Competitive Enterprise Institute
1001 Connecticut Ave NW • Suite 1250 • Washington, DC 20036
202.331.1010 • www.cei.org
Advancing Liberty – From the Economy to Ecology

November 29, 2007 **No. 126**

Promoting Healthy Biopharmaceutical Competition

The Promise of a Regulatory Pathway for Follow-On Biologics

By Gregory Conko*

The Hatch-Waxman Act, enacted by Congress 23 years ago, created an abbreviated approval pathway for generic copies of conventional, or what are known as "small-molecule," drugs. These drugs are composed of relatively simple molecules that can be synthesized easily, using their chemical formulas as blueprints for assembling individual chemical elements into a therapeutically useful molecule. Most of the products we think of as pharmaceuticals, from aspirin to Zoloft, are classified as "drugs."

Another class of pharmaceuticals, called biological products or biologics, is composed of much larger and more complex molecules that, historically, have been too intricate to synthesize chemically. These include vaccines, blood products, antitoxins, and therapeutic proteins and peptides. Their structure is so complex that they typically must be produced by, and extracted from, living organisms—bacteria, viruses, yeasts, plants, or animals—then purified into isolated products. And biologics are not just different from drugs chemically; they are also, generally speaking, regulated under a separate statute.

At the time Hatch-Waxman was enacted, little consideration was given to the possibility of generic biological products because their large, complex, and idiosyncratic nature made them impossible to duplicate with 1984 technology. Consequently, the Act applied only to products regulated as drugs. Much has changed over the past two decades, however, and it is now possible to duplicate certain types of biological products with a high degree of fidelity. Yet there still is no analogous pathway through which the Food and Drug Administration (FDA) may approve copycat biological products for commercial use. That could soon change, however, because Congress has been considering legislation to create just such a process. If the final legislation properly balances rapid approval of generic biologics with incentives for name-brand firms to

* *Gregory Conko is a Senior Fellow at the Competitive Enterprise Institute.*

continue innovating, Americans may soon benefit from healthy competition in the biopharmaceuticals market.

Background. Since the advent of the biotechnology industry in the 1980s, recombinant DNA techniques have revolutionized the practice of medicine and the pharmaceutical industry. Recombinant DNA—known colloquially as gene-splicing, genetic engineering, and biotechnology—has substantially improved the development of biological products, and has been used to create medicines that treat once intractable diseases, such as cancers, stroke, multiple sclerosis, diabetes, and cystic fibrosis.[1] Its biggest contribution has been to improve scientists' ability to duplicate naturally existing proteins—thus, most recombinant DNA products are biopharmaceutical proteins regulated as biologics. This medical revolution has not come cheaply, however.

The high cost of biopharmaceutical research and development, and its very strict accompanying regulatory oversight, lead to high consumer costs. Due to the industry's relative youth, most biopharmaceuticals are still protected by patents. But, because many of the patents are slated to expire in the coming decade, there is growing interest among patients, insurers, governments, and the generic drug industry in the production of "generic," or what the FDA calls "follow-on," biopharmaceuticals. Competition from the introduction of generic conventional drugs usually leads to a sizeable drop in price, so some experts speculate that the approval of follow-on biopharmaceuticals could save patients hundreds of millions, perhaps billions, of dollars each year.[2]

Skeptics argue that biopharmaceuticals are too complex and too prone to unexpected variations for generic companies to duplicate accurately, and that new clinical trials would be necessary to demonstrate the safety and efficacy of follow-on copies. However, within the last decade, scientific advances in protein characterization and purification have made it possible for generic manufacturers to make, and for regulators to evaluate, copycat biopharmaceuticals with little, and in some cases, no clinical testing needed to ensure safety and efficacy.[3] Although certain biologicals—including whole blood products, most vaccines, and some protein products—are too complex even to characterize adequately, let alone reproduce safely without validation in clinical trials, most protein-based biologics, particularly those made using recombinant DNA technology, can be characterized accurately enough to permit the comparison of structure, composition, and clinical activity required for abbreviated approval.

