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THE REGULATION OF BIOLOGIC MEDICINE: INNOVATORS' RIGHTS AND ACCESS TO HEALTHCARE

Dawn Willow*

I. The Importance of Biologic Medicine

The 21st century heralds the “biotech revolution” where biologic¹ medicinals promise cures for some of the most complex diseases. Currently, over 370 innovative biologic products are being tested, targeting more than 200 diseases, including cancers, neurological disorders, heart disease, diabetes, multiple sclerosis, AIDS and arthritis.² The biopharmaceutical industry represents one of the fastest growing segments of U.S. healthcare. From 1998 to 2002, the biopharmaceutical market has “outperformed the pharmaceutical market, increasing at a compound annual growth rate of almost 28 percent, compared with 14 percent for the remainder of the pharma market.”³ Moreover, analysts estimate that by 2010 biologic sales will exceed \$60 billion.⁴

Biopharmaceuticals are a major factor in ever-increasing prescription drug costs; these costs will only escalate as new biopharmaceuticals are added to the market. From 1998 to 2002, the monoclonal antibodies category of biologics has “grown at a compound annual rate of 63 percent, reaching sales of \$4 billion in 2002.”⁵ In 2003, six biotech pharmaceuticals, Procrit, Epogen, Neupogen, Intron-A, Humulin and Rituxan, generated sales of more than \$9.5 billion. The top three biotech pharmaceuticals, Neupogen, Epogen and Intron-A, cost at least \$15,000, \$10,000 and \$22,000 per patient, per year, respectively. Cerezyme, a biopharmaceutical drug product for an enzyme deficiency, costs over \$170,000 per patient, per year.⁶ By the end of 2006, an estimated \$13.5 billion worth of biopharmaceuticals are scheduled to go off-patent.⁷ Evidently, generic⁸ competition for biologics has the potential to offer consumers substantial savings and to lower America’s overall healthcare bill.

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¹ “Biopharmaceutical(s),” “biologic product(s)” and “biologic medicine” will be used interchangeably in the paper to mean “biologics.”

² Kevin Bibby et al., *Biopharmaceuticals – Moving to Center Stage*, IMS Health Incorporated, June 2003.

³ *Id.*

⁴ Table 7: Domestic Sales and Abroad, PhRMA Member Companies: 1970-2003, Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2004; See also Pharmaceutical Research and Manufacturers of America (PhRMA). *Pharmaceutical Industry Profile 2004* (Washington, DC: PhRMA, 2004).

⁵ *Id.*

⁶ David Ranii, High Cost of Living Well, *The News and Observer*, May 13, 2003, at page number.

⁷ Maureen A. Rouhi, Generics Next Wave: Biopharmaceuticals, *Chemical & Engineering News*, Sept.23, 2002, at 61-65.

⁸ When patents expire, other companies can make drugs, known as “generics,” using the same active ingredient. This paper will use the terms “generic(s)” and “follow-on(s)” synonymously.

By far, the U.S. is the most mature market for biologics with the largest number of products available, many of which have long track records.⁹ Earlier this year, an article in *Health Affairs* reported that prescription drugs accounted for 16 percent of total health care spending increases in 2002.¹⁰ In 2003, HMOs responding to the Milliman USA 2003 HMO Intercompany Rate Survey had average premiums of \$238.70 per member per month, of which outpatient prescription medicines accounted for 14.8 percent.¹¹ Innovative brand-name medicines account for approximately 7 percent of total health care spending and generics account for 3 percent.¹²

Currently, there are more than a dozen biopharmaceuticals for which U.S. patents have expired or will expire by 2006.¹³ The original or first version of a biologic is often referred to as the “pioneer” or innovator drug.¹⁴ The companies that market brand-name products contend that because biologics are not approved as new drugs, they should not be subject to the provisions under which the FDA currently approves new generic drugs. Furthermore, many innovators take the position that an approval system may be altogether impossible for biologics because it would compromise scientific integrity and violate intellectual property rights.

