -- Rx for an Industry: As Biotech Drug Prices Surge, U.S. Is Hunting for a Solution*, WALL ST. J., Dec. 28, 2005, at A1.

¶14 Over 250 biologics have received regulatory approval,<sup>4</sup> including novel treatments for cancer, insulin for diabetes, human growth hormone, erythropoietin (EPO) for anemia, various blood coagulant factors, and treatments for heart disease, multiple sclerosis, AIDS, arthritis, hepatitis, and asthma.<sup>5</sup> Hundreds more biologic products are currently undergoing human clinical trials or are at other stages in the development pipeline.<sup>6</sup>

¶15 Biologics represent the greatest opportunity for improvements in medicine. The development of new conventional pharmaceuticals has been declining for years, and the number of new drugs approved by the FDA has dropped dramatically over the past decade to about twenty per year.<sup>7</sup> Advances in medical biologics present the best hope of reversing this trend and improving pharmaceutical capability and outlook in the future.<sup>8</sup>

¶16 Biologics do not come cheaply. The average medical biologic costs tens of thousands of dollars annually, and the most expensive biologics can cost several hundred thousand dollars per year.<sup>9</sup> This is good news for biologic manufacturers, but raises significant concerns for consumers and governments facing spiraling health care costs.

¶17 There is some silver lining in the biologic cost cloud. The high cost of biologics results not only from the significant research, development, and regulatory approval expenses that must be recovered by biologic developers in order for innovation to continue, but also from monopoly pricing of biologics made possible by patent

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4. Robert Cohen, *Generic Biotechs Get Boost: Congress Will Be Lobbied Both Ways on Legislation*, NEWARK STAR-LEDGER, Feb. 15, 2007.

5. Biotechnology Industry Organization, *Biotechnology Industry Facts*, <http://www.bio.org/speeches/pubs/er/statistic.asp> (last visited Oct. 7, 2006); Food and Drug Administration, Center for Biologics Evaluation and Research, *Product Approval Information*, <http://www.fda.gov/cber/efoi/approve.htm> (last visited Oct. 7, 2006) (listing approvals of biological products or treatments for bladder cancer, to prevent hemorrhaging in hemophilia patients, to test for human immunodeficiency virus, and for hepatitis A and B); Food and Drug Administration, Center for Drug Evaluation and Research, *Therapeutic Biological Products Approvals*, [http://www.fda.gov/cder/biologics/biologics\\_table.htm](http://www.fda.gov/cder/biologics/biologics_table.htm) (listing approvals of biological treatments for asthma, anemia due to kidney failure and chemotherapy, breast and colon cancer, chronic leukemia, multiple sclerosis, rheumatoid arthritis, hepatitis C, angina, and myocardial infarction) (last visited Oct. 7, 2006); Food and Drug Administration, Center for Drug Evaluation and Research, *What's New by Date*, <http://www.fda.gov/cder/whatsnew.htm> (last visited Oct. 7, 2006) (approval for an inhalable form of insulin for diabetes treatment); Food and Drug Administration, Center for Drug Evaluation and Research, *CDER New and Generic Drug Approvals 1998–2004*, <http://www.fda.gov/cder/approval/index.htm> (last visited Oct. 7, 2006) (listing approvals for recombinant human growth hormone).

6. See Cohen, *supra* note 4; Marc Kaufman, *Clinical Trials of Drugs Fewer, Study Says; Report Also Notes Decline in Number of Principal Investigators in U.S.*, WASH. POST, May 4, 2005, at A2.

7. Alex Berenson, *Pricey Drug Trials Turn Up Few New Blockbusters*, N.Y. TIMES, Dec. 18, 2004; Narayan Kulcami, *R&D Spending on the Rise, BioSpectrum*, August 20, 2005, available at <http://www.biospectrumindia.com/content/BioBusiness/10508202.asp>.

8. Berenson, *supra* note 7; Kulcami, *supra* note 7.

9. *Cost Savings in Generic Biotech Drugs Detailed*, L.A. TIMES, Feb. 15, 2007; *Biologic Hearings*, *supra* note 2 (statement of Dr. Carole Ben Maimon, President and Chief Operating Officer, Barr Laboratories); David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 144 (2005); Anand, *supra* note 3; Cyril T. Zaneski, *"Miracle" Biotech Drugs Growing in Use and Cost*, BALT. SUN, Mar. 16, 2004, at 1A.

protection. The earliest biologics have recently come off-patent (e.g., on recombinant insulin and EPO),<sup>10</sup> potentially reducing the cost of these therapies. The pioneer versions of already off-patent biologics have sales over ten billion dollars per year; soon to be off-patent biologics have an additional fifteen billion dollars of sales annually.<sup>11</sup> Generic manufacturers are already working on generic versions of insulin, human growth hormone, EPO, and other biologics.<sup>12</sup>

¶ 18 Generic versions of off-patent biologics may not offer cost savings as extensive as traditional pharmaceutical generics because of the expense of complex manufacturing facilities, but the savings still could be substantial—some off-patent biologics, for instance, now generate gross profits in excess of ninety percent.<sup>13</sup> Estimates are that generic versions of biologics would reduce costs by about twenty to thirty percent, saving the government and private consumers billions of dollars annually.<sup>14</sup> Total potential cost savings from generic biologics are projected to be over seventy billion dollars for a ten year period.<sup>15</sup> Whether generic competitors can effectively enter the market, however, remains unresolved.

### III. PATENT LAW AND FDA APPROVAL

¶ 19 Commercialization of any new drug requires FDA regulatory approval. As discussed, many drug manufacturers protect their interest in particular drugs by acquiring patent rights. The intersection of FDA regulatory requirements and patent protection raises issues unique to the drug industry. It is this interaction that creates the generic biologic issue.

#### A. Patent Protection

¶ 20 When an entity obtains a patent on a new pharmaceutical, it receives the right to

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10. Dudzinski, *supra* note 9, at 244-52; see Dana K. Cassell, *Generic Biologics: One Step Closer to Reality*, DRUG TOPICS, Aug. 7, 2006 (listing off-patent biologics).

11. Abby Christopher, *Biogenerics and Drug Pricing: A Battle Royal*, PHARMACY TIMES, <http://www.pharmacytimes.com/Article.cfm?Menu=1&ID=4186>; *Research and Market Officials Detail Recent Developments*, LIFE SCI. WKLY., Feb. 6 2007; Press Release, Generic Pharm. Ass'n, GPhA to FDA: The Time is Now - Consumers Need Access to the Medicines of the 21st Century and Biogenerics Can Address Their Needs (Sept. 15, 2004), available at [http://www.prnewswire.com/cgi-bin/micro\\_stories.pl?ACCT=913120&TICK=GPHA&STORY=/www/story/09-15-2004/0002251049&EDATE=Sep+15+2004](http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=913120&TICK=GPHA&STORY=/www/story/09-15-2004/0002251049&EDATE=Sep+15+2004).

12. Dudzinski, *supra* note 9, at 182-83.

13. Anand, *supra* note 3.

14. *Cost Savings in Generic Biotech Drugs Detailed*, L.A. TIMES, Feb. 15, 2007 (reporting a study that estimated cost savings of 25% from four primary categories of generic biologics); Dudzinski, *supra* note 9, at 183 (noting the potential for multi-billion dollar savings from generic biologics); Marc Kaufman, *Biotech Drugs' Generic Future Debated; Medications Are Hard to Afford -- But May Also Be Hard to Copy*, WASH. POST, Feb. 10, 2005, at A1 (estimating the cost savings of generic biologics to be 20% to 30%).

15. Steve Miller & Jonah Houst, *Potential Savings of Biogenerics in the United States, Express-Scripts*, available at <http://www.express-scripts.com/ourcompany/news/outcomesresearch/onlinepublications/study/potentialSavingsBiogenericsUS.pdf>.

exclude others from making, using, selling, or importing the patented pharmaceutical for a certain period of time,<sup>16</sup> currently twenty years from the date of patent application.<sup>17</sup> Patent exclusivity rights limit competition, allowing the pharmaceutical company to charge a higher price for its drug.

