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Erika Lietzan

University of Missouri School of Law, lietzane@missouri.edu

Krista Hessler Carver

Covington & Burling

Jeffrey Elikan

Covington & Burling

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An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009

KRISTA HESSLER CARVER

JEFFREY ELIKAN

ERIKA LIETZAN*

On March 23, 2010, President Obama signed into law the Biologics Price Competition and Innovation Act of 2009 (BPCIA) which created a statutory pathway for, and scheme for litigation of patent issues relating to, “biosimilar” biological products.¹ This article discusses the history of the BPCIA and explains its provisions. Section I provides background and a history of the regulation of drugs and biological products in the United States. Section II describes the growing interest in biosimilar approval from the early 2000s through September 2006, when the legislative debate began in earnest. Section III describes the legislative and stakeholder process from September 2006 to enactment, and section IV describes the BPCIA. These sections show, and the conclusion in section V explains, that the regulatory and intellectual property issues addressed in the final 2010 legislation were debated, discussed, explored, and vetted by stakeholders — including the Food and Drug Administration (FDA), the Federal Trade Commission (FTC), Democrats and Republicans in both House and Senate, the United States Pharmacopoeia, the generic industry, the biosimilar industry, trade associations, professional organizations like the Drug Information Association (DIA), and European regulators — for (in some cases) as many as ten years. Moreover, as these sections also show, like the Hatch-Waxman amendments of 1984, the final legislation represented a true compromise of competing interests.

* Ms. Lietzan and Mr. Elikan are partners and Ms. Carver is an associate at Covington & Burling LLP in Washington, D.C. The authors were involved, directly or indirectly, with many of the stakeholder discussions described below. The views expressed here are solely those of the authors and do not necessarily reflect the views of the firm or its clients. The authors are grateful to Eveline Van Keymeulen, an associate in the firm’s Brussels office; Erica Andersen and Melissa Whittingham, associates in the Washington, D.C., office; Jaclyn Martinez, a summer associate in the Washington, D.C. office during summer 2010; and Jennifer Pelaia, in the firm’s library, for their assistance. They are also grateful to Janet Woodcock, Richard Kingham, and others quoted and discussed in these pages, for their review and comments; the views expressed in this article, of course, are those of the authors alone.

¹ Patient Protection and Affordable Care Act, Pub. L. No. 111-148, Title VII, Subtitle A, 124 Stat. 119, 804-821 (2010). The final legislation employs the term “biosimilar” to describe the products at issue, as do the Europeans; at various times from 1999 to 2010, however, stakeholders used different terms, such as *generic biologics*, *follow-on biologics*, *follow-on protein products*, and *comparable biological products*. On the whole, *generic biologic* was used by more stakeholders in the early 2000s and by fewer stakeholders by 2010. But the choice of term also depended on the speaker; the generic industry long preferred *generic biologic* for at least some of the products, and the innovative industry generally preferred *follow-on biologic* for all of the products. At some point the Food and Drug Administration (FDA) decided on *follow-on protein products*. Without a doubt, some degree of advocacy was inherent in these terminology choices. The authors use *biosimilar* when there is no obvious reason to particularize the terminology but otherwise attempt to use the term that is appropriate given the context. Any deviations from this approach are inadvertent. Also, when discussing the “innovator” and “generic” positions, the authors mean to refer to the general perspective of a research-based reference product manufacturer and the general perspective of a biosimilar manufacturer. The reality was more nuanced, because many companies envisioned or now envision manufacturing both. The “industry” positions should therefore not be imputed to any particular company or companies. Further, while we have been careful when characterizing positions stated by individual companies in public documents, there may be situations where individual companies believe the statements are taken out of context or no longer represent their views.

I. BACKGROUND

Federal regulation of biological drugs preceded federal regulation of non-biological drugs and has proceeded on separate but overlapping tracks ever since. Subsection A discusses federal regulation of non-biological drugs; biological drugs are addressed in subsection B.

A. *Federal Regulation of Non-Biological Drugs*

Federal regulation of non-biological drugs began in 1938, with key developments in the 1960s, the late 1970s, and the early 1980s. First, following the 1962 amendments, although many “generic” drugs had reached the market without new drug applications (NDAs), the agency subjected virtually all new drugs — including generics — to the NDA requirement.² Second, well before the Hatch-Waxman amendments, FDA developed an abbreviated new drug application (ANDA) policy and therapeutic equivalence ratings for copies of the drugs that reached the market prior to 1962.³ During this time period, the states began to implement drug substitution laws. Third, in the early 1980s, Congress wove together two competing pieces of legislation, one restoring lost patent life to innovators and the other creating an ANDA pathway for post-1962 drugs, in the Drug Price Competition and Patent Term Restoration Act of 1984, otherwise known as the Hatch-Waxman amendments.⁴ The result was legislation that (a) created a model and resulted in some experience for stakeholders considering how best to shape a pathway for approval of biosimilars, and (b) provided FDA an opportunity to explore the scientific standards for biosimilars through review of applications for biosimilar versions of proteins approved under the Federal Food, Drug, and Cosmetic Act (FDCA).

1. *The FDCA and Key Amendments*

Prior to enactment of the FDCA, drugs were regulated under the Food and Drugs Act of 1906.⁵ This statute prohibited the adulteration and misbranding of drugs marketed in interstate commerce,⁶ but these terms were defined narrowly,⁷ there was no safety requirement, and there was no premarket review by the federal government. The statute applied to “any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals.”⁸ This definition would theoretically have captured the biological medicines on the market at the time — for example, vaccines, anti-toxins, and therapeutic serums — but as discussed in the next subsection, these products were instead subject to facility inspection and licensure by the predecessor to the National Institutes of Health (NIH). The Food and Drugs Act was administered by the Bureau of Chemistry of the Department of Agriculture, the predecessor to FDA.⁹ The apparent overlap between the drug statute and the biologics statute has

² See *infra* I.A.2.

³ See *infra* I.A.3.

⁴ See *infra* I.A.4.

⁵ Food & Drugs Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906). This statute is sometimes called the Pure Food and Drugs Act.

⁶ *Id.* § 2.

⁷ *Id.* §§ 7, 8, 34 Stat. at 769-71.

⁸ *Id.* § 6, 34 Stat. at 769.

⁹ *Id.* § 4, 34 Stat. at 769; see also *FDA History - Part I, The 1906 Food and Drugs Act and Its Enforcement*, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm> (last visited Sept. 14, 2010).

continued to this day and played a significant role in the final years that preceded the enactment of the BPCIA.

Legislative efforts to strengthen federal oversight of drugs began in earnest in 1933, when Senator Copeland (D-NY) introduced a bill, a later version of which would become the FDCA.¹⁰ Early bills did not contain an explicit safety or pre-market review requirement,¹¹ but after an incident in 1937 where 105 people (34 of whom were young children) died after taking a sulfa drug that contained diethylene glycol as a solvent,¹² members of Congress added both to the pending legislation.¹³ The result was the FDCA, which — although amended many times since 1938 — has remained the framework for federal drug regulation to this day.

The 1938 statute defined a “drug” as, among other things, an article “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and an article other than food “intended to affect the structure or any function of the body of man or other animals.”¹⁴ This definition, like the definition in the 1906 statute, clearly captured biological medicines. It defined a “new drug,” which would be subject to premarket review, as a drug not generally recognized by experts as safe under the labeled conditions of use (GRAS), or one that was GRAS but not used to a material extent or for a material time.¹⁵ Before a new drug could be marketed, it was required to be tested in humans in accordance with regulations promulgated by the Secretary of Agriculture.¹⁶ When sufficient safety data were obtained from these trials,¹⁷ the sponsor could submit a new drug application (NDA), which would take effect in sixty days unless the government rejected the application.¹⁸

Drugs that were GRAS and had been used to a material extent or for a material time were old drugs and not subject to the new drug application requirement.¹⁹ Over the next twenty-four years, many manufacturers brought to market products that we would now consider “generic,” on the theory that a prior manufacturer had established the safety of the active ingredient in question (and therefore the ingredient was GRAS).²⁰ These “me-too” products were sometimes different with respect to dosage form, route of administration, or strength. The statute also provided that a drug already subject to the Food and Drugs Act of 1906 was not a “new drug,” if its labeling contained the same representations regarding its conditions of use.²¹ Following enactment of the 1938 law, a number of manufacturers concluded that their products were not new drugs and distributed those products without NDAs.²²

¹⁰ S. 1944, 73rd Cong. (as introduced by Mr. Copeland, June 12, 1933).

¹¹ See, e.g., S. 2000, 73rd Cong. (as introduced by Mr. Copeland, Jan. 4, 1934); S2858, 73rd Cong. (as introduced by Mr. McCarran, Feb. 21, 1934); H.R. 7964, 73rd Cong. (as introduced by Mrs. Jenckes, Feb. 14, 1934).

¹² See Paul A. Offit, *The Cutter Incident* 157-58 (2005). Because the Food and Drugs Act contained no safety requirement, the government had been forced to proceed against elixir sulfanilamide on a misbranding theory—specifically, that it was incorrectly labeled as an “elixir” but contained no alcohol. See *id.* at 158.

¹³ S. 5, 75th Cong. (as reported to the House, Apr. 14, 1938).

¹⁴ Pub. L. No. 75-717, § 201(g), 52 Stat. 1040, 1041 (1938).

¹⁵ *Id.* § 201(p), 52 Stat. at 1041-42.

¹⁶ *Id.* §§ 505(a), (b), and (i), 52 Stat. at 1052-53.

¹⁷ See *id.* § 505(b), 52 Stat. at 1052 (requiring submission to contain “full reports of investigations” performed to determine whether the new drug was safe for use).

¹⁸ *Id.* § 505(c), 52 Stat. at 1052.

¹⁹ *Id.* § 201(p), 52 Stat. at 1041-42.

²⁰ We now use the term “generic” to refer not to the active ingredient but to the finished drug product. See *infra* note 54.

²¹ Pub. L. No 75-717, § 201(p)(1), 52 Stat. at 1041-42.

²² 40 Fed. Reg. 26142, 26143 (June 20, 1975).

In some cases the manufacturer made its own determination that the drug was GRAS,²³ and in others the manufacturer relied on a “not new drug” opinion issued by the agency.²⁴ The agency kept no record of these opinions.²⁵

2. Implementation of the Kefauver-Harris Amendments

In 1962, following the thalidomide tragedy,²⁶ Congress substantially reworked the drug provisions of the FDCA.²⁷ Two changes are relevant here. First, Congress added an effectiveness requirement. It did this by redefining a “new drug” as a drug not generally recognized as safe “and effective” under the labeled conditions of use (GRASE), or one that was recognized as GRASE but that had not been used to a material extent or for a material time.²⁸ The “effectiveness” requirement was subject to a “substantial evidence” standard.²⁹ It retained grandfather (old drug) status for pre-1938 drugs, again only if their labeling remained the same as it had been prior to enactment of the FDCA in 1938.³⁰ Second, it converted the premarket notification process to a premarket approval process,³¹ and it required FDA to review for effectiveness all products with NDAs that had become effective since enactment of the FDCA.³²

FDA accomplished this through the Drug Efficacy Study Implementation (DESI) program. Panels of experts at the National Academy of Sciences (NAS) rated each drug’s effectiveness.³³ As to each drug found effective, FDA published a DESI notice in the Federal Register, requiring the manufacturer to submit a conforming application. Under FDA policy, the DESI notice applied not only to the drug with the NDA that had been reviewed by the panel, but also to all “identical, related, and similar” drugs on the market without NDAs—the me-too or “generic” drugs.³⁴ FDA also revoked all of its old drug opinions.³⁵ Manufacturers of those drugs were thus required to determine old drug (*i.e.*, GRASE or grandfather status) on their own, or submit an NDA. By and large, any drug that had reached the market after 1938 went through the DESI process.

3. Development of the Abbreviated New Drug Application Pathway

The abbreviated new drug application (ANDA) process for pre-1962 drugs predated the 1984 Hatch-Waxman amendments. FDA developed this process in regulations predicated on the 1962 statute, without any new statutory authority.