The Drug Price Competition and Patent Term Restoration Act of 1984¹⁵ (the “Hatch-Waxman Act”) established the regulatory framework for generic versions of brand drugs regulated under the Federal Food, Drug, and Cosmetic Act (“FD&C Act”). As a result of this law, there are more than 7,600 generic versions of the approximately 10,375 FDA-approved pharmaceuticals.¹⁶ The Generic Pharmaceutical Association (“GPhA”) is a trade association whose 120 members produce more than 90 percent of all generic drugs sold in the U.S. In 1984, generic drugs accounted for less than 19 percent of all filled prescriptions. Today, generic drugs represent more than 51 percent of all prescriptions dispensed in the United States.¹⁷ The federal government is the largest consumer of prescription drugs, purchasing approximately 12% of all prescription drugs (costing nearly \$21 billion in 2002).¹⁸ The generic pharmaceutical industry believes that the savings resulting from competition can be similarly applied to the biopharmaceutical industry.

⁹ Kevin Bibby et al., *Biopharmaceuticals – Moving to Center Stage*, IMS Health Incorporated, June 2003.

¹⁰ Katharine Levit et al., Health Spending Rebound Continues in 2002, 23 *Health Affairs*, No. 1 (2004), at 147-159.

¹¹ Milliman USA, 2003 HMO Intercompany Rate Survey (2003).

¹² Centers for Medicare & Medicaid Services, National Health Expenditures, Jan. 8, 2004, <http://www.cms.hhs.gov/statistics/nhe>.

¹³ *Generic Biologics: The Next Frontier*, ABN-AMRO Special Report, June 2001, available at http://www.microbix.com/PDFs/3487_Generic_Biologics_rpt.pdf.

¹⁴ An innovator drug will also be referred to as a brand-name drug in this paper.

¹⁵ Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585.

¹⁶ *FDA Orange Book. Approved Drug Products with Therapeutic Equivalence Evaluations*. The FDA's listing of approved drug products is commonly referred to as the "Orange Book." The FDA has published an electronic version of the *Orange Book*, which can be searched by active ingredient, company, or proprietary name. Available at <http://www.fda.gov/cder/ob/default.htm>.

¹⁷ Warren Strugratch, Carving a Niche in Generic Drugs, *The New York Times*, April 13, 2003, at 6; Gardiner Harris, Drug Firms' 'Bad Year' Wasn't So Bad, *The Wall Street Journal*, Feb. 21, 2003, at 4.

¹⁸ Centers for Medicare and Medicaid Services, Table 3: National Health Expenditures, by Source of Funds and Type of Expenditure: Selected Calendar Years 8-2002/1997, available at <http://www.cms.hhs.gov/statistics/nhe/historical/t3.asp>.

Ultimately, the decision to proceed with a program for follow-on biologics regulated under section 351 of the Public Health Service (PHS) Act and under section 505 of the FD&C Act is in the hands of Congress. This paper will address the needs and challenges in balancing innovators' rights and the public interest in access to affordable medicines while maintaining an acceptable quality of scientific integrity. In conclusion, I will propose policy considerations and legislation that aim to facilitate a regulatory pathway for biologics in consideration of these important legal, social, scientific, and economic issues.

II. The Public Interest: Access to Medicines & Reducing Healthcare Costs

The regulation of follow-on biologics is a rising concern for the biotech industry since many biologics are approaching the end of their patent life, and as a result, will open the market for more affordable generics. Congress and federal agencies are faced with the challenge of developing a regulatory process that will encourage innovation, competition and expanded access to follow-on biologic therapies while ensuring safety and efficacy. The 1984 Hatch-Waxman generic drug regulatory process may not be appropriate for all follow on biologics. A separate question is whether or not Congress should act to change the FD&C Act or the PHS Act to authorize the FDA to approve generic biologics through a modified process.