¶ 21 Despite some critiques that the patent system is unnecessary to incentivize innovation (and consequently that it imposes unnecessary costs on society),<sup>18</sup> pharmaceutical research and development is one area where there is considerable consensus that the patent system produces substantial social benefit.<sup>19</sup> New drug development is a costly enterprise. United States pharmaceutical companies spend over \$50 billion annually on research and development of new drugs.<sup>20</sup> Some experts estimate the average cost of bringing a new pharmaceutical to market to be as high as \$800 million.<sup>21</sup> The average cost of bringing a medical biologic to market exceeds \$1 billion.<sup>22</sup> Absent patent protection, drug manufacturers generally would have no way to recoup the costs of research and development: generic competitors could relatively easily duplicate new drugs and sell them for a lower price, as the competitors would not have to pay the extensive research and development expenses. As a result, absent patent protection, drug companies would reduce their development activities—there would be no way to recover the costs of research and development, let alone earn a profit. Society would be worse off as fewer pharmaceuticals would be developed. Patent protection solves this problem by granting the drug inventor an exclusivity period, enabling it to recover its expenses and earn a profit. Absent patent protection, there likely would be substantially less pharmaceutical research and development.<sup>23</sup>

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16. 35 U.S.C. § 271(a) (2000).

17. 35 U.S.C. § 154(a)(2) (2000).

18. See, e.g., ADAM B. JAFFE & JOSH LERNER, *INNOVATION AND ITS DISCONTENTS: HOW OUR BROKEN PATENT SYSTEM IS ENDANGERING INNOVATION AND PROGRESS, AND WHAT TO DO ABOUT IT* (2004); RICHARD A. POSNER, *ECONOMIC ANALYSIS OF LAW* 54 (2d ed. 1977).

19. See, e.g., Natasha N. Aljalian, *The Role of Patent Scope in Biopharmaceutical Patents*, 11 B.U. J. SCI. & TECH. L. 1, 9-11 (2005); Timothy J. Muris, Chairman, Fed. Trade Comm'n, *Competition and Intellectual Property Policy: The Way Ahead* (Nov. 15, 2001), <http://www.ftc.gov/speeches/muris/intellectual.htm>.

20. Narayan Kulcami, *R&D Spending on the Rise*, BIOSPECTRUM, August 20, 2005, available at <http://www.biospectrumindia.com/content/BioBusiness/10508202.asp>.

21. Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFF. 420, 420 (2004); John H. Barton & Ezekiel J. Emanuel, *The Patents-Based Pharmaceutical Development Process*, 294 J. AM. MED. ASS'N 2075, 2076 (2005). The approximate figure of \$800 million is strongly critiqued by others. See, e.g., PUBLIC CITIZEN, *RX R&D MYTHS: THE CASE AGAINST THE DRUG INDUSTRY'S R&D "SCARE CARD"* 7 (2001), available at <http://www.citizen.org/documents/acfdc.pdf> (contending that the cost of developing a new drug is \$114 to \$150 million).

22. *Average Cost to Develop a New Biotechnology Product Is \$1.2 Billion, According to the Tufts Center for the Study of Drug Development*, Tufts Center for Study of Drug Development, Nov. 9, 2006, <http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69>; Julie Schmit, *Legislation Calls for Cheaper Biotech Drugs*, USA TODAY, Feb. 15, 2007, at 7B.

23. Even absent patent protection, some pharmaceutical research and development would continue, as a significant amount of pharmaceutical research is funded or conducted by the government and academia. Wesley M. Cohen et al., *Links and Impacts: The Influence of Public Research on Industrial R&D*, 48 MGMT. SCI. 1, 5-9 (2002).

¶ 22 After the patent term expires, patented subject matter enters the public domain. In the case of patented drugs, generic manufacturers now may potentially make and sell the now off-patent drug. Aiding generic manufacturers in this pursuit is a core requirement of obtaining a patent: the inventor must disclose how to make and use the invention.<sup>24</sup> Inventors may not receive a patent in the first instance unless they enable others to make the invention so that the invention will be available for duplication after the patent expires. Because generic manufacturers never had to pay the large upfront research and development costs, they can charge far lower prices for generic versions of drugs and still earn a profit. Society finally gets to cash in on the full benefit of the patent bargain—here, the availability of less expensive pharmaceuticals.

¶ 23 Generic manufacturers, however, face one more particular hurdle before marketing a generic drug. Like its pioneer counterpart, the generic manufacturer must get FDA approval of the generic version of the drug—a process that can be expensive and lengthy.<sup>25</sup> Further, a generic manufacturer may not even begin this process until a patent expires—otherwise the generic manufacturer would infringe the patent in trying to get regulatory approval for its version of the drug. Absent a solution to this problem, patent owners could effectively extend their patent term beyond what is statutorily mandated—after patent expiration, it would still take years for a generic company to get FDA approval and then ramp-up production. The solution to this issue for conventional pharmaceuticals was the Hatch-Waxman Act of 1984.

## B. The Hatch-Waxman Act

¶ 24 The Hatch-Waxman Act establishes an expedited and simplified approval process for generic drug manufacturers. Hatch-Waxman was enacted to reduce health care costs for both the government and private citizens; as the congressional record notes, “generic drugs are three to fifteen times less costly than their brand name counterparts.”<sup>26</sup>

¶ 25 Traditional pharmaceuticals are regulated under the Federal Food, Drug, and Cosmetic Act (FDCA).<sup>27</sup> Under the FDCA, a company must obtain FDA approval prior to commercializing a “new drug.”<sup>28</sup> Approval of a new drug requires completion of a New Drug Application (NDA).<sup>29</sup> A NDA requires that the applicant provide information

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24. 35 U.S.C. § 112 (2000).

25. 21 U.S.C. § 355(a) (2000). In fiscal year 2006, the FDA will charge drug manufacturers \$767,400 for each application requiring clinical data (i.e., New Drug Applications and Biologic License Applications) and \$383,700 for each application not requiring clinical data (i.e., Abbreviated New Drug Applications). Establishment of Prescription Drug User Fee Rates for Fiscal Year 2006, 70 Fed. Reg. 44,109 (Aug. 1, 2005). The pharmaceutical industry estimates that it spent \$14.1 billion on clinical studies and \$4.1 billion on FDA review in 2003. PHARM. RESEARCH AND MFRS. OF AM., PHARMACEUTICAL INDUSTRY PROFILE 2005 4–5 (2005), available at <http://international.phrma.org/publications/publications/2005-03-17.1143.pdf>. As of 2003, the pharmaceutical industry estimated that a drug spent six years in the clinical trial stage and two years in FDA review. *Id.*

26. H.R. REP. NO. 98-857, pt. 1, at 14-20 (1984).

27. 21 U.S.C. §§ 301-99 (2000).

28. 21 U.S.C. § 355(a). The statute requires approval prior to “introduc[ing] or deliver[ing] the new drug] into interstate commerce.” *Id.*

29. *Id.* § 355(b)(1).

on the chemical parts and structure of the drug, information on how the drug is produced and packaged, drug and labeling samples, information on patents covering the drug, and demonstrate that the drug is safe and effective.<sup>30</sup> Demonstrating safety and efficacy requires an extensive amount of data from analytical tests, animal studies, and human clinical studies.<sup>31</sup> This data often takes many years and significant expense to acquire.<sup>32</sup> If the FDA approves the NDA, it publishes the drug and patent information in its *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the *Orange Book*.<sup>33</sup>

¶ 26 The Hatch-Waxman Act accelerates this standard approval process for generic drugs in two manners. First, Hatch-Waxman allows generic firms to file for new drug approval prior to expiration of the patent term.<sup>34</sup> The generic applicant must indicate why making or selling the drug will not infringe on the rights of the patent owner.<sup>35</sup> If the patent owner believes that the generic manufacturer will infringe a valid patent in making and selling the generic version, the patent owner can treat the generic application as an infringement and commence litigation concerning the validity of the relevant patents.<sup>36</sup> Either way, issues concerning the patent owner's exclusivity period can be settled. The generic firm thus can receive the approval and certainty necessary to prepare for production at the expiration of the patent term.

¶ 27 Just as significantly, the Hatch-Waxman Act also simplifies the approval process for generic drugs. Rather than requiring a full NDA, a generic manufacturer may file an Abbreviated New Drug Application (ANDA).<sup>37</sup> If the generic applicant can establish that its drug is equivalent to the already NDA-approved drug, then the generic applicant can rely on the FDA's safety and efficacy conclusion with respect to the NDA-approved pioneer drug.<sup>38</sup> Equivalence generally requires that the generic firm establish that the generic version of the drug is equivalent to the NDA-approved drug in active ingredient, dosage, strength, administration, and labeling.<sup>39</sup> If the ANDA establishes equivalence, the generic manufacturer does not have to separately establish safety and efficacy.<sup>40</sup> This allows generic manufacturers to avoid the significant expense of (repetitive) clinical

30. *Id.*

31. FOOD AND DRUG ADMINISTRATION, CTR. FOR DRUG EVALUATION AND RESEARCH, 2004 REPORT TO THE NATION: IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS 31 (2005), available at <http://www.fda.gov/cder/reports/rtn/2004/Rtn2004.pdf>; Complaint for Declaratory and Injunctive Relief at ¶ 15, *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006) [hereinafter *Sandoz Compl.*].