The only real remaining question is how an abbreviated approval process should be structured to protect incentives for pioneer firms to continue pursuing medical innovation. If a reasonable compromise can be brokered, creating a regulatory pathway for copycat biopharmaceuticals could be a constructive way to advance biopharmaceutical industry competition.

Late last year, Sens. Charles Schumer (D-N.Y.) and Hillary Clinton (D-N.Y.) and Rep. Henry Waxman (D-Calif.) introduced companion Senate and House bills to create an abbreviated approval pathway for generic and other follow-on biopharmaceuticals.[4] The bills met fierce opposition from many pioneer pharmaceutical firms because they would

enable generic competition in the biologics industry for the first time by piggy-backing on billions of dollars of clinical research paid for by the pioneer firms. The bills have since been effectively supplanted by the Biologics Price Competition and Innovation Act (S. 1695), a compromise bill, introduced by Sens. Edward Kennedy (D-Mass.), Orrin Hatch (R-Ut.), Mike Enzi (R-Wy.), and Clinton, that is intended to address several of the innovator firms' concerns.

The Kennedy-Hatch bill would create a regulatory pathway for "follow-on" biological products, which it calls "biosimilars," and require FDA to approve such products once manufacturers demonstrate that their molecules are "highly similar" to the pioneer products, even if the two have "minor differences in clinically inactive components." Applicants would be expected to submit analytical, animal, and clinical studies demonstrating the biosimilar products' safety, purity, and potency, though the agency may determine, at its discretion, that one or more of these elements are unnecessary. The bill also proposes a 12-year exclusive marketing period for pioneer manufacturers, during which generic manufacturers may not submit a follow-on application relying on prior approval of the reference product as evidence of safety and efficacy.

The Hatch-Waxman Act. Despite important differences between small molecule drugs and biological products, the origins of the generic conventional drug legislation can provide useful lessons for creating a follow-on biologics approval pathway. Under the terms of the original Food, Drug and Cosmetics Act of 1938 (FDCA), most generic manufacturers put their products on the market with no FDA review. Their products were copies of already approved products, not "new drugs," so they were not technically subject to the 1938 Act's review requirements.[5] Amendments to the Act passed in 1962[6] dramatically increased the scrutiny of new drugs and subjected generic drugs to the same testing and New Drug Application (NDA) process as pioneer products. This made it uneconomical to produce most generics, and few manufacturers were willing to expend the resources necessary to re-test copycat drugs.[7]

FDA's response to the dearth of new generic drugs was to create, administratively rather than through a grant of specific statutory authority, a shortened drug application process whereby generic manufacturers could demonstrate their products' safety and efficacy by relying almost entirely on studies conducted by others and published in the peer-reviewed scientific literature.[8] For a variety of reasons, however, this "paper NDA" had only limited success. So, in 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act[9]—known as the Hatch-Waxman Act for its primary sponsors.

Hatch-Waxman established two abbreviated approval pathways for duplicate versions of already approved drugs. The primary pathway, established under section 505(j) of the FDCA, grants FDA specific authority to approve an essentially identical copy of a previously approved drug once the manufacturer demonstrates that the copy contains the "same" active ingredient as the reference drug; is "bioequivalent" to the reference drug; and has the same strength, dosage, form, labeling, and conditions of use as the reference drug.[10] Because the active ingredients in the reference and copycat products are the same, FDA can conclude that the copy is safe and effective based on its prior evaluation of the

reference drug. Once approved, most 505(j) drugs are considered therapeutically equivalent to their reference products, can generally be interchanged freely with those reference drugs, and are therefore considered true "generics."[11]

In the other pathway, established in section 505(b)(2) of the FDCA, the approval process is abbreviated, but the manufacturer still must submit some amount of clinical or non-clinical data, determined by FDA at its discretion, demonstrating the product's safety and efficacy. As with the paper NDA, this can take the form of previously published research instead of, or in addition to, studies conducted by the manufacturer. It may also include reference to a previously approved product, but the application may not rely wholly on the reference drug's approval because the chemical structure of a 505(b)(2) drug need not be identical to the reference drug. The 505(b)(2) pathway is therefore generally used to approve a change in dosage, form, strength, or route of administration, a subtle change in formulation or active ingredient, or a new combined use of previously approved drugs.[12]