Passage of the Hatch-Waxman Act came at a critical juncture in America's efforts to make drug products affordable and accessible to consumers. In 1984, the pharmaceutical industry was at a crossroads in terms of drug pricing and innovation in this country. At that time, the industry was developing innovative products, but was charging monopoly prices even after patents had expired. The Hatch-Waxman Act endeavored to strike a balance between encouraging innovation and facilitating access to affordable medicine. The brand pharmaceutical industry has grown from a \$19 billion industry in 1984 to a more than \$200 billion industry in 2003. Simultaneously, the generic pharmaceutical industry has grown to include over seven thousand FDA-approved generic pharmaceuticals on the market, saving the national healthcare system billions of dollars each year. Examples of common biologics are erythropoietin to treat anemia, growth hormone¹⁹ to treat growth rate abnormalities, and insulin to treat diabetes mellitus (hormonal therapies). In fact, most insulin has been produced through genetically engineered bacteria for many years.²⁰ Additionally, biologics have contributed to novel therapies for cancer, congestive heart failure and cystic fibrosis and have helped to develop diagnostic test kits and immunoassays. However, some innovative therapies come with the considerable cost of research and development for the biotechnology companies resulting in substantial costs to patients in upwards of \$50,000 for one person per year.

Medicare drug-plan sponsors may not be required to cover biologics that treat rare diseases and disorders, according to the Biotechnology Industry Organization (BIO), which urged federal regulators to ensure drug plans include the unique and often costly therapies. BIO voiced its concern to the Centers for Medicare & Medicaid Service that the formulary provisions

¹⁹ Human Growth Hormones products include Nutropin and Nutropin AQ, are made by Genentech Inc.; Humatrope by Eli Lilly, Genotropin by Pfizer; Norditropin by Novo Nordisk; and Serostim and Saizen by Serono Laboratories Inc.

²⁰ Insulin products include Humalog, Humulin, and Humulin-L, from Eli Lilly; and NovoLog, Novolin, and Novolin L, from Novo Nordisk.

in the new Medicare drug law are not sufficient to ensure that enrollees have access to life-saving therapies because biologics.²¹

Currently, generic drug products account for approximately half of all prescriptions drugs and typically cost 50 to 70 percent less than their brand-name counterparts.²² According to the Congressional Budget Office, generic drugs save consumers an estimated \$8 to \$10 billion a year at retail pharmacies. The savings are even greater when the use of generics by hospitals is factored into the equation. Each year consumers save billions of dollars by purchasing lower price generic drugs. The FDA must examine other mechanisms to lower the cost of drug development and find ways to make the drug approval process more efficient, reliable, and affordable without compromising the rigor of drug review.

III. Regulatory Framework

In 1902, Congress enacted the Virus Act giving the government its first basis for regulating the processes used for manufacturing biologic products. In 1972, formal authority to regulate biologics was transferred from the National Institute of Health (NIH). The Hatch-Waxman Act (Drug Price Competition and Patent Term Act of 1984) sped up the approval process for generic drugs.

A. Hatch-Waxman Amendments and the Center for Drug Evaluation and Research

The enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 has been a success since its enactment. Historically, biological products included such as vaccines, blood, and anti-toxins regulated under the PHS Act. Today, while many biopharmaceuticals are approved under the PHS Act, others are approved under the Federal FD&C Act.

Some natural source proteins have been traditionally regulated as drugs, including insulin, hyaluronidase, menotropins, and human growth hormones. However, others such as blood factors are regulated as biological products. Insulin and human growth were regulated by the Center for Drug Evaluation and Research (CDER) under the FD&C Act as drugs, while cytokines and blood factors were regulated by the Center for Biologics Evaluation and Research (CBER) under the PHS Act. In 1993, CDER and CBER agreed to apportion responsibility of all recombinant proteins and monoclonal antibodies to CBER except hormones such as insulin and human growth hormones. Later in 2003, therapeutic products regulated by CBER were transferred to CDER, without change to the appropriate approval authority. As a result, some biologics are approved under the FD&C Act and some biologics are licensed under the PHS Act.