32. PHARM. RESEARCH AND MFRS. OF AM., *supra* note 23; TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, IMPACT REPORT: ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES (2005), available at <http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/ImpactReportSummaryNovDec2005.pdf> (noting that that drugs spend an average of seven years in clinical studies); PHARM. RESEARCH AND MFRS. OF AM., *supra* note 23, at 4-5 (indicating that the pharmaceutical industry spends more than \$25 billion on pre-clinical and clinical trials before submitting NDAs).

33. 21 C.F.R. §§ 314.3(b), 314.92(b) (2004).

34. 21 U.S.C. § 355(j)(2)(A)(vii)(III) (2003).

35. *Id.* § 355(j)(2)(A)(vii)(I)-(IV).

36. *Id.* § 355(j)(5)(B)(iii).

37. *Id.* § 355(j).

38. *Id.* § 355(j)(2)(A)(iv).

39. *Id.* § 355(j)(2)(A)(i)-(v).

40. *Id.* § 355(j)(2)(A).

trials. ANDA approval thus permits generic manufacturers to avoid the substantial research, development, and clinical study costs of pioneer drugs, allowing generic manufacturers to market their versions of the drug for a far lower price.

¶ 28 The ANDA procedures are contained in Title I of the Hatch-Waxman Act. The pioneer pharmaceutical industry also got something out of Hatch-Waxman. Title II of the Act permits patent owners to apply to have up to five years added onto their patent term to make-up for time lost while awaiting FDA regulatory approval.<sup>41</sup> Extending the exclusivity period allows the patent owner to reap higher monopoly profits for a greater period of time.

¶ 29 The Hatch-Waxman Act thus provides an expedited and less expensive review process for generic versions of traditional patented drugs. This process generally allows generic manufacturers to begin production the moment a pioneer drug goes off-patent, and to sell their generic version of the drug at a far lower price. Production of generic biologics, however, presents a different story.

#### IV. GENERIC BIOLOGICS

¶ 30 The production of generic versions of off-patent biologic products faces two hurdles. The first is legal: the Hatch-Waxman Act has not been interpreted to apply to biologics. The second is scientific: proving the equivalency of a generic biologic to an originally approved biologic is more complex than for conventional pharmaceuticals. Currently, these two hurdles are substantially foreclosing the generic biologic market and are costing consumers and governments billions of dollars a year in unnecessary health care expenses.

##### A. Legal Hurdles for Generic Biologics

¶ 31 The legal hurdles for generic biologics arise due to the regulation of drug approval pursuant to a system developed long before the modern biologics era (and prior even to Crick and Watson's discovery of DNA). This system has resulted in limitations on generic biologics that have little basis in logic.

##### 1. Biologic Regulation

¶ 32 As discussed, traditional pharmaceuticals are regulated as “drugs” under the FDCA.<sup>42</sup> “Drug” is defined broadly under the FDCA to include “[an] article intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man . . . , [or] [an] article (other than food) intended to affect the structure or any function of the body of man . . . .”<sup>43</sup> Biologics, of course, fit within this definition of “drug.” In fact, some

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41. 35 U.S.C. § 156 (2002). The length of time between FDA approval and the termination of the patent may not extend beyond fourteen years. *Id.* § 156(c)(3).

42. 21 U.S.C. § 321(g)(1) (2006); 21 U.S.C. § 355(a) (2003).

43. 21 U.S.C. § 321(g)(1) (2006). The word “article” is not defined in the FDCA or in its regulations.

biologics, particularly the earliest products to receive regulatory approval, were approved as drugs under the FDCA.<sup>44</sup>

¶ 33 Biologics currently, however, are evaluated as “biological products” pursuant to a “biologics licensing application” (BLA) under the Public Health Services Act (PHSA).<sup>45</sup> A “biological product” is defined under the PHSA as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”<sup>46</sup> Biologics fit the definition of biological product under the PHSA as well as the definition of drug under the FDCA.

¶ 34 The distinct approval processes for “drugs” and “biologics” are more the result of historical accident than calculated distinction.<sup>47</sup> The Biologics Control Act, a precursor to the PHSA, was enacted in 1902 to establish pre-market regulatory review for the manufacture of biologic products.<sup>48</sup> In the early 1900s, all biologics were derived from animals, and Congress enacted the Biologics Control Act out of concern about potential negative immunologic side effects of these products given their animal origin and their direct method of administration through injection.<sup>49</sup> The Biologics Control Act regulated “any virus, therapeutic serum, toxin, antitoxin, or analogous product” that was intended for the “prevention and cure of diseases of man.”<sup>50</sup> These biologics, of course, were not genetically manufactured, as modern biologics are. The Biologics Control Act would eventually evolve into the PHSA,<sup>51</sup> and, over a century later, the similarity of the statutory language is striking.

¶ 35 The precursor to the FDCA was the Pure Food and Drugs Act of 1906 (PFDA).<sup>52</sup> The PFDA arose out of concern over the safety of food, a concern highlighted by the infamous meat-packing plant descriptions in Upton Sinclair’s novel *The Jungle*.<sup>53</sup> The PFDA also provided certain regulation over adulterated or misbranded drugs.<sup>54</sup> The drug regulation provisions of the PFDA evolved into pre-market regulatory authority over all “new drugs” with the passage of the FDCA in 1938.<sup>55</sup>

¶ 36 The different regulation of biologics versus other drugs thus arose due to concerns over two distinct issues: concern over the effects of biologics derived from animals and

44. Andrew Wasson, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products*, 2005 DUKE L. & TECH. REV. 4, 9 (2005).

45. 42 U.S.C. § 262(a)(1) (2005).

46. *Id.* § 262(i).

47. See Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps: Crisis in the Regulation of Genetically Modified Plants and Animals*, 45 WM. & MARY L. REV. 2167, 2230–46 (2004) (critiquing the haphazard regulation of biotechnology products under statutes enacted long prior to the products’ existence).

48. Biologics Control Act of 1902, Pub. L. No. 57-244, ch. 1378, 32 Stat. 728.

49. Dudzinski, *supra* note 9, at 147–48.

50. Biologics Control Act §§ 1-4, 32 Stat. at 728–29.

51. Public Health Service Act, Pub. L. No. 78-410, ch. 373, 58 Stat. 682, 702 (1944).

52. Act of June 30, 1906, Pub. L. No. 59-384, ch. 3915, 34 Stat. 768.

53. Dudzinski, *supra* note 9, at 150.

54. *Id.*

55. Act of June 25, 1938, Pub. L. No. 75-717, ch. 675, 52 Stat. 1040.

concern over adulterated food or drugs. As the statutes enacted to protect against these problems evolved, however, they eventually created dual authority over biologics. Biologics fall both within the regulatory purview of the Biologics Control Act (now PHSa) and the FDCA. Congress recognized this regulatory overlap as early as the 1940s.<sup>56</sup> Congress decided, however, to maintain the status quo, although it clarified that biologics only need to obtain a BLA for commercialization of a new product, not also an NDA.<sup>57</sup> This decision implicitly recognizes that receipt of a BLA is sufficient to also satisfy the NDA standards.

¶37 Modern biologics (biologics derived through genetic engineering or recombinant DNA processes as opposed to directly from animals) blur the “biologic”/“drug” distinction even further. They are both biologics (being derived from living organisms) and drugs (they are manufactured for therapeutic effect in humans). Demonstrating the ambiguity of how to characterize modern biologics, the FDA apparently initially expected that such biologics would be evaluated pursuant to NDAs.<sup>58</sup> In fact, the first applications for regulatory approval of biologics created by recombinant DNA technology in the late 1970s were NDAs for recombinant human growth hormone and recombinant human insulin.<sup>59</sup>

¶38 The choice of governing statute, from the perspective of approving a drug for the first time, has little import. The NDA and BLA review processes now are nearly identical—in either case the applicant must establish, through clinical studies and other information, that their product is safe and effective.<sup>60</sup> Over the past decade both Congress and the FDA have moved to harmonize the two approval processes. Efforts by the FDA in the mid-1990s to streamline biologics approval, for instance, included making the BLA approval process more similar to the NDA process.<sup>61</sup> Similarly, in 1997, Congress enacted legislation that codified the BLA requirement for all biologics, reaffirmed that biologics are subject to the FDCA, and instructed the FDA to “minimize differences in the review and approval of products” under BLAs and NDAs.<sup>62</sup>

¶39 The primary differences between the two approval processes are that BLAs must meet additional requirements concerning manufacturing plant inspection and must demonstrate product stability.<sup>63</sup> NDA applicants are required to submit patent information and a statement of the full composition of the drug, requirements that BLA

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56. Dudzinski, *supra* note 9, at 152.