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ In September 1960, the William S. Merrell Company submitted a new drug application (NDA) for Kevador (thalidomide), which was proposed as a sleep medication. It had been available for several years in Europe (as Contergan) and in the United States as an investigational new drug, and by November 1961 had been associated with widespread and serious birth defects. The medical officer at FDA refused to clear the NDA, but the “pre-approval” requirement of the 1962 amendments was one of the legislative reactions to the experience. *See generally* Offit, note 12, at 213-97.

²⁷ Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962).

²⁸ *Id.* § 102(a), 76 Stat. at 781 (amending FDCA § 201(p)).

²⁹ *Id.* § 102(c), 76 Stat. at 781 (amending FDCA § 505(d)).

³⁰ *Id.* § 107(c)(4), 76 Stat. at 789.

³¹ *Id.* § 104, 76 Stat. at 784 (amending FDCA § 505).

³² *See id.* § 107, 76 Stat. at 788-89.

³³ 31 Fed. Reg. 9426 (July 9, 1966).

³⁴ 37 Fed. Reg. 23185 (Oct. 31, 1972).

³⁵ 33 Fed. Reg. 7758 (May 28, 1968).

There were efforts to expand this process to post-1962 drugs without legislation immediately prior to the 1984 Hatch-Waxman amendments.

FDA developed the abbreviated process in 1969, for generic versions of drugs that had reached the market prior to 1962 and that had been reviewed in the DESI process.³⁶ The agency later explained that “[i]mplicit in this policy decision was the recognition that the marketing history of these pre-1962 drugs, published studies and reports, and the experts’ reviews and analyses, all taken together, constituted a body of information sufficient, in the case of most DESI drugs determined to be effective, to conclude that the same drug produced by another manufacturer would also be safe and effective if properly manufactured and used under the same conditions.”³⁷ The agency also, at one point, characterized these drugs as GRASE, implying that they were actually not “new drugs” in the first instance.³⁸ FDA implemented the new policy by revising its regulations to permit the submission of an abbreviated application whenever the agency deemed an ANDA sufficient.³⁹

ANDAs, which were permitted once effectiveness criteria had been established through the DESI review, were not required to contain any safety or effectiveness data. Instead, they were required to contain bioavailability and bioequivalence data, when FDA deemed them necessary.⁴⁰ If the applicant sought to make changes to the product that had been reviewed under DESI, and those changes raised safety or effectiveness issues, clinical data were required.⁴¹ And in this case, *i.e.*, for a similar or related but not identical drug, the ANDA pathway was not available.⁴²

Drugs approved by FDA after 1962 lacked DESI findings of effectiveness. Accordingly, the ANDA policy did not apply, and generic applicants were obligated to use the NDA pathway. Seeking to reduce the burden on these applicants, FDA created the “paper NDA” policy. This policy allowed applicants to copy pre-1962 drugs, if there was sufficient evidence of safety and effectiveness in the public domain. It was articulated in a memorandum drafted by the Associate Director for New Drug Evaluation⁴³ and, following litigation,⁴⁴ published in the Federal Register.⁴⁵

³⁶ 34 Fed. Reg. 2673 (Feb. 27, 1969) (proposed rule); 35 Fed. Reg. 6574 (Apr. 24, 1970) (final rule).

³⁷ 43 Fed. Reg. 39126, 39127 (Sept. 1, 1978).

³⁸ *See, e.g.*, 40 Fed. Reg. 26142, 26147 (June 20, 1975) (ANDAs are a “partial substitute for old drug determinations” and are “appropriate only for those drugs which, from a generic standpoint, are generally recognized as safe and effective.”).

³⁹ *See, e.g.*, 21 C.F.R. § 314.1(f) (1980); 21 C.F.R. § 130.4(f) (1971).

⁴⁰ 45 Fed. Reg. 82052, 82054-55 (Dec. 12, 1980). In some cases, bioequivalence data were not required.

⁴¹ *See* 43 Fed. Reg. at 39129 (proposed 21 C.F.R. § 314.3); 48 Fed. Reg. 2751, 2755 (Jan. 21, 1983) (21 C.F.R. § 314.2(c)).

⁴² 48 Fed. Reg. at 2755 (“If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated new drug application is not appropriate for the similar or related drug product.”).

⁴³ *See* Memorandum to Division Directors from Marion J. Finkel, M.D., Associate Director for New Drug Evaluation (July 31, 1978); 45 Fed. Reg. 82052 (Dec. 12, 1980) (announcing and defending the policy, and responding to a petition that asked it to withdraw policy); *id.* at 82058 (“paper NDAs are based on published literature”).

⁴⁴ *Hoffmann-La Roche, Inc. v. Harris*, 484 F. Supp. 58 (D.D.C. 1979). Although the policy was the subject of several court cases, no court ruled on its validity. *See id.* at 59; *Am. Critical Care v. Schweiker*, No. 81-C-252, 1981 U.S. Dist. LEXIS 12363 (N.D. Ill. May 13, 1981). None of these cases directly addressed the validity of the paper NDA policy. One court did find the policy consistent with FDA’s regulations at the time, however, and another stated that the prior cases had “upheld” the policy. *Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221, 226 (4th Cir. 1981); *Upjohn Manufacturing Co. v. Schweiker*, 520 F. Supp. 58, 61 (W.D. Mich. 1981), *aff’d*, 681 F.2d 480 (6th Cir. 1982).

⁴⁵ 46 Fed. Reg. 27396 (May 19, 1981).

4. *Enactment of the Hatch-Waxman Amendments*

a. *History*

In the late 1970s, FDA began to develop regulations that would have permitted ANDAs for generic copies of drugs that had been approved between October 12, 1962, and December 31, 1967, where the agency had deemed the product appropriate for ANDAs.⁴⁶ FDA intended to add to the eligibility period over time and then shift the end date by one year each year.⁴⁷ ANDAs would be permitted only if the pioneer product had been marketed for at least sixteen years.⁴⁸ A proposed rule was leaked to the press in 1982,⁴⁹ but the agency never published the proposal, and enactment of the Hatch-Waxman amendments mooted the issue. An administratively created "monograph" approach, modeled on the over-the-counter drug review, was also considered at one point.⁵⁰ FDA also circulated draft legislation that would have eliminated the distinction between old drugs and new drugs and that would have authorized the creation of monographs for all drugs.⁵¹ Indeed, Congress considered several bills — supported by FDA — in the late 1970s that would have created an ANDA-style product licensing requirement pursuant to monographs that would be issued immediately upon approval of innovative products, without a data exclusivity period.⁵²

The Hatch-Waxman amendments were a compromise between innovator industry interests and generic industry interests. They represented the marriage of two strands of public policy thinking in the late 1970s and early 1980s—indeed, the joining together of two bills, one restoring to innovators a portion of the patent life that lapsed during research, development, and FDA premarket review,⁵³ and the other

⁴⁶ FDA first suggested that it would promulgate regulations regarding the marketing of post-1962 generic drug products in the preamble to a 1978 proposed rule amending the ANDA process for pre-1962 drugs. 43 Fed. Reg. at 39128. Specifically, it announced its intention to "extend the ANDA concept at a later time to post-1962 drug products by publishing criteria for making such a determination about these drugs." *Id.* On January 13, 1982, the agency published an entry in the Calendar of Federal Regulations stating that it would publish a Notice of Proposed Rulemaking in March 1982 regarding ANDAs for duplicates of drug products approved after October 10, 1962. 47 Fed. Reg. 1765, 1767 (Jan. 13, 1982). It never did so.

⁴⁷ Draft Proposed Rule, New Drugs Approved After October 10, 1962, for Human Use: Proposal to Accept Abbreviated New Drug Applications (Feb. 8, 1982) at 24 (on file with authors).

⁴⁸ *Id.* In addition to proposing a fifteen-year pre-eligibility period, the agency assumed a period of a year or two after designation of ANDA suitability during which the generic firm would submit, and the agency would review, its ANDA. Memorandum from J. Richard Crout, M.D., Director, Bureau of Drugs, FDA, to FDA Commissioner at 2-3 (Feb. 8, 1982) (on file with authors).

⁴⁹ See *Post-1962 ANDA Reg Proposal in the Works Would Build In 15-Year Gap Between Pioneer Approval Date and Generic Eligibility for ANDA*, THE PINK SHEET, Mar. 8, 1982, at 6.

⁵⁰ See 40 Fed. Reg. 26142, 26146 (June 20, 1975). The Assistant to the Director for Regulatory Affairs in the Bureau of Drugs published an article in 1974 stating that the agency intended to use a "monograph approach to the regulation of prescription drugs." Mary A. McEniry, *Drug Monographs*, 29 FOOD DRUG COSM. L. J. 166 (1974). Each monograph would specify the conditions under which the drug could be marketed without premarket approval. While the agency would begin with DESI drugs, "[d]rugs which are covered by NDAs, approved since 1962, will also be candidates for monographs." *Id.* at 168-70. She suggested this as an alternative to the ANDA and noted it would effectively render irrelevant the distinction between new drugs and old drugs. *Id.* at 170.

⁵¹ The Drug Regulation Reform Act of 1978, Draft (Dec. 5, 1977) (on file with authors).

⁵² S. 2755, 95th Cong. (as introduced by Mr. Kennedy, Mar. 16, 1978); H.R. 11611, 95th Cong., (as introduced by Mr. Rogers, Mar. 16, 1978).

⁵³ The innovative industry had long been concerned that after the 1962 amendments, clinical testing and FDA premarket review significantly eroded the effective patent life of new drug products. At their urging, in 1981 Congress began to consider legislation to fully restore the portion of the patent term that passed during the premarket regulatory process. H.R. 1937, 97th Cong. (introduced by Mr. Kastenmeier and Mr. Sawyer, Feb. 18, 1981). A measure to achieve that goal passed the Senate but failed in the House. S. 255, 97th Cong. (1981).

creating a generic drug approval pathway.⁵⁴ The Hatch-Waxman amendments were supported by members of Congress in both parties,⁵⁵ and both the Pharmaceutical Manufacturers Association (PMA) and the Generic Pharmaceutical Industry Association (GPIA) endorsed the final legislation.⁵⁶

Title I of the Hatch-Waxman amendments established procedures under which FDA could approve ANDAs for generic copies of drugs with approved NDAs. Title II amended the Patent Act to restore a portion of the patent term effectively lost during the premarket period. Although Title I applied only to drugs with NDAs, Title II applied both to drugs with NDAs and to biological products licensed under the Public Health Service Act. Congress amended the Hatch-Waxman provisions in, among other legislation, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.⁵⁷ The authors of this article cite the statute and regulations in place in March 2010, when the BPCIA was enacted.

b. *ANDA Pathway*

When a company seeks to market a generic drug product, it does not need to submit full reports from studies conducted to show its safety and effectiveness.⁵⁸ Indeed, as under the prior ANDA policy, the agency may not request preclinical or clinical data to support the generic drug's approval.⁵⁹ Instead, under section 505(j) of the FDCA, the generic applicant must show that the product has the same active ingredient(s) as the reference product and the same route of administration, dosage form, and strength.⁶⁰ If the generic applicant seeks to vary its product from the innovator product with respect to one of these aspects, it must submit a suitability petition, which FDA may grant only if no additional investigations are necessary to support safety and effectiveness.⁶¹ If additional data are needed, the applicant must proceed under section 505(b) of the statute. In addition to showing sameness with respect to these aspects, the generic applicant must establish that its product is bioequivalent to the innovator's product.⁶²

⁵⁴ The generic industry filed a lawsuit to compel FDA to approve duplicate versions of post-1962 drugs on the same basis as it approved duplicate versions of pre-1962 drugs. Complaint, *Nat'l Ass'n of Pharm. Mfrs., Inc. v. Heckler*, No. 88 Civ. 4817 (S.D.N.Y. June 24, 1983). The parties eventually agreed that the case was mooted in light of the Hatch-Waxman amendments. Stipulation and Order of Dismissal Without Prejudice, *Nat'l Ass'n of Pharm. Mfrs., Inc. v. Heckler*, No. 88 Civ. 4817 (S.D.N.Y. Jan 7, 1985). The generic industry also began to lobby Congress for a mechanism that would allow FDA to approve generic applications shortly after the innovator's patent expired. The industry's efforts were propelled by a 1983 Supreme Court ruling that generic drug products require their own NDAs or ANDAs, *i.e.*, that prior approval of the active ingredient was not sufficient. *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983). Representative Waxman responded by introducing legislation to establish an ANDA pathway for generic drugs. H.R. 4258, 96th Cong. (1979).