Generally, the FDA regulates the majority of biologic products under the PHS Act,²³ which is not part of the Hatch-Waxman regime. However, the PHS Act contains a provision

²¹ Medicare Rx Plans Should Cover Biologics for Rare Diseases, BIO Says, *Drug Daily Bulletin*, Oct. 13, 2004. Available at http://www.fdanews.com/dailies/drugdaily/1_195/news/30617-1.html.

²² U.S. Food and Drug Administration, Generic Drugs: What You Need to Know, *FDA Consumer Magazine*, Sept./Oct. 2002. Available at www.fda.gov/fdac/features/2002.

²³ 42 U.S.C. § 262 (1996).

stating that nothing in that Act shall affect the FDA's jurisdiction under the FD&C Act. Therefore, the FDA has the authority to regulate all biologics under the FD&C Act, as it has already done for some biopharmaceuticals including insulin and human growth hormone.²⁴ Congress made this assertion clear in the Food and Drug Administration Modernization Act (1997), changing the PHS Act to explicitly state that the FD&C Act applies to biologic products subject to regulation under the PHS Act.

Furthermore, precedent exists for the approval of biopharmaceuticals with reduced pre-clinical and clinical data packages under the PHS Act. These biologic products include Hepatitis B vaccines and the Hemophilus influenza type B vaccine, among others. In addition, FDA allows interchangeability for products approved under this Act. For example, the FDA-approved labeling for GlaxoSmithKline's yeast-derived Hepatitis B vaccine states that this product is comparable and interchangeable to other Hepatitis B vaccines derived from yeast and blood plasma.

B. Statutory Mechanisms

The FDA's statutory approval mechanisms differ for drugs and most biological products. However, many biological products are also considered drugs, as that term is broadly defined in the FD&C Act; the FD&C Act defines drugs by their intended use, as "(A) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and (B) articles (other than food) intended to affect the structure or any function of the body of man or other animals."²⁵ Under the PHS Act, a biologic product is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, or blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment or cure of a disease or condition of human beings."²⁶

The FDA approves chemical drugs under mechanisms found in section 505 of the FD&C Act, and licenses most biological products under section 351 of the PHS Act. New Drug Applications (NDAs) under section 505 of the FD&C Act and biologics license applications (BLAs) under the PHS Act require submission of complete clinical data reports. After the patent or other exclusivity periods expires for a drug approved under the FD&C Act, manufacturers can apply to the FDA under section 505(j) of the FD&C Act for approval of generic versions through the abbreviated new drug application (ANDA) process. Additionally, section 505(b)(2) provides an approval process for NDAs based on the FDA's earlier finding that a drug is safe and effective.

Under the current ANDA process established by the Hatch-Waxman Act twenty years ago, the safety of the innovator drug is established by the clinical trials conducted by the innovator prior to the approval of the New Drug Application. The generic applicant is not required to conduct the full scope of clinical trials in order to prove safety and efficacy; instead, the generic manufacturer must prove safety and efficacy through "bioequivalence." Hatch-Waxman relied on the use of surrogate markers or indicators—namely plasma levels, the rate and extent of absorption of the drug product into the blood stream, to represent the efficacy and

²⁴ See *id.* § 262(f).

²⁵ FD&C Act, § 201(g)(1).

²⁶ PHS Act, § 351(i).

safety measure that is the basis for approval of generic drugs. Would such a process, although employing different indicators specific to biologic products, be applicable to the approval of generic products? Is it impossible to develop scientific solutions that would in fact make such follow-on products possible with respect to at least some biopharmaceutical products? Would a case-by-case regulatory protocol be the best way to assess the safety, efficacy and therapeutic equivalence of follow on biologics? Complex scientific questions must be answered if regulators are to develop an appropriate regulatory pathway for biopharmaceuticals.