57. 42 U.S.C. § 262(j) (2006).

58. Dudzinski, *supra* note 9, at 162.

59. Stuart L. Nightingale, *Emerging Technologies and FDA Policy Formation: The Impact of Government Regulation on Developing Drugs from New Technologies*, 37 FOOD DRUG COSM. L.J. 212, 215 (1982).

60. 21 U.S.C. § 355(b)(1)(A) (2006); 21 C.F.R. § 601.2(a), (d) (2005).

61. See Well-Characterized Biotechnology Products; Elimination of Establishment License Application, 61 Fed. Reg. 2733, 2733–36 (proposed Jan. 29, 1996).

62. Food and Drug Administration Modernization Act of 1997 § 123(a), (f), (g), 111 Stat. 2296, 2323-24 (codified at 42 U.S.C. § 262(a)) [hereinafter FDAMA]. One provision of this Act raised unresolved issues concerning whether it intended to make ANDA procedures applicable to BLA-approved biologics. Dudzinski, *supra* note 9, at 177.

63. 21 U.S.C. § 355(b)(1); 42 U.S.C. § 262(a)(2)(c)(ii) (2006).

applicants are not subject to.<sup>64</sup> As noted above, that BLA approval is statutorily defined to also satisfy NDA approval reveals that the BLA requirements are effectively at least as rigorous as NDA requirements.

¶ 40 Despite the fact that BLA approval satisfies the NDA requirements, there is one very significant disparity between a BLA approved product and a NDA approved product—the FDA has determined that Hatch-Waxman's expedited approval process does not apply to BLA-approved products.<sup>65</sup>

¶ 41 This FDA decision may not be mandated by the statute. The expedited approval process of Title I of Hatch-Waxman does not mention biologics, and therefore leaves it unclear whether “new drugs” should be interpreted to include biologics.<sup>66</sup> As discussed, the plain language definition of “drug” in the FDCA clearly encompasses biologics. In addition, there is no indication that the congressional decision not to include biologics approved via BLAs within Title I was intentional.<sup>67</sup> Rather, when Hatch-Waxman was enacted in 1984, biologic generics apparently were not on legislators’ radar screens.<sup>68</sup> At that time, only a single biologic created by recombinant DNA technology had received FDA approval.<sup>69</sup>

¶ 42 Title II of Hatch-Waxman, which provides for potential patent term extension for time lost to the regulatory approval process, does explicitly include biologics.<sup>70</sup> This distinction is not entirely surprising, as biologics were already going through the FDA regulatory process at that time. The different treatment of biologics under the two titles does not lend itself to easy interpretation concerning congressional intent. Does the inclusion of biologics in Title II indicate that they should also be covered by Title I, as the basis for Hatch-Waxman was a negotiated agreement allowing pioneer manufacturers to acquire a longer practical patent term in exchange for an expedited approval process for generics?<sup>71</sup> Or does the inclusion of biologics in Title II demonstrate that Congress was sufficiently aware such that biologics must have been intentionally left out of Title I? Both the plain language and analysis of congressional intent are ambiguous concerning whether Congress intended Title I of Hatch-Waxman to apply to biologics.

¶ 43 This ambiguity has not been clarified by subsequent congressional activity. A Senate report on the 1997 legislation directing the FDA to harmonize the BLA and NDA processes stated that harmonization did not apply to generic biologic products, as the

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64. 21 U.S.C. § 355(b)(1); 21 C.F.R. § 601.2(a).

65. 57 Fed. Reg. 17,950, 17,951 (April 28, 1992) (stating that the ANDA procedures are not available for BLA-approved biologics); FDA Letter from Harry M. Meyer, Jr., Director, Ctr. for Drugs & Biologics, Nov. 16, 1984, in *ABBREVIATED NEW DRUG APPLICATIONS* 40 (Peter Barton Hutt & James C. Morrison eds., 1985).

66. Dudzinski, *supra* note 9, at 196 (noting that the express language of Hatch-Waxman does not exclude biologics from the ANDA process).

67. *Id.* at 171, 196.

68. Anand, *supra* note 3.

69. Dudzinski, *supra* note 9, at 167.

70. 35 U.S.C. § 156(f) (2002).

71. See Dudzinski, *supra* note 9, at 171, 196 (discussing the negotiations over Hatch-Waxman).

ANDA authority is not applicable to biologics.<sup>72</sup> But the same 1997 legislation also included a provision directing the Director of Health and Human Services to issue guidance on when abbreviated study reports could be included with a BLA.<sup>73</sup> This provision left unclear whether it impliedly indicated that some form of abbreviated pathway existed for BLA-approved biologics. Apparently, no action was ever taken pursuant to this provision.<sup>74</sup> Statutory language, legislative history, and congressional intent all appear to leave the FDA significant discretion in interpreting whether Hatch-Waxman applies to generic biologics. As discussed, the FDA has concluded it does not apply.

¶ 44 The FDA's decision not to apply Title I of Hatch-Waxman to biologics is essentially the whole ballgame for generic biologic products. Because Hatch-Waxman does not apply, a manufacturer who desires to produce a generic version of an off-patent biologic cannot begin the regulatory approval process until the pioneer biologic's patent has expired and cannot rely on the pioneer biologic's safety and efficacy findings. The generic biologic approval process is therefore much more expensive, lengthy, and uncertain than for conventional generics, and substantially forecloses biologic generics from the market. As a result, biologics approved under the PHSA are receiving functional exclusivity periods far greater than their congressionally enacted patent terms and continue to be sold at monopoly prices long after the expiration of their patent term.

## 2. Legal Solutions for Generic Biologics

¶ 45 The preceding discussion exposes the lack of a reasoned legal basis for the disparate treatment of generic biologics and traditional generics. The following analysis evaluates various avenues for the potential extension of an expedited approval process to generic biologics.

¶ 46 One obvious solution is legislative. Congress could enact legislation explicitly including BLA-approved biologics in Hatch-Waxman's expedited approval scheme (subject to certain restrictions discussed below), or create a separate but similar mechanism for the accelerated approval of biologic generics. It was FDA inaction concerning an expedited process for traditional generics that forced Congress to enact Hatch-Waxman in the first instance, so it may not be surprising that legislative action is required once again.

¶ 47 In February 2007, Representative Waxman, with the support of Senators Schumer and Clinton, introduced the Access to Life-Saving Medicine Act of 2007 (ALMA).<sup>75</sup> ALMA would amend the PHSA to create an expedited approval pathway for generic biologics.<sup>76</sup> A number of Representatives and Senators have expressed support for the

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72. S. REP. NO. 105-43 (1997).

73. FDAMA, *supra* note 62, § 118, 111 Stat. at 2316.

74. Dudzinski, *supra* note 9, at 177-78.

75. Access to Life-Saving Medicine Act of 2007, H.R. 1038, 110th Cong. (2007).

76. *Id.*

bill.<sup>77</sup>

¶ 48 Even absent congressional action, a process for the expedited approval of generic biologics may be available. The PHSA grants the Secretary of the Department of Health and Human Services, who oversees the FDA, the authority to approve licenses for biologics if the biologic product is “safe, pure, and potent” and is manufactured at a facility that assures such a product.<sup>78</sup> On this basis, the Secretary has the authority to provide for the expedited approval of generic biologics to the extent the safety, purity, and potency requirements are met and there is an acceptable statutory pathway. Several routes could achieve this goal.

¶ 49 The first would be an FDA decision to designate BLA-approved biologics as constructively NDA-approved as well. As discussed, biologics fall within the definition of “drug” under the FDCA. Also as discussed, the approval requirements of an NDA are generally harmonized with and subsumed by the requirements of a BLA. One of the primary differences, the submission of patent information, does not relate to safety or efficacy and can be handled through the ANDA process. To the extent there are remaining NDA requirements not satisfied by a BLA, the generic manufacturer could be required to meet these requirements. Once a biologic is designated as NDA-approved, the Hatch-Waxman ANDA process would be available for a biologic generic.