Reliance on the reference drug's safety and efficacy is appropriate only regarding those characteristics shared by the new drug and the reference drug. For any modification to the reference drug, an applicant must submit data establishing that the modified drug meets the statutory safety and efficacy requirements.[13] And, because "sameness" and "bioequivalence" have not been demonstrated, products approved under section 505(b)(2) may be prescribed as alternatives to the reference drugs, but they are not freely interchangeable.[14] Section 505(b)(2) drugs are therefore not considered true "generics," but merely "comparable" or "follow-on" products.[15] Nevertheless, this pathway permits the rapid introduction of comparable alternative products without the need for redundant testing. Manufacturer and agency resources can instead be focused on investigating relevant differences between the follow-on and reference products.

Updating Regulation. Many pioneer pharmaceutical firms that today question the soundness of follow-on biological products once opposed the introduction of Hatch-Waxman's generic drug pathways.[16] The reason is that follow-on approvals permit generic manufacturers effectively to free ride on hundreds of millions, or in some cases billions, of dollars' worth of pioneer data and then mount fierce price competition against name-brand firms. Pioneer manufacturers came to support the Hatch-Waxman Act, after limited extensions to the patent life of their pioneer drugs and certain additional periods of market exclusivity were added to the legislation.[17] The goal was to protect the incentives for pharmaceutical companies to continue to innovate, while ensuring that their monopolies eventually expire to allow generic competition.

Despite Hatch-Waxman's general success, critics today say the law is not a good model for follow-on biological products. They argue that, because current technology cannot ensure that copycat biologics are identical to their innovator reference products, it is not possible to produce true generic biologics.[18] However, some experts believe it is already possible to show that certain, relatively small and well-characterized, proteins are sufficiently similar in structure and function to warrant an interchangeability determination.[19] Even conceding that it is not currently possible to demonstrate

interchangeability, the state of the art in protein characterization and purification is advancing so rapidly that it likely will be possible in the very near future.

Giving FDA the authority now will create an appropriate incentive for generic manufacturers to develop the analytical techniques necessary to compare proteins generated from different production systems—a scientific achievement that would benefit society beyond the approval of generic products. It is better, then, that FDA have authority to liberalize the approval process—even if the agency temporarily chooses not to use it—than for the agency and generic manufacturers to have to wait for another legislative grant of authority once the science has advanced far enough.

In addition, Hatch-Waxman is not limited to generic products that can be shown to be identical to their reference drugs. It establishes a second abbreviated approval pathway for comparable products that are similar enough to provide reasonable alternative treatments to the reference drugs. Although many experts doubt that current technology is sufficient to demonstrate that two proteins generated from different manufacturing systems are the *same*, as required for true generic approval,[20] several real-world examples show that it currently *is* possible for generic manufacturers to demonstrate that two separate proteins are *similar* enough to qualify for approval as comparable products.

As long ago as 1996, FDA issued a guidance document explaining how manufacturers could make certain "manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy."[21] The document notes that improvements in test methods and product characterization have allowed manufacturers to "establish sensitive and validated assays for characterizing the product and the biological activity," to "provide the basis for FDA to assess product comparability without the necessity of repeating clinical trials."[22] Significant changes in the production or purification of biologics still often require at least limited clinical trials to demonstrate comparable safety and efficacy. Nevertheless, the flexibility promoted by the 1996 guidance tacitly recognized that recombinant DNA technology makes biological products much less prone to contamination and makes it far easier for manufacturers to confirm protein identity and purity. During the past 11 years, this technology has advanced rapidly, making many of the tools available only a decade ago seem crude by today's standards.

Furthermore, we know that FDA believes it is possible to approve certain follow-on biologics because the agency has already done so. In the United States, "drugs" are regulated under the FDCA, while most "biologics" are regulated under the Public Health Service Act (PHSA). However, a small number of protein products that would otherwise be legally classified as "biologics" are regulated as "drugs,"[23] and therefore fall within the authority of Hatch-Waxman's abbreviated approval pathways. FDA has already approved several comparable follow-on protein products under section 505(b)(2).[24]

Upon approving the follow-on growth hormone Omnitrope in 2006, FDA explained that the characteristics that made it eligible for the 505(b)(2) drug pathway included a single active ingredient, a well-known mechanism of action, and the ability to "extensively and adequately" characterize the protein.[25] Future follow-on "drug" products meeting these

and the other listed criteria likely would also qualify for abbreviated review. But not all protein products sharing these characteristics are regulated as drugs. Thus, FDA's scientific justification for approving follow-on protein products such as Omnitrope apply just as surely to small and well-characterized proteins regulated under the PHSA.