1. Approval of Generics under the FD&C Act

The ANDA process in section 505(j) was established through the 1984 Hatch-Waxman Amendments as an abbreviated approval mechanism for generic versions of drugs approved under section 505 of the FD&C Act. Under these statutory standards, a generic drug generally must contain the same active ingredient as an innovator product, be bio-equivalent to the innovator drug, and have the same dosage form, strength, route of administration, labeling, and conditions of use. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness. By establishing that the drug product described in the ANDA is the bioequivalent of the innovator drug product approved in the NDA, the ANDA applicant can rely on the FDA's finding of safety and effectiveness previously determined for its counterpart brand drug. The FDA works to ensure that all approved generic drugs have met the same rigid standards of quality, purity, and identity as the innovator drug. Generic drugs must be manufactured under the FDA's strict standards of good manufacturing practice regulations as required for innovator products. In addition, the FD&C Act also contains an alternative mechanism by which an NDA sponsor can obtain approval of new drug products. The 1984 Hatch-Waxman Amendments to the FD&C Act provides an approval pathway for generic products approved under ANDAs or NDAs that incorporate published literature or data not belonging to the applicant (505(b)(2)); whereas, the PHS Act has no analogous provisions. Both the ANDA and 505(b)(2) approval processes incorporate provisions related to the innovator's intellectual property rights. Patents listed with FDA by the innovator NDA holder at the time of NDA approval must be acknowledged by the ANDA or 505(b)(2) applicant. Additionally, the FDA approval will be delayed until patent disputes are resolved and statutory marketing exclusivity has expired.

2. Approval of Follow-on Versions of Biological Products Approved under the PHS Act

Unlike section 505 of the FD&C Act, the PHS Act has no provision for an abbreviated application that would permit approval of a "generic" or "follow-on" biologic based on the FDA's earlier approval of another manufacturer's application. From a legal perspective, for products approved under section 505 of the FD&C Act, the FDA believes existing authority allows applications for such products under section 505(b)(2) of the FD&C Act, relying on the earlier approval of the innovator product. In contrast, the FDA does not believe such authority exists for follow-on biologics application under section 351 of the PHS Act that relies on the prior approval of the biological product or on data submitted by another sponsor.

IV. Competing Interests in Biologic Regulation

A. Innovators' Rights

The Biotechnology Industry Organization (BIO) recently submitted a citizen petition requesting that the FDA consider various issues publicly before approving “follow-on therapeutic proteins.” A principal argument advanced by the brand-name industry is that a system for the approval of generics would be unconstitutional because it would amount to a taking of the innovator company’s property without just compensation. If the FDA were to review drug applications for follow-ons, it would have to rely on safety and efficacy data from the innovator to establish the safety and efficacy of the generic product. Additionally, the FDA might also need to rely on the manufacturing process and control information of innovator companies. Innovator companies argue that if the FDA were to use such proprietary information for the purpose of approving a generic product, it would be an unconstitutional taking of property under the Fifth Amendment of the U.S. Constitution, which precludes the taking of property for public use without adequate compensation. On the other hand, “no statute appears to explicitly state that the information is protected as a trade secret and cannot be used internally by the FDA.”²⁷ In fact, the Supreme Court held that an agency (such as the FDA) does not violate the Trade Secrets Act when it internally relies on previously submitted data during consideration of the application of a subsequent applicant.²⁸ Furthermore, the application of trade secret law may “extend the protection provided by the data exclusivity regulations, thereby raising anti-trust issues.”²⁹

However, in the use of section 505(b)(2) of the FD&C Act, the FDA is simply proposing to reduce the data requirements for generic biopharmaceuticals based on its approval of the brand product. The takings arguments advanced by the brand manufacturers would raise constitutional doubts about the status of a significant number of FDA and other regulatory agency programs. In certain regulatory programs, such as those covering food additives, medical devices, and over-the-counter drugs, the FDA allows the entire industry to rely on an FDA approval based on test data submitted by regulated companies. Nevertheless, the Hatch-Waxman Amendments already permit use of innovators’ safety and efficacy data in the approval of generic drugs under ANDA. Although an unconstitutional takings challenge to that statute could have been made, the ANDA approval provision has never been challenged.