¶ 50 A second approach concerns the products for which the ANDA process already is available. The ANDA process applies to “drug products” as defined pursuant to the Hatch-Waxman Act.<sup>79</sup> FDA regulations provide that ANDAs may be submitted only for drug products that are “listed.”<sup>80</sup> A listed drug, which are those listed in the *Orange Book*, are drugs that either have been approved by the traditional NDA procedure or through an ANDA.<sup>81</sup> The FDA could redefine “drug products” eligible for ANDAs to also include BLA-approved biologics. In this regard, upon petition, the FDA may declare that drugs not listed in the *Orange Book* are amenable to the ANDA process even if those drugs differ from the pioneer version in terms of “route of administration, dosage form, or strength.”<sup>82</sup> The FDA has approved numerous drugs and antibiotics through this

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77. See Waxman, Schumer, and Clinton Unveil Bill to Create Clear Pathway for Generic Biologic Drugs, Feb. 14, 2007, available at [http://www.henrywaxman.house.gov/pdfs/biologicspressrelease\\_2.14.07.pdf](http://www.henrywaxman.house.gov/pdfs/biologicspressrelease_2.14.07.pdf) (including statements of support from a number of Congresspersons). Senator Hatch also has indicated support for such legislation. Anand, *supra* note 3 (stating that Sen. Orrin Hatch is drafting legislation that would create procedures for FDA approval of off-patent biologics); Senator Orrin Hatch before Generic Pharmaceutical Association (Sep. 20, 2005), (transcript available at [http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.Detail&PressRelease\\_id=1434&Month=9&Year=2005](http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.Detail&PressRelease_id=1434&Month=9&Year=2005)) (statement of Sen. Hatch that he planned to add a biologics provision into an appropriation bill requiring the FDA to inform Congress of its attempts to create a regulatory mechanism for approval of generic biologics; the biologics provision apparently was not added).

78. 42 U.S.C. § 262(a)(2)(C) (2006).

79. 21 C.F.R. § 314.92(a) (2000).

80. *Id.* § 314.92(a)(1).

81. *Id.* § 314.3(b). As discussed, the FDA has explicitly excluded BLA-approved biologics from this definition. See *supra* note 63.

82. 21 U.S.C. § 355(j)(2)(C) (2003).

petition process.<sup>83</sup> Extension to biologics would appear appropriate.

¶ 51 The third approach concerns an occasionally invoked statutory provision that provides for somewhat of a hybrid between an NDA and an ANDA.<sup>84</sup> Section 505(b)(2) of the FDCA was enacted as part of Hatch-Waxman and roughly codified an earlier FDA “paper NDA” process.<sup>85</sup> Like the standard NDA procedure, section 505(b)(2) requires an applicant to submit full information on the safety and efficacy of their drug. But, unlike an NDA, section 505(b)(2) allows the applicant to rely on safety and efficacy investigations completed by someone else.<sup>86</sup> A generic biologic manufacturer could therefore submit a section 505(b)(2) application under the FDCA relying on the safety and efficacy studies of the pioneer biologic.

¶ 52 One biologic has been approved pursuant to section 505(b)(2). Sandoz Inc., a company in the Novartis Group, filed a section 505(b)(2) new drug application for approval of a generic version of recombinant human growth hormone called Omnitrope in 2003.<sup>87</sup> Recombinant human growth hormone is one of the few biologics regulated under the FDCA, and therefore provided a particularly attractive test case of the section 505(b)(2) route for generic biologics. Sandoz based its application on a characterization and comparison of its generic version with Pfizer’s pioneer human growth hormone (which Sandoz claimed demonstrated that the two versions were “indistinguishable”) and on the FDA’s prior approval of Pfizer’s biologic as safe and effective.<sup>88</sup> Pfizer petitioned the FDA to deny Sandoz’s application on the grounds that the FDA could not rely on Pfizer’s proprietary data to approve Sandoz’s generic and that the two biologics were different.<sup>89</sup>

¶ 53 On August 31, 2004, the FDA announced that it was postponing a decision on Sandoz’s Omnitrope application, declaring that the FDA was “unable at this time to reach a decision on the approvability because of unresolved scientific and legal issues that relate to [Sandoz’s application].”<sup>90</sup> The FDA noted issues concerning its authority to rely on the safety and efficacy finding of another manufacturer’s product and identified upcoming FDA workshops in late 2004 and early 2005 to consider these issues generally.<sup>91</sup> These workshops passed and the FDA still did not act, leading Sandoz to file a lawsuit against the FDA in federal district court seeking to require the FDA to act on its

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83. See Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, OGD Suitability Tracking Report, <http://www.fda.gov/cder/ogd/DrugSortpage.htm> (last visited Oct. 28, 2006).

84. Section 505(b)(2) has been used approximately 80 times. Dudzinski, *supra* note 9, at 199.

85. *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

86. 21 U.S.C. § 355(b)(2)(A).

87. Sandoz Compl., *supra* note 31, ¶ 66.

88. *Id.* ¶¶ 67–70, 83.

89. *Pfizer Petitions FDA to Deny Application for Growth Hormone Copy*, 10 FDA WEEK No. 23 (Jun. 4, 2004). There is no infringement issue in this case, as the patent on the pioneer biologic was held invalid and unenforceable. *Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp.*, 424 F.3d 1347, 1349 (Fed. Cir. 2005) (holding Claim 1 of the patent invalid and the entire patent unenforceable for inequitable conduct).

90. Dar Haddix, *Sandoz Files Lawsuit Against FDA to Force Decision on Omnitrope*, 22 GENERIC LINE No. 18 (2005); Sandoz Compl., *supra* note 31, ¶ 114.

91. Sandoz Compl., *supra* note 31, ¶¶ 118–22.

application.<sup>92</sup> In April 2006, the District Court ordered the FDA to act on Sandoz's Omnitrope application.<sup>93</sup>

¶ 54 In May 2006, the FDA approved Sandoz's 505(b)(2) Omnitrope application, but did so by concluding that Omnitrope was "sufficiently similar" to Pfizer's pioneer human growth hormone, rather than determining that the drugs were bioequivalent.<sup>94</sup> The FDA explicitly stated that the Omnitrope approval did not create a direct precedent for approval of other generic biologics, and that the section 505(b)(2) approval pathway could not be used for biologics originally approved pursuant to a BLA under the PHSA.<sup>95</sup> The FDA also emphasized that the specific human growth hormone biologic in this case was particularly well characterized and well understood.<sup>96</sup>

¶ 55 Pfizer's petition to the FDA to deny Sandoz's application in part challenged the potential use of Pfizer's "proprietary data."<sup>97</sup> The pioneer pharmaceutical and biotechnology industries generally contend that basing an expedited approval process for generic biologics on the safety and efficacy data of the pioneer biologic would constitute a Fifth Amendment taking of the pioneer manufacturer's property interest in its confidential data.<sup>98</sup> As Professor Yoo has argued, this contention appears to have limited merit.<sup>99</sup> First, in approving a generic biologic, the FDA need not rely on the pioneer manufacturer's actual data, but only on the fact of the FDA's approval of the biologic as satisfying safety and efficacy requirements, just as it does under Hatch-Waxman for traditional pharmaceuticals.<sup>100</sup> Pioneer manufacturers have no property interest in this public fact. Second, to the extent the FDA needs to consider the pioneer's confidential safety and efficacy data, the pioneer has no "reasonable investment-backed expectations" in preventing the FDA from considering this data, which is the general requirement for a regulatory taking of property.<sup>101</sup> In particular, the FDCA provides no assurances "regard[ing] . . . the use of application data for the approval of subsequent applications."<sup>102</sup> Third, any pioneer property interest in data would appear to be even

92. *Id.* ¶ 1. The FDA has filed a motion to dismiss based on Sandoz's failure to exhaust administrative remedies. Dar Haddix, *FDA May Fear Setting Precedent for PHS Act Biogeneric Approvals*, 22 *GENERIC LINE* No. 23 (2005).

93. Sandoz v. Leavitt, 427 F. Supp. 2d 29 (D.D.C. 2006).

94. *FDA Approves First Biologic Copy Made by a Generic Competitor*, *FDA WEEK*, June 2, 2006; *Omnitrope (somatropin [rDNA origin]) Questions and Answers*, available at <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>.

95. *FDA Approves First Biologic Copy Made by a Generic Competitor*, *FDA WEEK*, June 2, 2006. Despite the FDA's proclamations, Sandoz intends to seek further section 505(b)(2) approvals for generic biologics. Cassell, *supra* note 10.

96. *FDA Approves First Biologic Copy Made by a Generic Competitor*, *FDA WEEK*, June 2, 2006; *Omnitrope (somatropin [rDNA origin]) Questions and Answers*, available at <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>.

97. *Pfizer Petitions FDA to Deny Application for Growth Hormone Copy*, *supra* note 84.

98. John C. Yoo, *Takings Issues in the Approval of Generic Biologics*, 60 *FOOD & DRUG L.J.* 33, 34 (2005); Letter from Pharm. Research and Mfrs. of Am. to U.S. Food and Drug Admin. 1, 15–18 (Nov. 12, 2004) [hereinafter *PhRMA Letter*].

99. Yoo, *supra* note 98, at 33.

100. *Id.* at 40.

101. *Id.* at 39–43.