Finally, the United States is not alone in approving certain follow-on biologics. In 2003, the European Union (EU) passed legislation creating a pathway for the approval of what it calls "similar biological medicinal products," or "biosimilars."[26] Like Hatch-Waxman's section 505(b)(2), a biosimilar applicant can rely, to some extent, on the European Medicines Agency's (EMEA) prior approval of a reference product in order to meet some, though not necessarily all, of the quality, safety, and efficacy requirements. Depending upon the complexity of the underlying product, a biosimilar application could require a range of support materials—from limited or no clinical trial data for very small and well-characterized proteins to nearly complete data packages, such as might be required for an innovator product, for more complex and less familiar molecules. To date, EMEA has approved two biosimilar product applications;[27] the agency's Committee for Medicinal Products for Human Use has recommended two more for approval;[28] and at least one other was rejected due to concerns that the applicant had not adequately demonstrated comparability to the innovator product.[29]

This experience shows it is technically feasible to duplicate many biopharmaceuticals without sacrificing safety or efficacy, and that regulatory authorities are capable of making science-driven judgments regarding the adequacy of submitted data. Naturally, when determining how much original clinical data should be required to support approval of a follow-on biological product, FDA should take into consideration the complexity of a given protein's structure, the relevance of various structural features to the protein's therapeutic function, the amount of clinical experience with such proteins, and the extent of available scientific research on the proteins. More rigorous standards should apply when the agency considers interchangeability. However, it is no longer tenable to argue that FDA does not have technological capacity to evaluate follow-on protein products. Still, one significant issue remains: How can the U.S. government adequately balance the need to protect incentives for innovation while promoting competition?

Protecting Incentives for Innovation. One of the main arguments for follow-on biologics legislation has been that it would result in substantial cost savings to insurers, government health providers, and consumers, because many biopharmaceuticals are very expensive. For example, an average 10-month regimen of Genentech's colorectal cancer treatment Avastin can total as much as $46,000.[30]

Yet these high prices are not unwarranted. Creating, testing, receiving regulatory approval for, and manufacturing are far more complex and much more expensive for biopharmaceuticals than for small molecule drugs. Joseph DiMasi of Tufts University and Henry Grabowski of Duke University estimate that the average out-of-pocket cost of developing a new biological product totals well over $500 million.[31] But, like conventional drugs, most biopharmaceuticals never make it to market. When expenditures on failed products and other capital costs of research and development are

included, the average price of bringing a new biological product to market rises to roughly *$1.24 billion*. Biopharmaceuticals' high retail prices reflect the vast expense of developing them. Without such high prices, few investors would be willing to take risks on the biopharmaceutical industry, which would result in fewer lifesaving medicines.

To promote innovation, the Hatch-Waxman Act expanded the length of time pioneer manufacturers could sell their products without generic competition with two primary incentive mechanisms: a limited patent term restoration and an additional period of market exclusivity. If it is to be successful, follow-on biologics legislation must similarly protect incentives for biopharmaceutical innovation.

Patent Restoration. Because of lengthy testing and approval times, a sizeable portion of a new medicine's patent term is exhausted before it reaches the market, a phenomenon that gives medicines a comparatively short effective patent life. Hatch-Waxman addressed this problem by restoring a portion of the new medicine's patent term lost while it was being tested and while FDA reviewed the NDA.[32] Although the Hatch-Waxman approval pathways amended only the FDCA, and therefore do not apply to biological products regulated under the PHSA, the patent term restoration provisions amended the U.S. Patent Act, and they already explicitly apply to both drugs and biologics.[33]

However, patent restoration alone is unlikely to be sufficient for protecting pioneer biopharmaceutical manufacturers. As the Biotechnology Industry Organization (BIO) notes, "unlike a generic drug, which must be the same as an innovator product, a follow-on biologic may be only 'similar' to the corresponding innovator product."[34] Consequently, a follow-on biopharmaceutical application may, in certain circumstances, piggy-back on a pioneer manufacturer's invention without actually infringing the pioneer's patents. Consequently, much of the current debate over follow-on biologics has revolved around how to extend market exclusivity to biologics.