According to a Tufts University study, bringing a new drug to the public costs over \$800 million—more than doubling over the last decade.³⁰ Only a small fraction of drugs that undergo the initial stages of development reach early-stage trials, and only a small fraction of those drugs actually result in new drug applications to FDA.³¹ Brand companies rely on the protection provided by patents, data exclusivity and trade secrets to take on the risk of funding new R&D for new treatments and cures. When an innovator submits their product for approval and files a biologic license application (BLA), they provide the FDA with extensive trade secret and other confidential data that includes years of research and clinical studies to demonstrate the safety and

²⁷ *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1009 (1984).

²⁸ Narinder Banait, *Mondaq Bus. Briefing*, November, 15, 2005.

²⁹ *Id.*

³⁰ *Remarks by Mark B McClellan, M.D., Ph.D. Commissioner, Food and Drug Administration* March 28, 2003. Available at www.fda.gov/oc/speeches/2003/phrma0328.html.

³¹ *Id.*

effectiveness of their biologic. To realize the full benefits of medical innovation policies that protect incentives for companies must be adopted.

B. Scientific Integrity: Safety and Efficacy

The term “biologics” generally refers to any biological product that can only be made using a living system or organism, usually DNA, proteins, bacteria or other microorganisms. Biologics are inherently different from chemical drugs, which are synthesized from raw chemicals using more predictable and replicable processes. Since the production of biologics occurs in a living cell, the process is subject to considerable variability.

Due to the complex processes that are used to produce biologics, creating an exact copy of the original, pioneer biologic is often very difficult. The many sources of variability in the process, from bio-environmental factors such as gene splicing and culture media to physical factors such as temperature and chemical make-up of petri dishes, can lead to variability in the product as well. Biotechnology is used when the desired drug product is a large molecule that is difficult to produce through chemical synthesis. Because of simpler, more straightforward processes used in the production of chemical drugs, exact copies of the original drugs can be produced and marketed as “generics”. Brand manufacturers argue that science is not capable of detecting changes in protein structure between the brand biologic and the generic. Furthermore, the brand industry contends that biologics are impossible for generics manufacturers to successfully reverse-engineer without the proprietary good manufacturing practice (GMP) and good laboratory practice (GLP) protocols of the innovator company.

However, certain biopharmaceuticals, such as insulin and human growth hormone, are already regulated under the FD&C Act and are subject to the Hatch-Waxman Amendments. To the extent that generic biopharmaceuticals may not qualify for approval under the basic generic approval provision in the statute (section 505(j) of the FD&C Act) because simple blood level studies are not sufficient to establish equivalence, they could qualify under section 505(b)(2). Under section 505(b)(2), FDA can rely on its earlier approval decision of the brand product, and then require additional data, as appropriate, to confirm that the generic product is safe and effective.

The FDA believes that for some biologic products (primarily relatively simple peptide or protein products regulated under section 505 of the FD&C Act), science has progressed sufficiently to assess the degree of similarity between an innovator biologic and a follow-on biologic. The principle underlying such a determination is that the greater the degree of similarity or identity between two proteins, the greater the confidence that their clinical performance will be similar or the same.