102. *Id.* at 40.

more limited after a patent has expired.

¶ 56 The FDA has approved other biologics pursuant to section 505(b)(2), but these cases generally have involved pioneer developers changing their own biologics, not manufacturers relying on other firms' data.<sup>103</sup> The one exception, prior to the Omnitrope approval, was a section 505(b)(2) application by Unigene for the generic biologic Fortical. In their application, Unigene relied on the safety and efficacy data of the previously approved Novartis osteoporosis drug Miacalcin.<sup>104</sup> The Fortical application was opposed, not by Novartis,<sup>105</sup> but by an anonymous challenger on the basis that there was insufficient safety and efficacy data for Fortical.<sup>106</sup> The FDA denied the opposition, concluding that Unigene had demonstrated the bioequivalence of the active ingredients of Fortical and Miacalcin.<sup>107</sup> The active ingredient in Miacalcin had a simple structure that lent itself to characterization, and the structure of the active ingredient in Fortical was found to be identical or indistinguishable.<sup>108</sup> The FDA reached this conclusion despite the fact that the two pharmaceuticals are derived by different processes—Miacalcin is a synthetically manufactured chemical drug whereas Fortical is a recombinant product.<sup>109</sup>

¶ 57 Language in the FDA's letter denying the opposition to the Fortical 505(b)(2) application was viewed by some as laying the groundwork for an expedited route for generic biologics generally. The FDA letter reasoned:

The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to public health. In addition, the conduct of duplicative studies raises ethical concerns because it could subject human beings and animals to medically or scientifically unjustified testing.<sup>110</sup>

¶ 58 This reasoning and some other statements appeared to indicate that the FDA was

103. *FDA Approves First Biologic Copy Made by a Generic Competitor*, FDA WEEK, June 2, 2006.

104. Letter from Unigene Laboratories to the Food and Drug Admin. 1 (Apr. 11, 2005), available at [http://www.fda.gov/ohrms/dockets/dockets/04p0015/04P-0015\\_emc-000002-01.pdf](http://www.fda.gov/ohrms/dockets/dockets/04p0015/04P-0015_emc-000002-01.pdf).

105. The author of the citizen petition opposing the Fortical application would not identify who she represented. Novartis, the owner of Sandoz, supports the development of an expedited approval process for generic biologics. The Fortical 505(b)(2) application, and certainly Novartis' lack of opposition, may have been a strategic effort by Novartis to enhance the likelihood of FDA approval of Sandoz's 505(b)(2) application. See *505(b)(2) Approval May Augur FDA's Biogeneric Policy Arguments*, FDA WEEK, Aug. 26, 2005.

106. Letter from Buc & Beardsley to the Food and Drug Admin. 1 (Jan. 9, 2004), available at <http://www.fda.gov/ohrms/dockets/dockets/04p0015/04p-0015-cp00001-vol1.pdf>. This opposition letter did not raise a Fifth Amendment takings argument (which is further evidence that the opposition was not raised by Novartis, the only entity that could have a property interest in the Miacalcin safety and efficacy data).

107. Letter from the Food and Drug Admin. to Buc & Beardsley 4 (Aug. 12, 2005), available at <http://www.fda.gov/ohrms/dockets/dockets/04p0015/04p-0015-pdn0001-vol1.pdf> [hereinafter FDA Letter].

108. *Id.* at 8. The FDA also found that the active ingredient in Fortical was at least as bioavailable and had virtually identical immunogenicity to Miacalcin. *Id.* at 10–11.

109. *Id.* at 8–11; *505(b)(2) Approval May Augur FDA's Biogeneric Policy Arguments*, *supra* note 95.

110. FDA Letter, *supra* note 107, at 3.

considering a section 505(b)(2) expedited pathway for generic biologics,<sup>111</sup> and the FDA has received pressure from both federal legislators and state governors,<sup>112</sup> but the language of the Sandoz approval shows that the FDA is not about to establish a generic pathway yet.<sup>113</sup>

## B. Scientific Hurdles for Generic Biologics

¶ 59 The scientific and medical concerns surrounding generic biologics raise more legitimate issues than the legal arguments. Assuming that there is a regulatory path for the expedited approval of generic biologics, there still is the question of whether generic biologics can establish equivalency. If a generic biologic cannot establish equivalence to a pioneer biologic, then the generic cannot rely on the pioneer's safety and efficacy data, and new clinical trials would be required. This consequence is expensive and time-consuming and would effectively eliminate the prospect of generic biologics in most instances.

¶ 60 The active ingredients of most conventional drugs are small, relatively simple, homogeneous molecules.<sup>114</sup> Small molecule drugs are relatively easy to characterize and duplicate.<sup>115</sup> As a result, scientists can examine an asserted duplicate of a small molecule drug to test whether it is an identical product.<sup>116</sup> Small molecule drugs are relatively easy to copy and test for equivalence.

¶ 61 Biologics are generally more complex, heterogeneous, and larger-molecule drugs than conventional pharmaceuticals.<sup>117</sup> As a result, biologics are harder to precisely characterize than traditional small-molecule drugs.<sup>118</sup> In addition, the particular structure of biologic products depends significantly on the process by which they are manufactured.<sup>119</sup> Slight changes in the production process, such as in temperature,

111. Dudzinski, *supra* note 9, at 219; *505(b)(2) Approval May Augur FDA's Biogeneric Policy Arguments*, *supra* note 109; PhRMA Letter, *supra* note 98, at 5-6.

112. Stephanie Saul, *States, Bridling at Insulin's Cost, Push for Generics*, N.Y. TIMES, Jan. 11, 2007, at A1; Marilyn Serafini, *A New Front on Drug Costs*, NAT'L J., Feb. 10, 2007.

113. *FDA Approves First Biologic Copy Made by a Generic Competitor*, FDA WEEK, June 2, 2006; *Omnitrope (somatropin [rDNA origin]) Questions and Answers*, available at <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>.

114. Dudzinski, *supra* note 9, at 154-56. Examples include aspirin, acetaminophen, Benadryl, Prilosec, and Sudafed. *Id.*

115. Bruce Kuhlik, *The Assault on Pharmaceutical Intellectual Property*, 71 U. CHI. L. REV. 93, 95 (2004).

116. Dudzinski, *supra* note 9, at 155.

117. PHARM. RESEARCH AND MFRS. OF AM., PhRMA SCIENTIFIC COMMENTS FOR DOCKET # 2004N-0355, at 3 (2004) [hereinafter PhRMA SCIENTIFIC COMMENTS].

118. *Id.* See Anna Wilde Matthews & David P. Hamilton, *FDA Takes Step Toward Allowing Generic Versions of Biotech Drugs*, WALL ST. J., Feb. 18, 2004, at A1 ("Biotech companies argue that their medicines are too complex and prone to unexpected variations [to be reliably duplicated].").

119. Christian Combe et al., *Biosimilar Epoetins: An Analysis Based on Recently Implemented European Medicines Evaluation Agency Guidelines on Comparability of Biopharmaceutical Proteins*, 25 PHARMACOTHERAPY 954, 956 (2005); Huub Schellekens, *Follow-on Biologics: Challenges of the 'Next Generation'*, NEPHROLOGY, DIALYSIS, TRANSPLANTATION (Supp. 4) 20 (2005); PhRMA SCIENTIFIC COMMENTS, *supra* note 117, at 4

timing, or purification conditions, can have significant effects on the final product.<sup>120</sup> Not only might a slightly different manufacturing process produce a different biologic, but that difference might be one that scientists are unable to detect.<sup>121</sup> Large molecule biologics can be hard to duplicate, characterize, and test for equivalence. Consequently, the equivalence of generic biologics to pioneer biologics sometimes cannot be confirmed. Non-equivalent biologics may not only fail to work, but also could cause serious side-effects.<sup>122</sup>

¶ 62 Though these comparability concerns certainly exist for some medical biologics, the scope of concern also can get exaggerated.<sup>123</sup> The technical question of equivalence may pose an obstacle for certain complex products, such as those used to treat cancer and autoimmune diseases, which cannot yet be precisely characterized or controlled in manufacture.<sup>124</sup> But there are many simpler biologics that can be accurately characterized and tested, or that are not susceptible to manufacturing uncertainty.<sup>125</sup> These simpler biologics include various nucleic acids and proteins, particularly some that could replace natural proteins in the body, such as human growth hormone, insulin, EPO, and monoclonal antibodies.<sup>126</sup> As long as a given biologic can be precisely characterized, or tested for equivalence, or copied in manufacturing, equivalence can be scientifically confirmed.