Extended Market Exclusivity. Under Hatch-Waxman, pioneer drugs receive five years of post-approval "market" exclusivity during which another manufacturer may not submit a 505(j) application for a generic drug that relies in any way on data supporting approval of that reference product.[35] This is sometimes referred to as "data exclusivity" because it forbids FDA from consulting the reference drug's approved NDA to verify the generic product's safety and efficacy, even though the actual data in the application are not typically consulted. Pioneer drugs also qualify for three additional years of market exclusivity if they receive FDA approval for a new label indication that requires the submission of new clinical studies.[36] Section 505(b)(2) contains no such market exclusivity provisions, but a manufacturer submitting an application for a comparable drug must certify that no patents protecting the innovator drug have been filed with FDA, or that all such listed patents have expired, will soon expire, or are invalid.[37]

These market exclusivity provisions have proven to be important protections for pioneer firms, but similar protections may be even more important to biopharmaceutical manufacturers. As noted, bringing a new biopharmaceutical to market costs an average of $1.24 billion, compared to roughly $802 million for an average conventional drug. In

addition, the clinical development time for biopharmaceuticals is approximately 9 percent longer than for conventional drugs (an average of 98 months for biologics compared to 90 months for drugs), which in turn erodes a bigger portion of a biological product's effective patent life.[38] Combined, these factors mean that biopharmaceuticals manufacturers would have to generate a substantially larger amount of revenue over a slightly shorter time period to reap the same market exclusivity protections as small molecule drugs. Yet many biopharmaceuticals treat conditions with much smaller patient populations than most small molecule drugs do. Accordingly, Grabowski argues that extending the data exclusivity period for biopharmaceuticals to at least 10 years would "help balance innovation incentives and price competition when instituting a new regulatory pathway for biologicals."[39] That would not be unprecedented.

In 2004, the European Union established a so-called "8+2+1" exclusivity protocol for drugs and biologics approved by EMEA, under which generic firms may submit follow-on applications as little as eight years after the reference product's approval, though applications cannot be approved until two years later, or 10 years after the reference product's approval. This 10-year exclusivity period may also be extended for one additional year if a new label indication is approved and "significant pre-clinical or clinical studies were carried out in relation to the new indication."[40]

BIO has urged Congress to grant pioneer biopharmaceutical firms a 14-year market exclusivity period.[41] Generic manufacturers support a much shorter market exclusivity term, but appear willing to accept a period as long as eight years.[42] The Kennedy-Hatch-Enzi-Clinton bill proposes a 12-year exclusivity period—a figure that seems to please neither side. However long the optimal level of protection may be, it is essential that any legislation not promote generic competition at the expense of innovation incentives.

Conclusion. The Hatch-Waxman Act provides a useful model for drafting follow-on biologics legislation. Its major features include approval pathways for generic drugs that are identical to their reference products and for those that are merely comparable alternatives, as well as limited patent term restoration and market exclusivity periods for pioneer products. While critics argue that the Act did not strike the right balance between rapid access and incentives for innovation, the law nevertheless has benefited patients by enabling a robust pioneer pharmaceutical industry and generic competition.

While development and approval of true generic biologics may not currently be feasible with today's technology, it is likely to be possible in the very near future. And, in any event, the creation of comparable biological products is already a reality. Consequently, Congress should grant FDA authority to approve follow-on biological products and consider requests for an interchangeability determination. Equally important is the protection of incentives for pioneer firms to continue to pursue medical innovation. If a reasonable compromise can be reached, creating a regulatory pathway for follow-on biopharmaceuticals could be a constructive way to introduce healthy competition into the biopharmaceutical industry.