V. Healthcare Policies Relevant to Biologics Legislation

The policy issues surrounding the approval of biologics must consider the need to balance the rights of innovator companies with the economic needs of healthcare consumers, while ensuring high quality healthcare. The Hatch-Waxman Amendments were intended to balance two important public policy goals. First, Congress wanted to ensure that brand-name

drug manufacturers would have meaningful incentives for research and development through patent protection and marketing exclusivity to enable them to recoup their investments. Second, Congress sought to ensure that, once the statutory patent protection and marketing exclusivity for these new drugs expired, consumers would benefit from the rapid availability of lower priced generic versions of innovator drugs. Importantly, the Hatch-Waxman Amendments also link the timing of generic drug approvals to the patent status of the drug, providing exclusivity incentives to innovator companies. The following sections address three legislative responses to prescription drug concern that are relevant to future policy formulation for biologics.

Over the past few years, Congress and the public focused attention on two key provisions of Hatch-Waxman. These grant 180 days of marketing exclusivity for certain generic drug applicants and provide a 30-month stay on generic approvals when there is patent infringement litigation. On June 18, 2003, the FDA published its final rule to increase the availability of generic drugs by limiting the use of 30-month stays by brand-name drug sponsors and by clarifying the types of patents that must be submitted to FDA for listing in the *Orange Book*.³² The goal of FDA's rule intended to improve access to generic drugs and lower prescription drug costs for millions of Americans. Moreover, such changes would provide billions in savings for the Medicare and Medicaid programs. Elements of this rule were incorporated into the Medicare prescription drug law last year along with additional mechanisms to enhance generic competition.

For fiscal year 2004, Congress enacted an increase of \$8 million for the FDA's generic drug program, the largest infusion of resources into this program since its inception. This increase in the generic drug budget enables FDA to hire additional expert staff to review generic drug applications more quickly and initiate targeted research to expand the range of generic drugs available to consumers. Improvements in the efficiency of review procedures have led to significant reductions in approval times for generic drugs since 2002 and will save consumers billions more by reducing the time for developing generic drugs and making them available. These resources would help facilitate a regulatory scheme for biologics.

On March 16, 2004, the FDA issued a major report on medical product development, the Critical Path Report, which identifies the problems and potential solutions to the task of ensuring that innovations in medical science are demonstrated to be safe and effective for patients as quickly and inexpensively as possible. The report carefully examines the critical path of medical product development -- the crucial steps that determine whether and how quickly a medical discovery becomes a reliable medical treatment for patients. This effort provides an opportunity for the FDA to collaborate with academic researchers, product developers, patient groups, and other stakeholders to formulate cost-efficient and scientifically prudent regulatory pathway for biologics.

VI. Conclusion

In 1984, the biopharmaceutical industry was in its infancy, with only one biopharmaceutical product on the market. Presently, more than 150 biotech drugs are on the market, including human insulin, interferons, human growth hormones and monoclonal

³² *FDA Orange Book. Approved Drug Products with Therapeutic Equivalence Evaluations.*

antibodies. In the past year alone, more than 30 new biopharmaceutical drugs were approved. According to the trade group PhRMA, “[t]he biologics pipeline includes 154 treatments for cancer, 43 for infectious diseases, 26 for autoimmune diseases and 17 for HIV/AIDS and related conditions.”³³ PhRMA also recently announced that its member firms are developing 800 new drug products to treat diseases associated with aging, including 123 drugs for heart disease and stroke, 395 for cancer and 329 for diseases such as Alzheimer's, diabetes and osteoporosis. In order to realize the frontier of medical progress, policies must protect incentives to develop new drugs and medical devices. Promoting innovation requires the right combination of incentives, safeguards, and effective regulation to secure maximum benefit from new medical technologies, while assuring mechanisms for equitable access to the treatments.

Perhaps, the most effective legislation would provide for a tiered regulatory pathway, evaluating biologics individually rather than as a one general class of drugs. Such a scheme could enable the FDA to develop and implement a generic biologic approval scheme while preserving the Hatch-Waxman safeguards for innovators rights and scientific integrity. Still, the FDA will need to determine the requisite scientific standards for generic biologic medicines in light of the potential benefits and risks to public health.