⁵⁵ David G. Sewell, *Rescuing Science from the Courts: An Appeal for Amending the Patent Code to Protect Academic Research in the Wake of Madey v. Duke University*, 93 Geo. L.J. 759, 765 (Jan. 2005).

⁵⁶ The Generic Pharmaceutical Industry Association (GPIA) merged with the National Pharmaceutical Alliance (NPA) in 2000. GPIA subsequently merged with the National Association of Pharmaceutical Manufacturers (NAPM) to form the Generic Pharmaceutical Association (GPhA) in 2001. Prior to the merger, GPIA had "historically represented larger generic firms, including those affiliated with brand name companies, while NAPM...[had] been identified with smaller firms." See *GPIA/NPA Merger Seeks Unified Generic Industry Voice, Without NAPM*, THE PINK SHEET, May 15, 2000, at 16, 17. NPA was focused on "sales and marketing issues." See GPhA, *About GPhA: Industry History*, <http://www.gphaonline.org/about-gpha/history> (last visited on Sept. 14, 2010).

⁵⁷ 117 Stat. 2066, Pub. L. No. 108-173 (2003).

⁵⁸ See FDCA § 505(j)(2)(A).

⁵⁹ *Id.* § 505(j)(2)(A).

⁶⁰ *Id.* § 505(j)(2)(A)(ii) & (iii).

⁶¹ *Id.* § 505(j)(2)(C).

⁶² *Id.* § 505(j)(2)(A)(iv).

Congress also included provisions to allow innovators and generic companies to litigate patent validity and infringement issues prior to generic market entry. Specifically, each NDA applicant must identify to FDA the patents that claim its product or a method of using its product.⁶³ FDA lists these in the publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (the *Orange Book*). When a generic applicant files its ANDA, it must provide a certification with respect to every such patent.⁶⁴ It may state that there are no such patents listed or that the patent(s) have expired.⁶⁵ As to each listed and unexpired patent, however, it must certify that it does not intend to market until patent expiry or that it believes the patent to be invalid or not infringed.⁶⁶ The latter is a paragraph IV certification and requires notice to be sent to the NDA holder and the patent owner, if different.⁶⁷ The first generic applicant to file a paragraph IV certification to a listed patent is entitled to 180-day exclusivity, during which time no other ANDA that is based on the reference product may be approved.⁶⁸ Filing an ANDA with a paragraph IV certification is an act of patent infringement creating federal court jurisdiction for litigation.⁶⁹ For forty-five days after the notified party receives notice of a paragraph IV certification, the generic applicant is barred from bringing a declaratory judgment action, and the notified party has the opportunity to bring a patent infringement suit.⁷⁰

The generic applicant's certification dictates which provision governing the timing of ANDA approval applies. If the generic applicant makes a paragraph III certification, that it will wait until patent expiry, final approval of its ANDA may not be effective until that expiry date.⁷¹ If the generic applicant makes a paragraph IV certification and neither the NDA holder nor the patent owner files suit within forty-five days, final approval of the ANDA may be effective immediately (unless there is a paragraph III certification as well or another paragraph IV certification as to which the notified party does sue).⁷² If the generic applicant makes a paragraph IV certification and suit is brought within forty-five days, final approval is stayed for thirty months or until a court decision of validity and non-infringement.⁷³ If the case is resolved in favor of the patent owner, the court must order that final approval take effect no earlier than patent expiry.⁷⁴ If the litigation is ongoing at the conclusion of the thirty months, FDA must approve the ANDA if it is otherwise approvable, and the generic applicant may market its product. In this case, however, it risks damages for patent infringement if it later loses the lawsuit. The patent owner may bring a patent infringement suit later, but if it brings suit after the forty-five day notice period, there is no thirty-month stay of generic approval.⁷⁵

⁶³ *Id.* § 505(b)(1).

⁶⁴ *Id.* § 505(j)(2)(A)(vii).

⁶⁵ *Id.* § 505(j)(2)(A)(vii)(I) & (II).

⁶⁶ *Id.* § 505(j)(2)(A)(vii) (III) & (IV).

⁶⁷ *Id.* § 505(j)(2)(B).

⁶⁸ *Id.* § 505(j)(5)(B)(iv); see Erika Lietzan, David Korn, and Shaw Scott, *A New History and Discussion of 180-Day Exclusivity*, 64 *FOOD & DRUG L.J.* 335 (2009).

⁶⁹ 35 U.S.C. § 271(e)(2).

⁷⁰ FDCA § 505(j)(5)(B)(iii).

⁷¹ *Id.* § 505(j)(5)(B)(ii).

⁷² *Id.* § 505(j)(5)(B)(iii).

⁷³ *Id.*

⁷⁴ 35 U.S.C. § 271(e)(4).

⁷⁵ There have been disputes over whether patents were properly listed. See, e.g., *Organon Inc. v. Mylan Pharms., Inc.*, 293 F. Supp. 2d 453 (D.N.J. 2003); see also 21 U.S.C. § 355(j)(5)(C)(ii)(I) (allowing a counterclaim in a patent infringement action if a patent is improperly listed). In 2003 Congress amended the law to provide that generic applicants would not be blocked by multiple (successive) thirty-month stays through the listing of additional patents while their applications were pending. Pub. L. No. 108-173, § 1101, 117 Stat. at 2449 (codified at 21 U.S.C. § 355(j)(5)(B)(iii) (2000 & Supp. III 2005)).

Congress also included a new paragraph (2) in section 505(b) of the FDCA. The purpose and effect of this provision were and still are the subject of considerable debate. Section 505(b)(2) states that

An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include [a paragraph I, II, III, or IV certification] with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval⁷⁶

Put another way, if an application submitted under paragraph (1) — a new drug application — pertains to a drug for which the clinical investigations were *not* conducted by or for the applicant and for which the applicant lacks a right of reference or use, the applicant must include the same patent certifications as must an ANDA applicant. The patent certification must be made with respect to every patent that claims the drug for which the investigations were conducted or that claims a use for the drug.⁷⁷ Further, the same patent litigation rules apply; *e.g.*, if this applicant includes a paragraph IV certification, then the patent owner or BLA holder may sue within forty-five and obtain a thirty-month stay.⁷⁸ These applications are referred to as “505(b)(2) applications.”

FDA takes the position that a 505(b)(2) application may rely on the agency’s earlier finding that the reference product was safe and effective (although some argue that this inherently constitutes reliance on the actual data in the reference product’s NDA) and that it may include additional data, for example clinical data, to bridge any differences between the reference product and its own.⁷⁹ There are mixed views within industry, with many innovators of the view that this provision was instead intended to codify FDA’s previously existing paper NDA policy. Under this interpretation, the provision would permit literature-based applications, but only if the information available in the public domain was sufficient to satisfy the standard for NDA approval. The issue has never been resolved by a court. Because the agency’s view allows it to accept applications for products that cannot satisfy the generic approval standard (for example, the sameness requirement) and that contain some clinical data (which generic applicants may not), section 505(b)(2) provided a theoretical pathway for approval of biosimilar versions of proteins that happened to be approved under the FDCA. This issue is discussed in subsection B.3.

c. *Data Protection*

Data “protection” usually means two things: (1) protection of preclinical and clinical data from public disclosure by a medicines agency, and (2) prevention of reliance on those undisclosed data (or marketing approval based on the data) by other applicants or a medicines agency for some period of time. The latter is also

⁷⁶ FDCA § 505(b)(2).

⁷⁷ *Id.* § 505(b)(2)(A).

⁷⁸ *Id.* § 505(c)(3)(C).

⁷⁹ Letter from Steven K. Galson, M.D., M.P.H., Director, Center for Drug Evaluation and Research (CDER), FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP, Stephan E. Lawton, Esq., BIO, and Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006), Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA 2004-N-0059 (formerly 2004P-0231, 2003P-0176, 2004P-0171, and 2004N-0355), at 5-6.

referred to as data exclusivity or regulatory exclusivity. Congress addressed both issues in the Hatch-Waxman amendments.

Prior to the Hatch-Waxman amendments, applicants could not rely on the data in approved post-1962 NDAs, nor could they rely on the fact of FDA approval of these NDAs.⁸⁰ Had the agency concluded the ANDA rulemaking under consideration at the time, there would have been a 15- or 16-year period of data exclusivity.⁸¹ FDA regulations also generally provided for nondisclosure of preclinical and clinical data in NDAs. These regulations dated to the early 1970s⁸² and were predicated on section 301(j) of the FDCA, the Federal Trade Secrets Act, and exemption 4 of the Freedom of Information Act.⁸³ Although a "summary" of the safety and effectiveness data submitted in an NDA would be released upon NDA approval, the full data package could be disclosed in only five situations.⁸⁴ These included the situation where FDA had determined the drug was not a "new drug" (in which case NDAs would no longer be required) and the situation where FDA had determined the drug could be marketed without submission of safety and effectiveness data (for example, if it was a generic copy of a pre-1962 DESI drug).⁸⁵ Even in these five situations, if there were "extraordinary circumstances," the agency would not disclose the data. FDA explained that the phrase "extraordinary circumstances" was intended to preclude disclosure where the data continued to have competitive value.⁸⁶

Congress provided new drug applicants with either three or five years of data exclusivity. Specifically, if the drug product contained only a new chemical entity (NCE), no generic application could be submitted for five years.⁸⁷ There was an exception for generic applications containing paragraph IV certifications, which could be submitted after four years.⁸⁸ If any ingredient in the proposed drug was not a new chemical entity, but the application was supported by clinical data (other than bioavailability data) necessary to its approval, then a generic application seeking approval of the drug for the same conditions of use could not be approved for three years.⁸⁹ Further, any supplement for a new condition of use would be entitled to three years of protection for that new condition of use, assuming it was supported by clinical data (other than bioavailability data) essential to its approval.⁹⁰ There

⁸⁰ See *supra* at I.A.3.

⁸¹ See *supra* at I.A.3.

⁸² See 39 Fed. Reg. 44602 (Dec. 24, 1974).

⁸³ Under section 301(j) of the FDCA, "[t]he using by any person to his own advantage or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this Act, any information acquired under authority of section [505] concerning any method or process which as a trade secret is entitled to protection" is a prohibited act and, therefore, a federal crime. FDCA §§ 301(j), 303(a). Under the Federal Trade Secrets Act, it is a federal crime for an officer or employee of the United States or of any U.S. department or agency to publish, divulge, disclose, or make known in any manner or to any extent not authorized by law "any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus. . . of any person, firm, partnership, corporation, or association." 18 U.S.C. § 1905. Exemption 4 of the FOIA protects "trade secrets and commercial or financial information obtained from a person [that is] privileged or confidential." 5 U.S.C. § 552(b)(4).

⁸⁴ 39 Fed. Reg. at 44655.

⁸⁵ *Id.*

⁸⁶ See, e.g., *id.* at 44638 ("A situation in which one IND or NDA directly affects another might be viewed as an extraordinary circumstance.")

⁸⁷ FDCA § 505(j)(5)(F)(ii).

⁸⁸ *Id.* §§ 505(j)(2)(A)(vii)(IV); 505(j)(5)(F)(ii).

⁸⁹ *Id.* § 505(j)(5)(F)(iii).