Notes

[1] Biotechnology Industry Organization, *Biotechnology Industry Facts*, available at http://www.bio.org/speeches/pubs/er/statistics.asp (accessed Aug. 17, 2007).
[2] John Reichard, *Witnesses Differ Over Biotech Savings From Waxman Bill*, CQ HEALTHBEAT NEWS, Mar. 26, 2007, available at http://public.cq.com/docs/hb/hbnews110-000002478236.html.
[3] *See* , *e.g.*, 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, 220-36 (2005).
[4] Access to Life-Saving Medicine Act, S. 623, 110th Cong. (2007); H.R. 1038, 110th Cong. (2007). The bills were originally introduced in September 2006 as S. 4016, 109th Cong. (2006); H.R. 6257, 109th Cong. (2006).
[5] Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 ANTITRUST L.J. 585, 588-89 (2003-04).
[6] Drug Amendments of 1962, Pub. L. No. 87-781, § 102(a)–(b), 76 Stat. 780 (codified at 21 U.S.C. §§ 321, 331–32, 348, 351–53, 355, 357–60, 372, 374, 376, 381).
[7] Weiswasser & Danzis, *supra* note 5.
[8] Marion J. Finkel, *NDA's for Duplicate Drug Products of Post-1962 Drugs* (July 31, 1978), reprinted in Publication of "Paper NDA" Memorandum, 46 Fed. Reg. 27396, 27396–97 (May 19, 1981); *See also Id.*, at 589.
[9] Pub. L. No. 98-417, §§ 101, 103(a), 98 Stat. 1585, 1585–92, 1593–94 (1984) (codified at 21 U.S.C. §§ 355(b)(2), (j) [FFDCA §§ 505(b)(2), (j)]).
[10] A generic drug is bioequivalent to a previously approved drug if the rate and extent of absorption of the generic drug's active ingredient is not significantly different from that of the innovator drug. § 355(j)(8)(B).
[11] *See* FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, *Introduction* v (27th ed. 2007) available at http://www.fda.gov/cder/orange/obannual.pdf.
[12] Melissa R. Leuenberger-Fisher, *The Road to Follow on Biologics: Are We There Yet?* 23 BIOTECHNOLOGY L. REP. 389, 395 (2004).
[13] *Id.*
[14] Dudzinski, *supra* note 3, at 170-71.
[15] *See* Lauren S. Schlesselman, *Understanding the 505(b)(2) approval process*, DRUG STORE NEWS, Summer 2006, at 9.
[16] *See* Janet A. Gongola, *Prescriptions for Change: The Hatch-Waxman Act and New Legislation to Increase the Availability of Generic Drugs to Consumers*, 36 IND. L. REV. 787, 791-94 (2003).
[17] Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187 (1999).
[18] *See*, *e.g.*, Daniel E. Troy, Jeffrey P. Kushan & Gary L. Vernon, The Difference with Biologics: The Scientific, Legal, and Regulatory Challenges of any Follow-On Biologics Scheme, Biotechnology Industry Organization White Paper (Apr. 25, 2007), at 12-17.
[19] *See*, *e.g.*, Dudzinski, *supra* note 3, at 220-36.
[20] *See*, *e.g.*, Janet Woodcock et al., *The FDA's assessment of follow-on protein products: a historical perspective*, 6 NAT. REV. DRUG DISCOV. 437 (June 2007).
[21] CENTER FOR BIOLOGICS EVALUATION AND RESEARCH AND CENTER FOR DRUG EVALUATION AND RESEARCH, FDA GUIDANCE CONCERNING DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (Apr. 1996), available at http://www.fda.gov/cber/gdlns/comptest.pdf.
[22] *Id.* at 7.
[23] Since 1941, the FDA has been required by law to regulate insulin as a drug, even though insulin would fit more neatly into the category of biologics. FREDERIC J. GEISSEL, *The U.S. Food and Drug Regulatory Process: Administrative Aspects of Certification of Insulins*, in INSULINS, GROWTH HORMONE, AND RECOMBINANT DNA TECHNOLOGY 201 (John L. Gueriguian et al. eds., 1981). In 1981, FDA reassigned authority over certain protein-based products from its Center for Biologics Evaluation and Research (CBER) to its Center for Drug Evaluation and Research (CDER), classifying insulin, human growth hormone, and a handful of other comparatively small and "well-characterized" proteins as "drugs." And, in