[P]olicymakers under intense pressure to control costs may adopt policies that seem, based on the experience of other governments, to reduce medical costs in the short run – instead of finding ways to act on creative but difficult health policy reforms, ones that make health care more affordable while still encouraging innovation. Because they tread on the meaningful rewards for developing valuable intellectual property that has made the United States the world leader in many areas of high technology, such reforms may reduce drug costs in the short run. . . . This would lead to higher long-term costs from failures . . . to achieve continuing improvements in our public health.³⁴

First, congress must provide explicit language for the FDA’s regulatory authority in the approval of generic biologics. Court decisions support the FDA’s authority to allow approval of generic biologics by means of establishing bioequivalence. In *Serono Laboratories, Inc. v. Shalala*, the United States Court of Appeals for the District of Columbia Circuit held that the FDA may make scientific judgments regarding what constitutes "sameness" when comparing the active ingredients in two drug products.³⁵ Significantly, FDA guidance permits product-based comparison of biologics, stating:³⁶

[W]hen a biologics manufacturer institutes a change in its manufacturing process, before FDA approval of its product but after completion of a pivotal clinical study, it may not be necessary for

³³ More than 300 Biologics, 800 Drugs in the Pipeline, PhRMA Says, Nov. 1, 2004, *available at* http://www.fdanews.com/dailies/drugdaily/1_208/news/31383-1.html.

³⁴ *Remarks by Mark B McClellan, M.D., Ph.D. Commissioner, Food and Drug Administration*
March 28, 2003.

³⁵ *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1320 (DC Cir. 1998).

³⁶ *Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products*, U.S. Food and Drug Administration, April 1996, *available at* <http://www.fda.gov/cder/guidance/compare.htm>.

the manufacturer to perform additional clinical studies to demonstrate that the resulting product is still safe, pure, and potent.

Thus, the FDA review of bioequivalence may be based on the characteristics of the final biologic product, rather than similarity of the production processes. In a tiered approach to biologic approval, the FDA could review each biologic on a case by case basis, recognizing the unique characteristics of biologics that create obstacles to bioequivalence. A given biologic can be placed in a category according to the complexity and understanding of the biologic where tiered categories designate the requisite rigor for the approval process. Some indicators of complexity may include: number of active macromolecules, size of biologic molecules, number of active epitopes, and the level of characterization of the causes and effects of variations due to posttranslational modifications.

A tiered approach need not require costly, extended clinical trials for all biologic products as a single class. Rather, extended trials would be necessary only for those biologics in which the FDA requires a heightened evidentiary basis for bioequivalence and only to the extent that bioequivalence can be established for a particular biologic, or category of biologics. In this way, generic manufacturers will not be burdened with the unnecessary costs associated with extensive trials, which could off-set cost saving if the scheme was a one-size fits all approval process. While the tiered scheme prevents simpler biologics from having to go through the rigors of unnecessary trials that the more complex biologics would require, some of the most complex and expensive biologics may not be able meet respective class standards for safety and efficacy, or may not be profitable for generic companies to produce because of the extensive trials necessary to prove bioequivalence; for these biopharmaceuticals, consumers may not benefit from the cost savings offered by a generic product.

Still, with more than 340 biologics undergoing clinical trials,³⁷ promising to treat common medical conditions such as AIDS, cancer, diabetes, and autoimmune, blood, digestive and cardiovascular disorders, generic competition has great potential to offer consumers (including the federal government as the biggest drug consumer) substantial cost savings and to lower America's overall healthcare bill. Ultimately, if the current standards designed to regulate generic forms of drugs do not apply to the new generations of biologics, then Congress, federal regulators and the biologics industry must implement a system that promotes access to safe and effective biologics at a reasonable costs, while recognizing the intellectual property rights of innovators in order to encourage further research and development of beneficial drugs.

³⁷ More than 300 Biologics, 800 Drugs in the Pipeline, PhRMA Says, Nov. 1, 2004, *available at* http://www.fdanews.com/dailies/drugdaily/1_208/news/31383-1.html.