⁹⁰ *Id.*

were special provisions for new drugs on the market at the time of enactment; if an NCE was approved between January 1, 1982, and September 24, 1984, approval of an ANDA based on that NCE could not be effective until ten years after the NCE approval. Approval of an ANDA based on any other NDA or supplemental NDA approved during the same period could not be effective until two years after enactment.⁹¹ The legislation was silent regarding NCEs approved prior to January 1, 1982, and the agency gave them no exclusivity.⁹²

Congress also addressed the disclosure of safety and effectiveness data in an NDA, in a new section 505(l) of the FDCA.⁹³ This provision essentially codified the existing FDA disclosure regulations, with an adjustment to reflect the new ANDA pathway. Specifically, the safety and effectiveness data that had not previously been disclosed were to be made to the public in five situations, with an exception for “extraordinary circumstances.”⁹⁴ These situations were that: (1) no work was being or would be undertaken to have the application approved; (2) FDA had rejected the application, and all legal appeals had been exhausted; (3) approval of the application had been withdrawn, and all legal appeals had been exhausted; (4) FDA had determined that the drug was not a new drug; and (5) approval of the first ANDA could be made effective. FDA made a conforming change to its regulations in 1985.⁹⁵

B. Federal Regulation of Biological Drugs

Federal regulation of biological products has always been separate from, and yet overlapping with, federal regulation of non-biological products. Three aspects of the federal regulation of biological drugs are relevant to this article. First, the governing statutes were enacted at separate times, were for decades administered by separate agencies, and at least historically focused on different issues. Second, the precise scope of the biologics law has at times been unclear, and a number of protein products were for one reason or another approved instead under the FDCA. Third, all biologic drugs are nevertheless also drugs and subject to the FDCA, including the rules on misbranding and adulteration of drugs and, at least theoretically, the

⁹¹ *Id.* §§ 505(j)(5)(F)(i), 505(j)(5)(F)(v).

⁹² See FDA, Drug Approval Reports, Original New Drug Approvals (NDAs and BLAs) by Month, <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.ReportsMenu> (showing that Procordia was approved on Dec. 31, 1981 and deemed an NME), and FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (Orange Book) AD13 (6th ed. 1985) (showing that Procordia did not receive exclusivity).

⁹³ FDCA § 505(l)(1).

⁹⁴ The legislative history generally supports the argument that Congress intended to codify the agency’s prior concept of extraordinary circumstances. See 130 Cong. Rec. 24977 (Sept. 12, 1984) (pre-enactment statement of Senator Hatch). *But see* 130 Cong. Rec. 31729-31730 (Oct. 10, 1984) (post-enactment statement of Representative Waxman). There is support in the legislative history also for the proposition that Congress did not envision disclosure of data during the applicable patent term. See H.R. Rep. No. 98-857, pt. 1, at 36 (1984) (stating that by section 104 of the House bill, which proposed to add language identical to that eventually passed, the House Committee on Energy and Commerce did “not intend that safety and effectiveness data and information be released under this section if an ANDA challenging the validity of a patent is approved before there has been a court decision holding the patent invalid and if the NDA holder brings an action to restrain the disclosure”).

⁹⁵ 47 Fed. Reg. 46622, 46665 (Oct. 19, 1982); 50 Fed. Reg. 7452, 7515 (Feb. 22, 1985) (replacing “[a] final determination has been made that the drug may be marketed without submission of data and information on safety, or effectiveness, or both” with “for applications submitted under section 505(b) of the act, the effective date of the approval of the first application submitted under section 505(j) of the act which refers to such drug, or the date on which the approval of an application under section 505(j) which refers to such drug could be made effective if such an application had been submitted”).

requirement to have an NDA. The resulting overlap but lack of perfect symmetry both complicated and arguably facilitated development of the BPCIA.

1. *The Biologics Act and Public Health Service Act*

Aside from a brief experiment in the early 1800s with regulation of vaccines,⁹⁶ the federal government did not regulate biological products until the beginning of the 20th century. Vaccines had been around since the late 1700s, and various other biological products, including viruses, therapeutic serums, toxins, and anti-toxins, were available. Most of these products were manufactured using methods that would seem crude today and that created a danger of contamination. For example, the diphtheria anti-toxin available at the turn of the century was produced in horses that had been injected with a small amount of diphtheria and that had generated anti-toxins.⁹⁷ The serum of these immunized horses was extracted and injected into children. The smallpox vaccine was made by scraping pus from the skin of cattle infected with cowpox.⁹⁸ Following incidents where these two biologics were contaminated with tetanus and resulted in the death of children,⁹⁹ Congress passed the Biologics Act of 1902.¹⁰⁰ At this time, the federal government did not regulate non-biological drugs.

The 1902 statute required biologics to be manufactured in establishments holding a license issued by the federal government.¹⁰¹ As a condition of licensure, the government retained the right to inspect the facility.¹⁰² A manufacturer was required to label its product with the name of the product; the manufacturer's name, address, and license number; and an expiry date.¹⁰³ Although the statute contained no explicit safety requirement, the inspection authority and licensure requirement implicitly conveyed an obligation to maintain a manufacturing process that would ensure the safety of the resulting product. Establishment licenses were required until 1997.

Six years after enacting the FDCA, Congress revised and recodified the Biologics Act as section 351 of the Public Health Service Act (PHSA).¹⁰⁴ The statute now provided that an establishment license could be issued only upon a showing that "the establishment *and the products* for which a license [was] desired" met standards designed to ensure the "safety, purity, and potency" of the products.¹⁰⁵ Although it would have been possible to read this provision differently, the new language was interpreted as requiring both an approved establishment license application

⁹⁶ An Act to encourage vaccination, Ch. 37, 2 Stat. 806 (1813) (enactment); An Act to repeal the act, entitled "An Act to encourage vaccination," Ch. 50, 3 Stat. 677 (1822) (repeal).

⁹⁷ National Institutes of Health, A Short History of the National Institutes of Health: Biologics, http://history.nih.gov/exhibits/history/docs/page_03.html (last visited Sept. 14, 2010). The Pasteur rabies vaccine was initially made by injecting the virus into the brains of rabbits and then extracting the vaccine. Later the vaccine was made in fertilized duck eggs. *Preventing the Incurable*, TIME, Aug. 14, 1964; see also Ken Flieger, *First Vaccine From Rabid Rabbits*, FDA CONSUMER, June 1990, at 26. Influenza vaccines are still grown in fertilized eggs. Letter from Margaret A. Hamburg, M.D., Commissioner of Food and Drugs, to Nation's Healthcare Professionals on H1N1 Vaccine (Nov. 10, 2009), available at <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm189691.htm>.

⁹⁸ F. Fenner et al., *Smallpox and its Eradication* 260-63 (Geneva: World Health Organization) (1988) (excerpt from Edward Jenner, *The Origin of the Vaccine Inoculation* (1801)).

⁹⁹ See Paul A. Offit, *The Cutter Incident* 59 (2005).

¹⁰⁰ Pub. L. No. 57-244, 32 Stat. 728 (1902).

¹⁰¹ *Id.* § 1, 32 Stat. at 728-29.

¹⁰² *Id.* § 3, 32 Stat. at 729.

¹⁰³ *Id.* § 1, 32 Stat. at 728.

¹⁰⁴ Pub. L. No. 78-410, 58 Stat. 682, 702-703 (1944).

¹⁰⁵ *Id.* § 351(d), 58 Stat. at 702-03 (emphasis added).

(ELA) and an approved product license application (PLA). This dual licensure requirement lasted until 1997. As noted, Congress added an explicit requirement that biologics be safe, pure, and potent.¹⁰⁶

Between 1944 and 2010, the most important change to section 351 occurred in 1997.¹⁰⁷ Congress eliminated the dual licensure requirement, creating a single biologics license application (BLA) requirement.¹⁰⁸ This followed an effort at the agency to abolish, by regulation, the requirement for dual licenses for well-established therapeutic biotechnology-derived proteins.¹⁰⁹ Congress also provided that no biological product could be introduced into interstate commerce without an effective license, rephrasing the existing statutory provision in a way that paralleled the FDCA provision governing new drugs.¹¹⁰

2. Provisions Addressing Overlap

Overlap between the FDCA and the PHSA has been an issue since enactment of the Food and Drugs Act in 1906, which defined the term drug to include any substance or mixture of substances intended to be used for the cure, mitigation, or prevention of disease of either man or other animals.¹¹¹ This was broad enough to capture products that were already subject to the Biologics Act, but the statute did not address the overlap. In the 1938 statute, the term drug was again defined broadly enough to include the products that were already subject to licensure under the Biologics Act. Congress included this time a provision that nothing in the new law should be construed as in any way “affecting, modifying, repealing, or superseding” the 1902 statute.¹¹² In the December that followed, FDA published a regulation stating that a new drug would not be subject to section 505 of the FDCA if it was licensed under the 1902 statute.¹¹³ When Congress recodified the Biologics Act in 1944, it included a provision stating that nothing in the new statute should be construed as in any way affecting, modifying, repealing, or superseding the 1938 law.¹¹⁴

In 1972, the Secretary of Health, Education, and Welfare gave FDA express authority to apply the FDCA — including the requirement that drugs be proven safe and effective — to biological products.¹¹⁵ The Secretary also, a few months later, fully transferred authority over biological products to the agency.¹¹⁶ FDA responded

¹⁰⁶ *Id.*

¹⁰⁷ Minor changes were made to section 351 in 1958, 1970, 1979, 1986, 1992, and 1996, perhaps the most significant of which was the decision in 1970 to clarify that blood, blood components, and blood derivatives — all non-immunological products — fell within the scope of the statute. Pub. L. No. 85-881, 72 Stat. 1704 (1958) (revising provision that specified entity directed to issue regulations); Pub. L. No. 91-515, 84 Stat. 1297, 1308 (1970) (adding vaccines and blood, among other things, to the list of products regulated); Pub. L. No. 96-88, 93 Stat. 668, 695 (1979) (relating to the renaming of the Department of Health, Education, and Welfare); Pub. L. No. 99-660, 100 Stat. 3743, 3751-3752 (1986) (relating to export of partially processed biological products); Pub. L. No. 102-300, 106 Stat. 238, 240 (1992) (relating to the renaming of the Department); Pub. L. No. 104-134, 110 Stat. 1321-320 (1996) (amending provision on export of partially processed biological products to conform to an amendment to the FDCA).

¹⁰⁸ Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123, 111 Stat. 2296, 2323 (1997).

¹⁰⁹ See Press Release, U.S. Dep’t of Health and Human Services (HHS), Reinventing Regulation of Drugs Made from Biotechnology (Nov. 9, 1995); see also 60 Fed. Reg. 63048 (Dec. 8, 1995).

¹¹⁰ Pub. L. No. 105-115, § 123(a)(1), 111 Stat. at 2323 (amending PHSA § 351(a)).

¹¹¹ 34 Stat. 769.

¹¹² Pub. L. No. 75-717, § 902(c), 52 Stat. at 1059.

¹¹³ 3 Fed. Reg. 3161, 3168 (Dec. 28, 1938).

¹¹⁴ Pub. L. No. 78-410, § 351(g), 58 Stat. at 703.

¹¹⁵ 37 Fed. Reg. 4004 (Feb. 25, 1972); see FDCA § 201(g).

¹¹⁶ 37 Fed. Reg. 12865 (June 29, 1972).

by conducting the "Biologics Review," which was modeled on the DESI review and involved an assessment of every marketed biological product for effectiveness.¹¹⁷ Under the regulation that had been in place since 1938, however, the agency still did not require NDAs to be submitted and approved.

In 1997, Congress added section 351(j) to the FDCA, confirming again that the FDCA applies to biological products but adding that products with approved BLAs need not have approved NDAs.¹¹⁸ Section 351(j) codified the agency practice of not requiring NDAs for licensed biologics.