¶ 63 Belying pioneer industry's contentions that equivalency cannot be demonstrated, some of the same companies and industry groups that make these arguments also have

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120. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY, EXPOSURE-RESPONSE RELATIONSHIPS—STUDY DESIGN, DATA ANALYSIS, AND REGULATORY APPLICATIONS (2003) (“[C]hanges in the [biologic] manufacturing process often lead to subtle unintentional changes in the products, resulting in altered pharmacokinetics.”); PhRMA SCIENTIFIC COMMENTS, *supra* note 117, at 4-5.

121. Combe et al., *supra* note 119, at 954-55; Schellekens, *supra* note 119, at iv33, iv35; PhRMA SCIENTIFIC COMMENTS, *supra* note 117, at 6, 8.

122. PhRMA SCIENTIFIC COMMENTS, *supra* note 117, at 9-10. *See also* Schellekens, *supra* note 107, at iv33-34.

123. *See, e.g.*, Kuhlik, *supra* note 115, at 105 (Senior Vice President and General Counsel of the Pharmaceutical Research and Manufacturers of America writing, “the complexities of biological product manufacturing and testing would make any determination of comparability between different manufacturer’s products daunting, if not impossible.”); PhRMA SCIENTIFIC COMMENTS, *supra* note 117, at 6-10.

124. Dudzinski, *supra* note 9, at 186. *See* Testimony of Sara Radcliff, Managing Dir., Science & Regulatory Affairs, Biotechnology Indus. Org., (Sept. 4, 2004), available at <http://www.bio.org/healthcare/followon/fdatestimony.asp> (explaining the difficulty in proving equivalence for protein-based biological products); Food and Drug Admin., Gleevec Questions and Answers, <http://www.fda.gov/cder/drug/infopage/gleevec/qa.htm> (last visited Oct. 28, 2006); Medline Plus Drug Information, Influximab Injection, <http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a604023.html> (last visited Oct. 28, 2006) (identifying treatments for autoimmune disease and cancer as complex biologics).

125. *The Law of Biologic Medicine Hearing Before the S. Comm. on the Judiciary*, 108th Cong. (statement of Lester Crawford, Acting Comm’r, Food and Drug Admin.) (2004), available at <http://www.fda.gov/ola/2004/fob0623.html>; Dudzinski, *supra* note 9, at 186-93, 222-23; Generic Pharmaceutical Association, *GPhA: Consumers Need Access to Affordable Biopharmaceuticals*, [http://www.prnewswire.com/cgi-bin/micro\\_stories.pl?ACCT=913120&TICK=GPHA&STORY=/www/story/02-16-2005/0003025278&EDATE=Feb+16,+2005](http://www.prnewswire.com/cgi-bin/micro_stories.pl?ACCT=913120&TICK=GPHA&STORY=/www/story/02-16-2005/0003025278&EDATE=Feb+16,+2005) (last visited Oct. 28, 2006).

126. Dudzinski, *supra* note 9, at 186-91, 224-29.

criticized the FDA for being overly demanding in licensing additional biologic manufacturing facilities for previously approved biologics.<sup>127</sup> Similarly, the FDA has allowed pioneer manufacturers to change their manufacturing processes without requiring new clinical trials,<sup>128</sup> at times only requiring a laboratory demonstration of equivalence.<sup>129</sup> In these cases, pioneer industry has contended that they can characterize their end products and manufacturing processes precisely enough to ensure identical agents at different facilities or through different processes.<sup>130</sup>

¶ 64 Also supporting the argument that there can be a safe expedited approval process for certain generic biologics, the European Agency for the Evaluation of Medicinal Products (EAEMA), the FDA's counterpart in Europe, has instituted a "biosimilar" standard to evaluate generic biologics.<sup>131</sup> The EAEMA already has approved a generic version of a human growth hormone biologic.<sup>132</sup>

¶ 65 The FDA is receiving stepped up pressure to act to resolve the regulatory problems in this area,<sup>133</sup> but no action has been taken to date. The FDA's failure to act here is eerily similar to the FDA's failure to institute an expedited generic approval pathway prior to Congress' mandating it by passing Hatch-Waxman in 1984. Congress criticized the FDA for its failure then: "While the FDA has been considering since 1978 an . . . ANDA policy . . . , it has not [done so]. Because of the agency's failure to act, [Hatch-Waxman] is necessary."<sup>134</sup> History may be repeating itself.<sup>135</sup>

### C. Patent Invalidity for Non-Enablement

¶ 66 What is most striking about pioneer industry's contention that equivalence cannot be established for generic biologics is that this argument actually (and apparently unintentionally) concedes that certain pioneer patent claims are not valid. To the extent that generic manufacturers cannot replicate pioneer biologics, the pioneer patents are not fully enabling; the patents do not allow a person having ordinary skill in the art to make

127. Alison McCook, *Manufacturing on a Grand Scale*, SCIENTIST, Feb. 2005, at 34.

128. Anand, *supra* note 3.

129. *Id.*

130. *Id.*; McCook, *supra* note 127, at 34.

131. DrugResearcher.com, EU Accepts BioPartner's Interferon as First "Biosimilar" Filing, Oct. 24, 2004, <http://www.drugresearcher.com/news/ng.asp?id=55616>. Sandoz filed an application for approval of Omnitrop, a generic version of human growth hormone, with the EAEMA, but the application was denied. *News in Brief*, NATURE BIOTECHNOLOGY, May 2004, at 497.

132. Sabine Louët, *Lessons from Eprex for Biogeneric Firms*, 21 NATURE BIOTECHNOLOGY 956, 956-57 (2003).

133. See, e.g., *Waxman, Schumer, and Clinton Unveil Bill to Create Clear Pathway for Generic Biologic Drugs*, Feb. 14, 2007, available at [http://www.henrywaxman.house.gov/pdfs/biologicspressrelease\\_2.14.07.pdf](http://www.henrywaxman.house.gov/pdfs/biologicspressrelease_2.14.07.pdf); *Hatch Addresses Generic Pharmaceutical Association*, Mar. 2, 2007, available at [http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.View&PressRelease\\_id=1751](http://hatch.senate.gov/index.cfm?FuseAction=PressReleases.View&PressRelease_id=1751); 148 CONG. REC. S7875, S7877-78 (Aug. 1, 2002) (statement of Sen. Orrin Hatch urging the FDA to address the necessary issues to create an approval pathway for generic biologics); S. 2677, 107th Cong. (2002), 148 CONG. REC. S6015, S6019, S6021-22 (Jun. 25, 2002) (bill introduced by Sen. Jay Rockefeller to provide for studying the feasibility of generic biologics); *supra* note 112.

134. H.R. REP. NO. 98-857, pt. 1, at 16 (1984).

135. Access to Life-Saving Medicine Act of 2007, H.R. 1038, 110th Cong. (2007).

the patented subject matter. This failure renders the patents invalid.

¶ 67 In order to obtain a patent, a patent application must enable persons having ordinary skill in the art “to make and use” the invention.<sup>136</sup> The enablement requirement serves multiple purposes. First, it enforces the disclosure requirement of a patent—a patent only is granted in exchange for disclosure of the invention to the public.<sup>137</sup> Second, the enablement requirement helps to delimit the boundaries of a patent by ensuring that the scope of the claims accord with the inventor’s contribution.<sup>138</sup>

¶ 68 The leading Supreme Court case on enablement concerns an electric light invention by Thomas Edison. Sawyer and Man held a patent claiming an “incandescing conductor for an electric lamp, of carbonized fibrous or textile material.”<sup>139</sup> Sawyer and Man had actually used carbonized paper in their particular incandescent lamp, but claimed all “carbonized fibrous or textile material” in their patent.<sup>140</sup> Edison independently discovered that a particular species of bamboo, when carbonized, was the best filament.<sup>141</sup> Sawyer and Man sued the Edison Electric Light Company for infringing their patent because carbonized bamboo is a “carbonized fibrous or textile material,” and therefore fell within their patent claims.<sup>142</sup> The Supreme Court held that Edison’s use of carbonized bamboo did not infringe the Sawyer and Man patent because, even though covered by the claim language, it was not enabled by the patent disclosure: “If the description be so vague and uncertain that no one can tell, except by independent experiments, how to construct the patented device, the patent is void.”<sup>143</sup>

¶ 69 Thus, even if a patent provides certain ways to make and use the patented subject matter, it does not satisfy the enablement requirement unless it enables the full scope of the claimed invention.<sup>144</sup> The teaching necessary for enablement does not need to be contained entirely within the patent; enablement may rely on the knowledge available to a person having ordinary skill in the art and on some experimentation by that person.<sup>145</sup> However, if a patent requires an “undue” amount of experimentation in order to practice the invention, the patent is not enabled.<sup>146</sup> “[T]he specification must teach those of skill

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136. 35 U.S.C. § 112 (1994).