1991, FDA re-apportioned products again, giving CDER authority over hormone products, chemically synthesized biologics, and certain products derived from non-human animal and solid human tissue sources, among others. *See* FOOD AND DRUG ADMINISTRATION, INTERCENTER AGREEMENT BETWEEN THE CENTER FOR DRUG EVALUATION AND RESEARCH AND THE CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (Oct. 15, 1991), available at http://www.fda.gov/oc/ombudsman/drug-bio.htm.

[24] These include GlucaGen in 1998, Follistim in 2002, Hylenex and Fortical in 2005, and Omnitrope in 2006.

[25] Letter from Steve Galson, Director, FDA Center for Drug Evaluation and Research, to Kathleen M. Sanzo, Morgan, Lewis & Bockius LLP, Stephan E. Lawton, Biotechnology Industry Organization, and Stephen G. Juelsgaard, Genentech, FDA Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 (May 30, 2006), at 13, available at http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf.

[26] Section 4, Part II, Annex I to Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, as amended by Commission Directive 2003/63/EC of 25 June 2003, Official Journal of the European Union L 159, 27/6/2003; Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, Official Journal of the European Union L 136 (Apr. 30, 2004), available at http://ec.europa.eu/enterprise/pharmaceuticals/review/doc/final_publ/dir_2004_27_20040430_en.pdf.

[27] Testimony of Nicolas Rossignol, Administrator, Pharmaceuticals Unit , European Commission Directorate General for Enterprise & Industry, before the Senate Committee on Health, Education, Labor and Pensions (March 8, 2007), available at http://help.senate.gov/Hearings/2007_03_08/Rossignol.pdf.

[28] European Medicines Agency, "Meeting highlights from the Committee for Medicinal Products for Human Use, 15-18 October 2007," EMEA Press Release, Doc. Ref. EMEA/479200/2007 (October 18, 2007), available at http://www.emea.europa.eu/pdfs/human/press/pr/47920007en.pdf.

[29] Testimony of Nicolas Rossignol, *supra* note 27.

[30] Geeta Anand, *Prescribing Caution: From Wall Street, a Warning About Cancer-Drug Prices*, WALL ST. J., Mar. 15, 2007, at A1.

[31] Joseph A. DiMasi & Henry G. Grabowski, *R&D Costs for New Biotech Compounds*, MANAGERIAL AND DECISION ECONOMICS (forthcoming); Henry Grabowski, Iain Cockburn, & Genia Long, *The Market For Follow-On Biologics: How Will It Evolve?* 25 HEALTH AFFS. 1291 (2006).

[32] 35 U.S.C. § 156.

[33] 35 U.S.C. § 156(f).

[34] Biotechnology Industry Organization News Release, BIO Calls For 14 Years of Data Exclusivity in Any Follow-On Biologics Legislation: Data Exclusivity Is Necessary to Support Future Biotech Medical Breakthroughs (May 3, 2007), available at http://www.bio.org/news/newsitem.asp?id=2007_0503_01.

[35] 21 U.S.C. § 355(j)(5)(F)(ii). However, a generic manufacturer may submit a 505(j) application four years following approval of the reference drug if the generic manufacturer certifies that no patents protecting the innovator drug are listed on record with FDA, or that all listed patents have expired.

[36] 21 U.S.C. § 355(j)(5)(F)(iii).

[37] 21 U.S.C. § 355(b)(2)(A).

[38] DiMasi & Grabowski, *supra* note 31.

[39] Henry G. Grabowski, Statement before the House of Representatives Committee on Oversight and Government Reform, Hearing on "Follow-on Protein Products" (Mar. 26, 2007).

[40] Directive 2004/27/EC of the European Parliament and of the Council, *supra* note 26, at L 136/39.

[41] Biotechnology Industry Organization News Release, *supra* note 34.

[42] Catherine Larkin, *Drug-Safety Bill May Leave Out Generic Biologics, Lobbyist Says*, BLOOMBERG NEWS SERVICE (Aug. 13, 2007).