3. Protein Products Approved under the FDCA

The overlap just described may be partially responsible for the fact that a number of protein products — including biotechnology-derived therapeutic protein products — are the subject of NDAs effective (and later approved) under the FDCA rather than ELAs and PLAs, or BLAs, approved under the PHSA. The first of these were bovine-derived and porcine-derived insulin. Insulin had been marketed as early as the 1920s¹¹⁹ and could, in theory, have been viewed as a biological product (although it was not immunological in nature and therefore was unlike the products the statute had arguably been designed to sweep within federal oversight). It was, at the time, covered by patents owned by the University of Toronto, which imposed a strict batch certification requirement on its licensees,¹²⁰ and perhaps this requirement was viewed as providing a sufficient assurance of safety that FDA needed not grapple with the question of jurisdiction under the Biologics Act.¹²¹ After the FDCA was enacted in 1938, however, insulin NDAs were submitted and took effect under the sixty-day rule.¹²² Human growth hormone, derived from the pituitary gland of cadavers, was approved in the mid 1970s.¹²³ Various other hormones, including conjugated estrogens derived from the urine of pregnant mares, were available by the 1950s and regulated under NDAs.¹²⁴ Thus by the time of the biotechnology

¹¹⁷ 38 Fed. Reg. 4319, 4322 (Feb. 13, 1973) ("Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological or other effect of the biological product, when used under adequate directions, for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, treatment or prevention of disease in man. Proof of effectiveness shall consist of controlled clinical investigations . . . unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation, and that an alternative method of investigation is adequate to substantiate effectiveness.").

¹¹⁸ Pub. L. No. 105-115 § 123(g), 111 Stat. at 2324 (enacting 42 U.S.C. § 262(j)).

¹¹⁹ Michael Bliss, *The Discovery of Insulin* 133-141 (1982).

¹²⁰ Fred B. Linton, *Leaders in Food and Drug Law*, 5 FOOD & DRUG L. J. 771, 782-83 (1950). Although it first collaborated only with Eli Lilly, the University eventually licensed several companies to make insulin for commercial sale. Bliss, *supra* note 119, at 137-141.

¹²¹ The University of Toronto's insulin patents expired in December 1941. Several manufacturers had indicated their intent to manufacture and market insulin once the patents expired, and the medical profession concluded there would be a "grave danger" to patients if the University's batch-testing requirement was no longer enforced. They and other stakeholders secured rapid introduction and passage of an amendment to the FDCA requiring batch certification as a condition of marketing insulin. Linton, *supra* note 120, at 782-83 (1950); see also Carl M. Anderson, *The 'New Drug' Section*, 1 FOOD DRUG COSM. L. Q. 71, 83 (1946); Alan H. Kaplan, *Fifty Years of Drug Amendments Revisited: In Easy-to-Swallow Capsule Form*, 50 FOOD & DRUG L. J. 179 (1995). The bill was signed one day before the patents expired. Pub. L. No. 77-366, 55 Stat. 851 (1941). From 1941 to 1997, insulin was regulated under this provision of the FDCA.

¹²² The first insulin NDA went into effect at the end of 1939. FDA, *Ever Approved Drug Products Listed by Active Ingredient*, at 2291 (printout dated Aug. 2, 1989) (on file with authors).

¹²³ FDA, *Ever Approved Drug Products*, *supra* note 122, at 4513.

¹²⁴ See, e.g., FDA, *Ever Approved Drug Products*, *supra* note 122, at 1736.

revolution that began in the 1970s and gained momentum in the 1980s, a variety of naturally derived therapeutic proteins were regulated under the FDCA.

FDA never explained its decision to require NDAs for these products. The overlap of the statutes is undoubtedly partly responsible. Some of the approvals may be attributable to a regulation from 1947 that excluded “hormone[s]” from the list of products “analogous” to therapeutic serums and therefore within the PHSA definition of “biological product[s].”¹²⁵ (FDA has not, however, applied that rule consistently. Erythropoietin is a hormone, and it is the subject of an approved BLA.) There may also be product-specific reasons, such as the reason for insulin suggested in the preceding paragraph. It is also possible, as previously suggested, that at least until the 1970s federal regulators viewed the biologics statute as primarily aimed at immunological products. Another possibility is that FDA was focused on the manufacturing process; insulin and human growth hormone were extracted from animal or human tissue, much as many traditional drugs were extracted from plants, whereas biologics were derived from manufacturing processes that consisted of controlled production in living systems.

In 1986, during the biotechnology revolution, FDA made the decision that recombinant versions of previously marketed naturally derived proteins would be regulated as new products under the same statute as their naturally derived predecessors.¹²⁶ This was, in fact, what it had already been doing. It had approved an NDA in 1982 for recombinant human insulin, the first approved biotechnology-derived drug.¹²⁷ Under this principle, recombinant human growth hormone would require an NDA. Recombinant conjugated estrogens, had they been possible, would have required an NDA.

Because a number of naturally derived and biotechnology-derived therapeutic protein products are subject to the NDA requirement, FDA has had, since 1984, the theoretical authority to approve both ANDAs and 505(b)(2) applications for these therapeutic proteins. By 2010, it had used both provisions to approve protein products, although in virtually every case prompting controversy and sometimes prompting litigation. In addition, it had refused to use the ANDA authority in at least one case, citing the complexity and lack of characterization of the proposed reference product.

FDA’s use of the ANDA provisions to approve therapeutic proteins has been limited. In 1997, it approved a generic version of Serono’s Pergonal (menotropins).¹²⁸ Menotropin is a hormone derived from the urine of post-menopausal women, and it is used to treat infertility in women. It contains two active ingredients, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH comprise

¹²⁵ 12 Fed. Reg. 411 (Jan. 21, 1947); see 21 C.F.R. § 600.3(h)(5). The statute has always applied to listed categories (e.g., a virus, therapeutic serum, or toxin) and “analogous” products. FDA stated that a product is analogous to a therapeutic serum if it is “composed of whole blood or plasma or containing some organic constituent or product *other than a hormone* or an amino acid derived from whole blood, plasma, or serum.” 12 Fed. Reg. at 411 (emphasis added).

¹²⁶ See FDA, Statement of Policy for Regulating Biotechnology Products, 51 Fed. Reg. 23309, 23310 (June 26, 1986) (acknowledging that there were “no statutory provisions or regulations that address biotechnology specifically” and indicating that review of biotechnology products would proceed under existing mechanisms based on “the intended use of each product on a case-by-case basis”). Also in the 1970s and 1980s, the biotechnology industry developed biotechnology-derived proteins that were related to or derived from the immune system and as to which there had been no naturally derived predecessor product. FDA essentially viewed these products as analogous to therapeutic serums and licensed them under the PHSA.

¹²⁷ HHS News, P82-50 (Oct. 29, 1982); FDA, Ever Approved Drug Products, *supra* note 122, at 2287.

¹²⁸ See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

less than five percent of the product, with lactose and uncharacterized urine proteins (UUP) constituting the rest. Lederle filed its ANDA in 1990, and Ferring acquired the rights to the ANDA while the application was pending. Serono argued against approval, first on the ground that the UUPs were different in the Lederle product and later on the ground that the active ingredients were themselves different, on account of a variation in the carbohydrate side chains attached to the amino acid backbone (which was identical).¹²⁹ FDA approved the ANDA in 1997, responding to Serono that the isoform variations were not “clinically significant for the product’s intended uses” and that the UUPs were simply impurities that could differ.¹³⁰ The D.C. Circuit deferred to what it viewed as a “reasonable” interpretation of the FDCA, specifically that the ANDA provisions require clinical equivalence, chemical identity to the extent possible, and limited isoform variation.¹³¹ It noted also that if absolute chemical identity were required, “not only menotropins but other categories of protein products would be excluded from the ANDA process as well.”¹³²

Despite this precedent, FDA has not since approved an ANDA for a therapeutic protein product. Indeed, it has declined to approve ANDAs, and has required 505(b)(2) applications, for conjugated estrogens.¹³³ Premarin, the reference product, “is derived from the urine of pregnant mares and contains a number of different estrogens.”¹³⁴ Precisely how each of the various estrogens contributes to the drug’s overall effectiveness has not been determined.¹³⁵ FDA has announced and apparently still maintains that it will not approve an ANDA due to the inability to fully characterize the reference product.¹³⁶ Instead it approved a 505(b)(2) application for Cenestin, a synthetic conjugated estrogen derived from plant material.¹³⁷

In 2005, FDA approved a 505(b)(2) application for Fortical (salmon calcitonin recombinant), for which the reference product was the chemically synthesized Miacalcin (calcitonin salmon). In doing so, it noted that the active ingredient of Fortical is relatively simple (a thirty-two amino acid, non-glycosylated peptide) that can be fully characterized, that Miacalcin itself — as a chemically synthesized peptide — can be fully characterized, that the mechanism of action of salmon calcitonin is well understood, and that the applicant had demonstrate that the active ingredients were identical in primary, secondary, and tertiary structures.¹³⁸ In 2006, as discussed further below, it approved a 505(b)(2) application for Omnitrope (human grown hormone, recombinant), which public information suggests was very similar to the application for Omnitrope that had been submitted in Europe under the new European biosimilar authorities.

¹²⁹ *Id.* at 1316-17.

¹³⁰ Letter from Janet Woodcock, M.D., Director, CDER, FDA, to A. Peter Frank, Serono Laboratories, Inc., Docket 92P-0487 (June 17, 1997), at 11-13.

¹³¹ *See Serono*, 158 F.3d at 1318, 1320.

¹³² *Id.* at 1319.

¹³³ HHS News, P97-12, *FDA Statement on Generic Premarin* (May 5, 1997).

¹³⁴ *Id.*

¹³⁵ *Id.*

¹³⁶ *Id.*

¹³⁷ *See* Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Stuart Land and Nancy L. Buc, (Mar. 24, 1999), Docket No. FDA-1998-P-0398 (formerly 98P-0311), at 6. In approving the Cenestin application, the agency relied on “human clinical safety data” relating to the applicant’s product and “extensive published literature on the clinical effects of estrogen, as well as on estrogen toxicology, specifically on carcinogenicity.” Further, the applicant had “substantiated the effectiveness” of its product “in an appropriately designed clinical trial.” *Id.*

¹³⁸ *See* Letter from Steven K. Galson, M.D., M.P.H., Acting Director, CDER, FDA, to Nancy L. Buc and Carmen M. Shepard (Aug. 12, 2005), Docket No. FDA-2004-P-0003 (formerly 2004P-0015); *see also* Letter from Ronald S. Levy, Unigene Laboratories, to FDA (Apr. 11, 2005), Docket No. 2004P-0015.

4. Harmonization in the 1990s and 2000s

Beginning in the early 1990s, the Administration attempted, and then Congress directed, harmonization of the rules governing biological drugs and non-biological drugs. Due probably to inherent differences between these products and differences between the governing statutes, this had not been fully accomplished even by 2010. But increased similarities between the regulation of biologics and the regulation of non-biologic drugs likely increased the pressure on Congress to create an abbreviated pathway for approval of biologics.

There were at least four components to the harmonization trend in the 1990s and 2000s. First, responding to the Clinton Administration's Reinventing Government initiative, FDA in November 1995 proposed to eliminate the dual licensure — ELA and PLA — requirement for well-characterized therapeutic biotechnology-derived drugs.¹³⁹ This administrative effort was mooted by enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA), which eliminated the dual licensure requirement for all biologics and substituted the BLA requirement.¹⁴⁰ Also, as noted previously, the 1997 legislation made parallel the PHSA provision requiring BLAs and the FDCA provision requiring NDAs.¹⁴¹ Second, as also previously noted, Congress confirmed again that the FDCA applies to biological products.¹⁴² Third, an uncodified provision of FDAMA directed the Secretary of Health and Human Services to “take measures to minimize differences in the review and approval of products required to have approved biologics license applications under section 351 of the [PHSA] and products required to have approved new drug applications under section 505(b)(1) of the [FDCA].”¹⁴³ Fourth, following FDAMA, FDA took a number of steps to minimize the differences between BLA review and NDA review. In 2003, for example, it consolidated review and responsibility for most therapeutic protein products, whether subject to NDAs or BLAs, in FDA's drug center.¹⁴⁴ Some of these proteins had previously been licensed and regulated by the biologics center. The agency has also urged all applicants to use the International Conference on Harmonization (ICH) Common Technical Document (CTD) format for their applications.¹⁴⁵

¹³⁹ See *supra* at text accompanying note 108.

¹⁴⁰ See *supra* at text accompanying note 110.