137. *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1344 (Fed. Cir. 2005).

138. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (“[A]s part of the quid pro quo of the patent bargain, the applicant’s specification must enable one of ordinary skill in the art to practice the full scope of the claimed invention.” (citing *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993))); *ADELMAN ET AL., CASES AND MATERIALS ON PATENT LAW* 447 (2d ed. 2003).

139. *Consolidated Elec. Light Co. v. McKeesport*, 159 U.S. 465, 468 (1895).

140. *Id.*

141. *Id.* at 473.

142. *Id.* at 471–72.

143. *Id.* at 474.

144. *Invitrogen Corp. v. Clontech Lab., Inc.*, 429 F.3d 1052 (Fed. Cir. 2005); *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (“[S]pecification must enable one of ordinary skill in the art to practice the full scope of the claimed invention.” (citing *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993))); *MANUAL OF PATENT EXAMINING PROCEDURE* § 706.03(c) (“The PTO will make a scope of enablement rejection where the written description enables something within the scope of the claims, but the claims are not limited to that scope.”) [hereinafter *MPEP*].

145. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

146. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

in the art ‘how to make and how to use the invention as broadly as it is claimed.’”<sup>147</sup>

¶ 70 Under pioneer industry’s own arguments, it appears that many of their biologic patents fail enablement. Pioneer industry contends that generic manufacturers cannot duplicate the biologics produced by pioneer firms—that generic manufacturers cannot make the product produced by the pioneer. The generic manufacturers are not enabled.

¶ 71 It is true that some portions of the patented subject matter are enabled: persons having ordinary skill in the art can make some form of the biologic that is claimed. But, generic manufacturers cannot make all forms of the claimed invention—e.g., they cannot make the form that the pioneer manufacturer produces—and enablement requires that persons having ordinary skill in the art be able to make the full scope of the claimed invention. Pioneer firms appear caught in a Catch-22: either they must concede that generic manufacturers can produce equivalents of pioneer biologics, or pioneer biologic patents are not enabled.

¶ 72 Early in the biotechnology revolution it was recognized that certain biological claims could not be enabled solely by means of a written description where the biological material necessary to produce the claimed product was not commonly available.<sup>148</sup> For these reasons, patent applicants are permitted to deposit biological material in an independent depository that will make samples available to members of the public in an effort to satisfy the enablement requirement.<sup>149</sup> Deposit of biological material thus can serve as a means of enabling a person having ordinary skill in the art to make the invention by providing necessary starting material that otherwise would not be available to the person having ordinary skill in the art without undue experimentation.<sup>150</sup>

¶ 73 Deposit, however, generally will not solve the biologics enablement problem discussed here. To the extent that the deposited biological material has to be altered at all

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147. *In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993) (citing *Vaeck*, 947 F.2d at 496).

148. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200 (Fed. Cir. 1991); *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988) (“Where an invention depends on the use of living materials . . . , it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure.”); *In re Lundak*, 773 F.2d 1216, 1220 (Fed. Cir. 1985) (“When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification.”).

149. 37 C.F.R. § 1.801 (1989); MPEP § 2402; *Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345–46 (Fed. Cir. 2000); *Wands*, 858 F.2d at 735 (“One means that has been developed for complying with the enablement requirement is to deposit the living materials in cell depositories which will distribute samples to the public who wish to practice the invention after the patent issues.”). The Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure requires signatory countries, like the United States, to recognize a deposit with any depository that has been approved by the World Intellectual Property Organization. Budapest Treaty on the International Recognition of the Deposit of Microorganisms, art. 3, Apr. 28, 1977, available at <http://www.dsmz.de/patents/bptreaty.htm>.

150. *Invitrogen Corp. v. Clontech Lab., Inc.*, 429 F.3d 1052 (Fed. Cir. 2005); *Wands*, 858 F.2d at 735 (“A deposit has been held necessary for enablement where the starting materials (i.e., the living cells used to practice the invention, or cells from which the required cells can be produced) are not readily available to the public. Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the cells of the invention from the starting materials.”).

to achieve the claimed product (or any product falling within the claims), the accuracy of these alterations cannot be guaranteed or validated, according to pioneer industry's non-equivalence arguments. Therefore, the full scope of the claims is not enabled. Deposit by itself does not satisfy the enablement requirement; it is only a means for the patent owner to provide unavailable biological material so that a person having ordinary skill in the art can make the invention.<sup>151</sup> Deposit is not a substitute for actually enabling a patent.<sup>152</sup> Deposit alone can only satisfy enablement in the specific case where the deposited material (and only the deposited material) is what is actually claimed, and the deposited material is capable of self-replication. In this precise case, the applicant has enabled others to make the invention through placing it in a publicly available depository.

¶ 74 One may foresee a particular challenge to the enablement problems identified here—that we actually are unsure whether they are enabled or not. A crafty pioneer manufacturer may argue that the problem with expedited approval for generic biologics is not that they are definitively not equivalent, but that we do not know and cannot tell whether they are equivalent or not. This distinction may be critical. An issued patent is presumed valid.<sup>153</sup> The party challenging a patent for failing enablement has the burden of proving (by clear and convincing evidence) that the patent disclosure is not enabling.<sup>154</sup> In our context, this would mean that a generic firm would have to demonstrate that it cannot duplicate the pioneer biologic. For the reasons discussed above, in a certain sense a challenger could not meet this burden because scientists cannot tell whether the generic biologic is equivalent or not. Such a result, however, would be contrary to the goals and requirement of enablement. A person having ordinary skill in the art who cannot know whether he or she has made an invention has not been informed “how to make” the invention.

¶ 75 This enablement argument should not be read to indicate that medical biologic patents should generally be held non-enabling. Rather it may indicate that patent law needs to be revised with respect to the biologic enablement. Current enablement doctrine indicates that certain complex protein claims can never be fully enabled under the existing state of science—a drastic and highly problematic result.

¶ 76 The enablement problem arises because any actual embodiment of biologic subject matter is so dependent on nuances in manufacturing processes that outcome products are not reproducible by others, and scientists will not be able to tell whether they have been reproduced for complex molecules. Where this is the case, a solid argument can be made that patent doctrine should be revised to make such claims enabling. Any such change, however, may require legislative action. Section 112 of the Patent Act

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151. *Ajinomoto*, 228 F.3d at 1345-46; *In re Argoudelis*, 434 F.2d 1390 (C.C.P.A. 1970); MPEP § 2402.

152. The Federal Circuit has held that deposit satisfies the written description requirement. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). The written description requirement, however, pertains to whether the applicant possessed the invention claimed—i.e., recognized what the claims encompassed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). This requirement, unlike enablement, may be actually accomplished by deposit of biological materials.

153. *Eureka Co. v. Bailey Co.*, 78 U.S. 488, 491 (1871).

154. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931 (Fed. Cir. 1990).

requires the patent specification to inform a person having ordinary skill in the art how to make the invention; it would be hard to interpret this language not to require enablement of the full scope of the claimed subject matter.

¶77 Any revision to change in enablement law, in addition, should be narrowly limited. As discussed, pioneer firms contend that they can reproduce manufacturing facilities and processes so precisely that they can ensure production of equivalent biologics at alternate facilities and using alternate processes. Where this is the case, if correct, it means that enablement can be accomplished in these instances. The firms have simply chosen not to include enough manufacturing information in their patents to provide for reproduction. In these instances, manufacturers should not be allowed to both keep their manufacturing processes secret and also be entitled to an exception to the full scope enablement requirement. Any exception to the enablement requirement for complex biologics should be strictly limited to instances where the patent owners disclose all they know about manufacturing the biologic and the owners themselves cannot make equivalent versions of their own biologic.

## V. CONCLUSION

¶78 The spiraling cost of health care rates is one of the nation's leading concerns. Generic biologics offer one part of a solution to this problem, potentially saving consumers and governments billions of dollars annually. There is no reasoned basis for a status quo under which potentially safe and effective generic versions are effectively foreclosed for most biologic products. An expedited approval process for generic biologics can be established immediately for any biologic that can be either accurately characterized or tested, or which is not susceptible to problematic manufacturing variation. Considering the FDA's existing responsibility in initially approving biologics as safe and effective, there is no reason that the FDA cannot serve as a gatekeeper to determine which generic biologics can establish equivalence and which cannot.

¶79 One means of promoting the goal of generic biologics is the enablement quandary presented in this article. The main arguments that the pioneer pharmaceutical and biotechnology industry assert against the safety of generic biologics actually demonstrate that the industry's own patents are not valid. Pioneer industry must either concede the limitations of their arguments or disclaim their patents. Pressing this point may force some movement on the generic biologic front.