¹⁴¹ See *supra* at text accompanying note 110.

¹⁴² See *supra* at text accompanying note 118.

¹⁴³ Pub. L. No. 105-115, § 123(f), 111 Stat. at 2324, see FDCA § 505 note.

¹⁴⁴ See FDA, *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, <http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm> (last visited Sept. 29, 2010); 68 Fed. Reg. 38067 (June 26, 2003). CDER was given primary review authority for “[p]roteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors).” Letter of Jesse L. Goodman, M.D., M.P.H., Director, CBER, FDA, and Janet Woodcock, M.D., Director, CDER, FDA, to Sponsors (June 30, 2003), available at <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm186789.htm> (last visited Sept. 29, 2010). CBER was left with review and licensure authority for blood and blood products; human cells, tissues, and cellular and tissue-based products; vaccines; gene therapy products; and certain other biologics. FDA, *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, <http://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm136265.htm> (last visited Sept. 29, 2010).

¹⁴⁵ See, e.g., FDA, *Draft Guidance for Industry: Submitting Marketing Applications According to the ICH-CTD Format – General Considerations* 7 (Aug. 2001). The International Conference on Harmonization (ICH) is a project that brings together the regulatory authorities of Europe, Japan, and the United States, as well as experts from the pharmaceutical industry in all three regions, to discuss and harmonize technical aspects of pharmaceutical regulations. See ICH, www.ich.org (last visited Sept. 17, 2010).

Differences, however, still remained. For example, there was an apparent difference between the regulations governing disclosure of preclinical and clinical data in approved NDAs and the corresponding regulations for BLAs. As noted earlier, FDA had concluded in the 1970s that safety and effectiveness information in NDAs was confidential commercial information and/or trade secret and could not, as a general rule, be disclosed to the public by the agency.¹⁴⁶ The agency took a different approach with respect to information submitted in BLAs. Specifically, the agency concluded that the information in BLAs was at least in theory less commercially valuable, because it was not scientifically possible for an applicant to submit those data in support of another biological product.¹⁴⁷ This apparent difference may have been more theoretical than actual; to the authors' knowledge the agency never released the full preclinical and clinical package from a BLA.¹⁴⁸ A second difference, which remains to this day, is the agency's closer scrutiny of the means by which biological products are manufactured. This was evident, for example, in a different approach to establishment inspection: responsibility lay in the field for drugs and at the Center for biologics.¹⁴⁹ It was also evident in a more robust review of proposed manufacturing changes¹⁵⁰ and, at times, the requirement that manufacturing changes be implemented through an entirely new application rather than a supplement.¹⁵¹

C. *European Approval of Biosimilars*

Unlike the United States, Europe does not have a bifurcated system for drug approval and biologics approval. It does have the complication of both centralized and Member State level marketing authorizations, but biotechnology-derived products are approved at the European level, which simplified the development of a policy on biosimilars. Key moments relevant to the history of biosimilars were creation of initial harmonized drug authorization procedures in 1965, additional efforts to harmonize medicines regulation through Europe in the 1970s, development of more specific rules on abridged applications in 1986, development of the biosimilar pathway from 2003 to 2005, and approvals of biosimilars beginning in 2006.

1. *Development of Generic Pathway*

Until 1965, several European countries maintained no general system for authorizing the marketing of medicines. Council Directive 65/65/EEC, issued in the wake of the thalidomide episode, required Member States to establish systems for

¹⁴⁶ See *supra* text accompanying note 80 to note 86.

¹⁴⁷ 39 Fed. Reg. at 44641 (“[U]nlike the situation with new drugs, no competitor can utilize [the innovator’s safety and effectiveness data] to gain approval for [a follow-on] product.”).

¹⁴⁸ See generally Letter from Robert A. Long, Jr., Partner, Covington & Burling, to FDA (July 13, 2005), Docket Nos. FDA-2004-P-0214 & FDA-2003-P-0003 (formerly 2004P-0171 & 2003P-0176) at 6 (discussing agency’s response to Berlex request for data in the BLA for Avonex).

¹⁴⁹ See *ORA To Take Lead on All Biologics Inspections, Draft Report Says*, FDA WEEK, May 9, 1997, at 1, 8-12 (text of FDA’s April 24, 1997, “Team Biologics” Draft, announcing transition from CBER to Office of Regulatory Affairs, *i.e.*, “shift . . . to the field”).

¹⁵⁰ See, e.g., Doug Testa, *Other Post-licensing Requirements*, BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW (Parexel, 2004), at 242.

¹⁵¹ FDA, *Draft Guidance for Industry, Comparability Protocols — Protein Drug Products and Biological Products — Chemistry, Manufacturing, and Controls Information*, at 8-9 (Sept. 2003); see 68 Fed. Reg. 52776 (Sept. 5, 2003).

premarket approval of medicines on the basis of safety, efficacy, and quality.¹⁵² It created one alternative to the full application: a bibliographic application that relied on published literature, at least in part, to support the safety and effectiveness of the proposed product.¹⁵³ Subsequent amendments made it clear that a bibliographic application would be accepted only if the product's constituents had a well established medicinal use in Europe, which was in 1999 defined to mean at least a decade of use.¹⁵⁴ The directive did not contain any special provisions relating to biological products.

Two directives in the 1970s significantly advanced the process of harmonizing medicines regulation in the European Community and are relevant to the history of biosimilars in Europe. First, Council Directive 75/319/EEC laid down rules on drug manufacturing, including requirements for manufacturing licenses and good manufacturing practices.¹⁵⁵ It also created a procedure under which Member States were recommended to recognize each other's decisions on marketing authorization applications. And it created the Committee on Proprietary Medicinal Products (CPMP), which is composed of representatives from the national drug approval authorities and which was tasked with oversight of the multi-state process. Second, Council Directive 75/318/EEC harmonized requirements for dossiers submitted in marketing authorization applications.¹⁵⁶ It excluded a number of medicinal products, including vaccines and other immunological products, as to which there was no consensus among the Member States.

Two years after the United States enacted the Hatch-Waxman amendments, European authorities created an abridged marketing authorization pathway.¹⁵⁷ Abridged applications, now called generic applications, were exempt from the requirement to contain data showing safety and effectiveness. Instead, a generic applicant was to demonstrate that its product was bioequivalent and "essentially similar" to a product authorized in the European Community a requisite number of years prior as well as marketed in the country where the generic application was filed.¹⁵⁸ The default data exclusivity period was six years, but Member States were given the option to increase the period to ten years or to recognize no period of exclusivity after expiry of a patent protecting the original product. Products

¹⁵² Council Directive 65/65/EEC of 29 January 1965 on the approximation of provisions laid down by law, regulation, or administrative action relating to proprietary medicinal products, 1965 O.J. (No. 22) 369.

¹⁵³ *Id.* at Article 4.8(a).

¹⁵⁴ Commission Directive 1999/83/EC of 8 September 1999 amending the Annex to Council Directive 75/318/EEC on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products, 1999 O.J. (L. 243) 9.

¹⁵⁵ Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation, or Administrative Action relating to proprietary medicinal products, 1975 O.J. (L. 147), as amended.

¹⁵⁶ Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products, 1975 O.J. (L. 147) 1.

¹⁵⁷ Council Directive 87/21/EEC of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation, or administrative action relating to proprietary medicinal products, 1987 O.J. (L. 15) 36.

¹⁵⁸ As in the United States, an analytical package was also required. The European Court of Justice held in 1998 that two products would be deemed essentially similar if they had the same qualitative and quantitative composition in terms of active principles, they were in the same pharmaceutical form, they were bioequivalent, and there was no apparent difference between them in safety or efficacy. (Case C-368/96, *The Queen v. the Licensing Authority established by the Medicines Act 1968 ex parte Generics (UK) Ltd.*, 1998 E.C.R. I-7967).

authorized under a "concertation" procedure developed in 1987, however, were entitled to ten years of protection. The concertation procedure required coordination among the Member States for marketing authorization of certain product types, including biotechnology-derived medicines.¹⁵⁹ In 1995, a "centralized" procedure replaced the concertation procedure and also provided ten years of protection.¹⁶⁰ Products authorized under the centralized procedure, including biotechnology-derived medicines, may be marketed anywhere in the European Union.

Legislation in the mid 1990s created a mutual recognition procedure, which effectively harmonized labeling, dosage forms, and other product characteristics for a particular drug within the countries to which the authorization decision applied.¹⁶¹ Biological medicines that had already been approved through the concertation procedure were automatically transferred to the mutual recognition procedure (*i.e.*, for subsequent variations, known in the United States as supplements), but a handful were transferred to the centralized procedure at the request of the marketing authorization holders. Going forward, all biotechnology-derived medicines would be subject to the centralized procedure. This legislation also created the European Agency for the Evaluation of Medicinal Products (EMA).

In 2001, much of the EU's directive-based legislation was codified as Directive 2001/83/EC.¹⁶² And in 2003, amendments to Annex I to the Directive (which may be made at the European Commission level) addressed a number of issues specific to biological medicines.¹⁶³ In addition to defining the phrase "biological medicinal product,"¹⁶⁴ the revised Annex required that changes in the process for manufacturing such a product be supported by preclinical and clinical data demonstrating that the safety and effectiveness of the changed product were comparable to those of the original product.¹⁶⁵ Also in 2001, in its *Notice to Applicants*, the European Commission set out a definition of the phrase "new active substance." This definition was primarily intended to guide the determination whether an innovator's product was eligible for review under the centralized procedure, which was open to "new active substances." An isomer, complex, derivative, or salt of a chemical substance previously approved in the EC would be considered new only if it differed in properties with regard to safety and efficacy from the chemical substance

¹⁵⁹ Council Directive 87/22/EEC of 22 December 1986 on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology, 1987 O.J. (L. 15) 38.

¹⁶⁰ Council Regulation (EEC) No. 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, 1993 O.J. (L. 214) 1. This legislation took effect in 1995. The procedure was mandatory for the biological products that had previously been subject to the concertation procedure, available at the CPMP's discretion for new chemical entities, and available for any other products deemed by the CPMP to constitute a significant therapeutic advance.

¹⁶¹ Council Directive 93/39/EEC of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products. 1993 O.J. (L. 214) 22.

¹⁶² European Parliament and Council Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use, O.J. (L 331) 67.

¹⁶³ Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, O.J. (L 159) 46.

¹⁶⁴ A "biological medicinal product" is a product "the active substance of which is a biological substance." A "biological substance," in turn, is "a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and control." Listed examples include immunological medicinal products and biotechnology-derived products. See Annex I of Directive 2001/83/EC, part I, ¶ 3.2.

¹⁶⁵ See Annex I of Directive 2001/83/EC, part I, ¶ 3.2.1.2(f) and 3.2.2.3.

previously authorized. In contrast, a product containing a biological substance previously authorized in the EC would be deemed new if it differed in molecular structure, nature of the source material, or manufacturing process, regardless of whether the differences were shown to be clinically relevant.¹⁶⁶

Legislation that took effect in late 2005 clarified the requirements for generic applications and established a new, uniform ten-year period of exclusivity that applies to medicines authorized through the centralized procedure and those approved at the Member State level.¹⁶⁷ Under this rule, generic applications will not be accepted until eight years after approval of the reference product, and the generic product may not be marketed until ten years after this approval.¹⁶⁸ If a new indication is approved during the first eight years and is deemed by the relevant medicines agency “to bring a significant clinical benefit in comparison with existing therapies,” then generic products may not be marketed until eleven years after approval of the reference product.¹⁶⁹ Separately, one year of data exclusivity is available to protect a new use supported by “significant pre-clinical or clinical studies,” even where the base exclusivity has expired.¹⁷⁰ The 2004 legislation also renamed the key institutions: the EMEA became the European Medicines Agency (now, EMA), and the CPMP became the Committee for Medicinal Products for Human Use (CHMP).¹⁷¹

2. *Development of the Biosimilar Pathway*

Since 1995, all marketing authorization applications for biotechnology derived medicinal products have been required to be submitted to the EMA for approval under the centralized procedure. Naturally derived biological products could, and still can, be approved at the Member State level. Biological medicines are entitled to the same data exclusivity term as non-biological medicines: ten years with the possibility of an eleventh year as well as a separate one-year term for new indications. Some Member States maintain separate reviewing bodies for biological medicines,¹⁷² but the EMA does not. Issues specific to biological medicines, such as those relating to changes in manufacturing process, may be referred to the CHMP’s Biological Medicinal Products Working Party, but otherwise the reviewing processes for biological and non-biological medicines are the same.

¹⁶⁶ European Commission, *The Rules Governing Medicinal Products in the European Union, Notice to Applicants — Medical Products for Human Use, Vol. 2a — Procedures for Marketing Authorisations*, ch. 1, App. III. (May 2001).

¹⁶⁷ 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, 2004 O.J. (L 136) 34; Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, 2004 O.J. (L 136) 1. These took effect on October 30, 2005 and November 20, 2005, respectively. The new data exclusivity rules apply only to reference products granted marketing authorization after the effective date of the new legislation. See Article 2 of Directive 2004/27/EC and Article 89 of Regulation 726/2004/EC, respectively.

¹⁶⁸ Directive 2004/27/EC *supra* note 167, at Article 10.1.

¹⁶⁹ Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC, Article 10; see also Regulation (EC) No 726/2004, *supra* note 167, at Article 14.1.

¹⁷⁰ Directive 2004/27/EC, *supra* note 167, at Article 10.5.

¹⁷¹ Council Regulation (EC) No. 726/2004, *supra* note 167, at Article 1 and Article 5.

¹⁷² Germany, for example, maintains a reviewing body separate from the *Bundesinstitut für Arzneimittel und Medizinprodukte* (BfArM) for biological medicines.

As noted, by 2003 there were two relevant alternatives to the full marketing authorization application: a bibliographic application (which had been available since 1965) and a generic application (which had been available since 1986).¹⁷³ No provision of Directive 87/21/EEC (which had established the generic pathway) precluded use of the generic pathway for biosimilars. Nor did the original 1965 directive preclude use of the bibliographic pathway. The European Commission — which is the entity that issues marketing authorizations following the issuance of an opinion from the CHMP — decided, however, that neither pathway was suitable for biosimilars, largely because of difficulties in ensuring that the active ingredients were the same and the reference product studies therefore applicable.¹⁷⁴

In its 2003 amendments to Annex I of Directive 2001/83/EC, the Commission included a new marketing authorization procedure for “similar biological medicinal products.”¹⁷⁵ The new procedure applied to biotechnology-derived medicinal products (which, as noted, are centrally authorized) as well as certain other biological products, including vaccines and blood derivatives (which may be authorized at the Member State level). Under the new provision, medicines agencies may, and normally must, demand safety and effectiveness data to support a biosimilar application, and the precise nature of the additional data is to be described in guidelines.¹⁷⁶ The amendment to the Annex took effect in October 2003 and was

¹⁷³ Hybrid and mixed applications were also theoretical possibilities. A hybrid application is required where the strict definition of a “generic medicinal product” is not met, where the bioavailability studies cannot be used to demonstrate bioequivalence, or where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form, or route of administration of the generic product compared to the reference product. This application relies in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data. See Directive 2004/27/EC, *supra* note 167, at Article 10.3. A mixed application consists of a combination of limited non-clinical and/or clinical studies carried out by the applicant and bibliographical references. See European Parliament and Council Directive 2001/83/EC, *supra* note 162, at Annex I, Part 2.

¹⁷⁴ For example, following a favorable scientific opinion issued by the CPMP in June 2003 with respect to a bibliographic application submitted by Sandoz AG for its somatropin product Omnitrop, the European Commission decided for legal and policy reasons not to issue a decision granting a marketing authorization. Sandoz initiated litigation in the EC Court of First Instance, challenging the Commission’s action. (Case T-105/04, *Sandoz v. Commission*, removal from the register). The case was withdrawn by Sandoz on July 13, 2006, following approval of an application for Omnitrope submitted under the new procedure for similar biological medicinal products. The applicant had also changed the spelling of the product name.

¹⁷⁵ See European Parliament and Council Directive 2001/83/EC, *supra* note 162, at part II, ¶ 2, as amended by Commission Directive 2003/63/EC, *supra* note 163, at Annex I, part II, ¶ 4.

¹⁷⁶ The relevant provision states as follows:

The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided. When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.

— Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (*i.e.*, toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

— Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

— The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

later confirmed by an amendment to the Directive itself.¹⁷⁷ The relevant language is extremely brief and broadly worded by U.S. standards.

3. Implementation of the Biosimilar Pathway

The language in Directive 2001/83/EC has been implemented at the EMA level through general — sometimes referred to as “umbrella” or “over-arching” — guidelines on preclinical, clinical, and quality issues, among other things,¹⁷⁸ as well as a series of guidelines specific to individual product classes.¹⁷⁹ The CHMP has typically begun with a concept paper on each topic, calling for suggestions from the public as to the content of the guideline. It has then issued a draft guideline for further public consultation. The CHMP considers the views of its expert working parties and the comments of the relevant authorities in EC Member States, before finalizing the guideline. The process usually takes twelve to eighteen months from issuance of a concept paper to adoption of a final guideline.

As a general rule, the CHMP requires physical, chemical, and biological characterization of the biosimilar, in comparison with the reference product.¹⁸⁰ The guidelines also require comparative non-clinical studies assessing pharmacodynamics, pharmacokinetics, toxicity, and any special safety concerns, as well as comparative clinical trials that begin with pharmacokinetic and pharmacodynamic studies, followed by safety and effectiveness trials (using, if appropriate, validated surrogate

¹⁷⁷ Directive 2004/27/EC, *supra* note 167, at Article 10.4. The relevant language states as follows: Where a biological medicinal product which is similar to a reference biological product does not meet the conditions in the definition of generic medicinal products, owing to, in particular, differences relating to raw materials or differences in manufacturing processes of the biological medicinal product and the reference biological medicinal product, the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex I and the related detailed guidelines. The results of other tests and trials from the reference medicinal product's dossier shall not be provided.

¹⁷⁸ See EMEA, Guideline on Similar Biological Medicinal Products (CHMP/437/04), adopted September 2005; EMEA, Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005), adopted February 2006; EMEA, Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005), adopted February 2006.

¹⁷⁹ See EMEA, Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products containing Low-Molecular-Weight-Heparins, EMEA/CHMP/BMWP/118264/2007, adopted March 2009; EMEA, Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues—Guidance on Similar Medicinal Products containing Recombinant Erythropoietins (EMEA/CHMP/BMWP/94526/2005 Corr.), adopted March 2006; EMEA, Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues—Guidance on Similar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor (EMEA/CHMP/BMWP/31329/2005), adopted February 2006; EMEA, Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues—Guidance on Similar Medicinal Products containing Somatropin (EMEA/CHMP/BMWP/94528/2005), adopted February 2006; EMEA, Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues—Guidance on Similar Medicinal Products containing Recombinant Human Soluble Insulin (EMEA/CHMP/BMWP/32775/2005), adopted February 2006.

¹⁸⁰ See, e.g., EMEA, Guideline on Comparability of Biotechnology-Derived Medicinal Products after a Change in the Manufacturing Process (EMEA/CHMP/BMWP/101695/2006), adopted July 2007, at 3 (“Thus the comparability exercise may be limited to strict process validation of the change or be extended to various quality criteria such as in-process controls, thorough analytical and biological characterisation of the product and stability data.”)

endpoints for effectiveness).¹⁸¹ Each therapeutic indication must ordinarily be separately justified, but the CHMP may allow extrapolations from data submitted for one indication if it determines that an adequate scientific basis exists for the approval of the biosimilar for other indications based on the submitted data.¹⁸² The guidelines also require immunogenicity testing both before and after approval.¹⁸³

Approval of biosimilars in Europe beginning in 2006 placed enormous pressure on Congress to move forward with biosimilar legislation. In 2006, the EC granted marketing authorizations for two biosimilars containing somatropin (Omnitrope¹⁸⁴ and Valtropin¹⁸⁵). Also in 2006, the CHMP issued an unfavorable opinion on a third product, Alpheon (interferon alfa-2a).¹⁸⁶ Key negotiations over the U.S. biosimilar legislation occurred in the summer of 2007. Three biosimilar recombinant human erythropoietin alfa products were approved in August 2007 (Binocrit,¹⁸⁷ Epoetin Alfa Hexal,¹⁸⁸ and Abseamed¹⁸⁹), and two epoetin zeta products were approved in December 2007 (Retacrit¹⁹⁰ and Silapro¹⁹¹). Three insulin applications (Insulin Human Rapid Marvel, Insulin Human Long Marvel, and Insulin Human 30/70 Mix Marvel) were withdrawn in December 2007.¹⁹² Four filgrastim products were

¹⁸¹ See, e.g., EMEA, Guidance on Similar Medicinal Products containing Recombinant Human Soluble Insulin, *supra* note 179, at 4 (“The clinical activity of an insulin preparation is determined by its time-effect profile of hypoglycaemic response, which incorporates components of pharmacodynamics and pharmacokinetics. Pharmacodynamic data are of primary importance to demonstrate comparability of a similar rh-insulin.”)

¹⁸² See, e.g., EMEA, Guideline on Similar Medicinal Products containing Recombinant Interferon Alpha (EMA/CHMP/BMWP/102046/2006), adopted October 2007, at 6 (“In principle extrapolation from one therapeutic indication to another is appropriate where the mechanism of action is known to be the same as the condition(s) for which similarity in efficacy has been established. If indication(s) are sought, where the mechanism of action is not known to be the same, such extrapolation should be justified by relevant data.”)

¹⁸³ See, e.g., EMEA, Guidance on Similar Medicinal Products containing Recombinant Human Soluble Insulin, *supra* note 179, at 5 (“The issue of immunogenicity can only be settled through clinical trials of sufficient duration, i.e., at least 12 months using subcutaneous administration. The comparative phase of this study should be at least 6 months, to be completed pre-approval. Data at the end of 12 months could be presented as part of post-marketing commitment.”); see also EMEA, Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (EMA/CHMP/BMWP/14327/2006), adopted December 2007.

¹⁸⁴ Sandoz GmbH (Austria) received a marketing authorization for Omnitrope, EMA/H/C/000607, on April 12, 2006.

¹⁸⁵ BioPartners GmbH (Germany) received a marketing authorization for Valtropin, EMA/H/C/000602, on April 24, 2006.

¹⁸⁶ The company that had applied for authorization was BioPartners GmbH. See Refusal Assessment Report for Alpheon (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000585/WC500070792.pdf).

¹⁸⁷ Sandoz GmbH (Austria) received a marketing authorization for Binocrit, EMA/H/C/000725, on August 28, 2007.

¹⁸⁸ Hexal AG (Germany) received a marketing authorization for Epoetin Alfa Hexal, EMA/H/C/000726, on August 28, 2007.

¹⁸⁹ Medice Arzneimittel Pütter GmbH & Co KG (Germany) received a marketing authorization for Abseamed, EMA/H/C/000727, on August 28, 2007.

¹⁹⁰ HOSPIRA UK Limited (UK) received a marketing authorization for Retacrit, EMA/H/C/000872, on December 18, 2007.

¹⁹¹ STADA Arzneimittel AG (Germany) received a marketing authorization for Silapo, EMA/H/C/000760, on December 18, 2007.

¹⁹² On December 20, 2007, “Marvel LifeSciences Ltd. officially notified the CHMP that it wishe[d] to withdraw its applications for marketing authori[z]ations for Insulin Human Rapid Marvel, Insulin Human Long Marvel and Insulin Human 30/70 Mix Marvel, for the treatment of diabetes mellitus.” EMEA, Questions and Answers on the Withdrawal of the Marketing Authorisation Application for Insulin Rapid Marvel, Insulin Human Long Marvel, Insulin Human 30/70 Mix Marvel at 1 (Jan. 24, 2008), available at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500015341.pdf.

approved in September 2008 (Biograstim,¹⁹³ Filgrastim ratiopharm, Ratiograstim,¹⁹⁴ and Tevagrastim¹⁹⁵), and two more were approved in February 2009 (Filgrastim Hexal¹⁹⁶ and Zarzio¹⁹⁷). An interferon beta-1a application was withdrawn in May 2009 after the CHMP issued a negative opinion in February 2009.¹⁹⁸ An application for an epoetin theta product (Ratioepo), which had received a positive opinion from the CHMP, was withdrawn by the company for administrative reasons in February 2010.¹⁹⁹ By the time the final U.S. legislation was subject to vote in the House and Senate, eleven biosimilars had been approved in Europe. Various member states had considered the question of biosimilar substitution and in general concluded that it was inappropriate,²⁰⁰ and there were early reports on biosimilar market penetration that arguably signaled the need for caution in estimating cost savings in the United States.²⁰¹

D. *Relevant Developments in U.S. Patent Law*

In the years leading up to enactment of the BPCIA, there were several important developments in U.S. patent law that arguably affected the scope of patent rights for

¹⁹³ CT Arzneimittel GmbH (Germany) received a marketing authorization for Biograstim, EMEA/H/C/000826, on September 15, 2008.

¹⁹⁴ Ratiopharm GmbH (Germany) received a marketing authorization for Ratiograstim, EMEA/H/C/000825, and Filgrastim ratiopharm, EMEA/H/C/000824, on September 15, 2008.

¹⁹⁵ Teva Generics GmbH (Germany) received a marketing authorization for Tevagrastim, EMEA/H/C/000827, on September 15, 2008.

¹⁹⁶ Hexal AG (Germany) received a marketing authorization for Filgrastim Hexal, EMEA/H/C/000918, on February 6, 2009.

¹⁹⁷ Sandoz GmbH (Austria) received a marketing authorization for Zarzio, EMEA/H/C/000917, on February 6, 2009.

¹⁹⁸ On May 28, 2009, "BioPartners GmbH officially notified the CHMP that it wishe[d] to withdraw its application for a marketing authori[z]ation for Biferonex, for the treatment of relapsing-remitting multiple sclerosis." Questions and Answers on the Withdrawal of the Marketing Authorisation Application for Biferonex, at 1 (June 25, 2009), available at http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/01/WC500061395.pdf.

¹⁹⁹ On February 25, 2010, ratiopharm GmbH officially notified the CHMP that it wished to withdraw its application for a marketing authorization for Ratioepo, for the treatment of symptomatic anaemia in adults with chronic renal failure or non-myeloid cancer. In its withdrawal letter, the company stated that "the reason for this withdrawal is that the European Commission did not accept a second marketing authorisation for epoetin theta in the name of ratiopharm GmbH due to the fact that no co-marketing partner was identified at the time of adoption of the opinion of the CHMP."

²⁰⁰ For example, Spanish law included biologics on a list of drugs that could not be automatically substituted by pharmacists. Order SCO/2874/2007 from the Spanish Ministry of Health and Consumer Affairs, passed in September 2007, established a list of medicines that are excluded from substitution pursuant to article 86.4 of Law 29/2006 (de garantías y uso racional de los medicamentos y productos sanitos). This order includes "los medicamentos biológicos." See also Press Release, EuropaBio, Spain prevents automatic substitution of biological medicines, providing clarity for pharmacists and patients (Oct. 12, 2007). To give another example, pursuant to Article L. 5125-23 of the French Public Health Code, pharmacists may deliver a medicinal product of the same generic group in substitution to the medicinal product prescribed by the physician, subject to certain conditions. By not expressly providing for the inclusion of biosimilar products in generic groups as it does for generic products, French law prohibits substitution for similar biological products.

²⁰¹ Biosimilar versions of first-generation epoetin products were introduced in Germany in 2007 (epoetin alfa) and 2008 (epoetin zeta). By February 2009, biosimilars had captured only fifty-three percent of the German market, and innovator epoetin products intended for the German market retained thirty-eight percent of the market. *German Biosimilars Take More than Half*, GENERICS BULLETIN, May 15, 2009, at 14. Parallel imports accounted for the remaining 9.5 percent. Innovative filgrastim products intended for the German market retained just over a third of the market six months after biosimilars were introduced; biosimilars had captured twenty-two percent of the market during this time frame. *Id.* Parallel imports accounted for the remaining forty-four percent of the market. *Id.*

biologic inventions and that therefore informed discussion of the patent litigation provisions of the biosimilars legislation.

The first of these developments concerned the written description requirement — the statutory requirement that a patent application include a written description of the claimed invention sufficient to enable a person of ordinary skill to make and use the invention.²⁰² Application of the written description standard in the field of biologics has been very strict, with the Federal Circuit requiring that biotechnology “compounds” claimed in patent applications be “fully characterized” — by structure, formula, chemical name, or physical properties, or by depositing the compound in a public depository.²⁰³ In parallel, the United States Patent and Trademark Office has issued guidelines indicating that patent claims directed to a genus of proteins will satisfy the written description requirement only if a “representative number of species” is described sufficiently.²⁰⁴ For these reasons, inventors are more likely to be limited to the specific protein or nucleic acid structures identified in the patent specification and less likely to be able to obtain, and successfully enforce, broader claims directed to the entire genus of nucleic acids or proteins.

The second important development concerned the doctrine of equivalents, a judicially created doctrine intended to prevent a third party from avoiding a finding of patent infringement by departing insubstantially from the literal scope of the patent claims.²⁰⁵ Under well-established principles, a patentee may not avail itself of the doctrine of equivalents if that would involve asserting patent claim coverage the patentee gave up during prosecution of the underlying application. This exception to the doctrine of equivalents — termed “prosecution history estoppel” — was broadened in 2002 by the Supreme Court so that if a patent claim is amended during patent prosecution a presumption arises against an expanded reach of the claim through the doctrine of equivalents.²⁰⁶ Because patent claims are frequently amended, a patentee will often be estopped from asserting infringement through the doctrine of equivalents even where the accused infringer has departed only insubstantially from the literal scope of the patent claims.

Many innovators and patent owners argued, during the years leading up to enactment of the BPCIA, that these developments could spell trouble for patentees seeking to obtain and enforce claims to biologic inventions. It might be impossible, they argued, to obtain a suitable genus claim because of application of the written description requirement. At the same time, it might be impossible to enforce

²⁰² 35 U.S.C. § 112, ¶ 1 (2006).

²⁰³ See *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc); *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 923 (Fed. Cir. 2004) (“A description of what a material does, rather than of what it is, usually does not suffice The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described.”) (citing *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) (omissions in original); *Noelle v. Lederman*, 355 F.3d 1343 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997); *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

²⁰⁴ See U.S. Patent and Trademark Office, *MANUAL OF PATENT EXAMINING PROCEDURE*, § 2163.05, at 2100-182-83 (8th ed., 8th rev. 2010) (“[W]hen there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. . . . What constitutes a ‘representative number’ is an inverse function of the skill and knowledge in the art. . . . For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.”).

²⁰⁵ “[T]o permit imitation of a patented invention which does not copy every literal detail would be to convert the protection of the patent grant into a hollow and useless thing. Such a limitation would leave room for—indeed encourage—the unscrupulous copyist to make unimportant and insubstantial changes” *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607 (1950).

²⁰⁶ *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 737-41 (2002).

narrow claims to capture “equivalents,” which may constitute a great number of “biosimilar” products. Some therefore argued that the relative importance of patent protection and data exclusivity might be different in the biological drug context than it had been in the context of chemically synthesized drugs.

Perhaps the most important development affecting patent rights in the years leading to enactment of the BPCIA, however, concerned remedies rather than substantive rights. In *eBay Inc. v. MercExchange, L.L.C.*, the Supreme Court held that the traditional four-factor test should be applied by courts when determining whether a permanent injunction should issue upon a finding of patent infringement.²⁰⁷ Under the traditional test, a plaintiff must demonstrate that (1) it was irreparably injured; (2) remedies available at law, such as damages, will not sufficiently compensate the plaintiff for its injuries; (3) the balance of hardships favors injunctive relief; and (4) the public interest would not be harmed by a permanent injunction.²⁰⁸ Previously, courts issued permanent injunctions virtually as a matter of course once infringement and validity had been determined.²⁰⁹ The Hatch-Waxman amendments provided an automatic permanent injunction,²¹⁰ presumably reflecting the previous rule as to the availability of injunctive relief. As one of the authors of this article observed during negotiations of the BPCIA, the *eBay* decision effectively meant that there would be no parallel provision in the biosimilar legislation.

II. GROWING INTEREST IN BIOSIMILARS, 1998 TO 2006

The question of when, and how, FDA might approve biosimilars had been mentioned by the late 1990s. For example, as noted earlier, section 123 of FDAMA directed FDA to harmonize the review and approval processes governing FDCA products and PHSa products.²¹¹ Immediately following enactment of this legislation, Senators Edward Kennedy (D-MA) and James Jeffords (I-VT) wrote to the agency explaining that this provision was not intended to authorize creation of a generic approval pathway for biologics.²¹² When Commissioner Henney was vetted by the Senate prior to her confirmation in 1998, she was asked to commit not to move forward with a generic biologics approval system.²¹³ The trade press reported that one year later Senator Hatch (R-UT) had met with industry and consumer groups to discuss generic biologics at a conceptual level.²¹⁴

²⁰⁷ 547 U.S. 388, 394 (2006).

²⁰⁸ See, e.g., *id.* at 391; *Amado v. Microsoft Corp.*, 517 F.3d 1353, 1361 (Fed. Cir. 2008) (“[C]onclud[ing] that the district court’s ultimate decision to dissolve the injunction was not an abuse of discretion, when, after applying the traditional four-factor test, it determined that an injunction was no longer equitable under the circumstances.”).

²⁰⁹ See, e.g., *MercExchange L.L.C. v. eBay, Inc.*, 401 F.3d 1323 (Fed. Cir. 2005), *vacated and remanded*, 547 U.S. 388 (2006); *Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1547–48 (Fed. Cir. 1995); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1247 (Fed. Cir. 1989) (“It is the general rule that an injunction will issue when infringement has been adjudged, absent a sound reason for denying it.”).

²¹⁰ 35 U.S.C. § 271(e)(4)(A) (2006) (“[T]he court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed . . .”).

²¹¹ See *supra* text accompanying note 143.

²¹² See Letter from Sen. James M. Jeffords & Sen. Edward M. Kennedy to Dr. Michael A. Friedman, Lead Deputy Commissioner, FDA (Dec. 3, 1997) (on file with authors); see also FDA, *USP Should Set Generic Biologics Standards, Sen. Hatch Proposes*, THE PINK SHEET, Aug. 12, 2002, at 16–17. See also FDA Reform Debate May Spur ‘More Informed’ Oversight of FDA by Congress, Senate Staffers Says; PDUFA Reauthorization Sets 5-year Cycle for FD&C Act Review, THE PINK SHEET, Dec. 15, 1997, at 10.

²¹³ See FDA, *USP Should Set Generic Biologics Standards, Sen. Hatch Proposes*, THE PINK SHEET, Aug. 12, 2002, at 16–17.

²¹⁴ FDA, *USP Should Set Generic Biologics Standards, Sen. Hatch Proposes*, THE PINK SHEET, Aug. 12, 2002; see also *BIO Wants Waxman/Hatch Reform Isolated from Generic Biologics*, THE PINK SHEET, Nov. 15, 1999.

One could tell the story from 1999 to 2010 as a story of steadily mounting pressure on FDA and Congress, culminating in House and Senate passage of bills in 2009 and enactment in March 2010. The truth is more nuanced. In fact, while there were considerable pressures on the agency and the legislature to move forward, there were also some false starts at and mixed signals from the agency, and the legislative process stalled several times. The market presence of recombinant proteins that had been approved under the FDCA both complicated and accelerated the discussion, and approval of Omnitrope in May 2006 (along with biosimilar approvals in Europe) made legislation within a few years all but inevitable. This section discusses the period from 1999 to 2006, when Representative Henry Waxman (D-CA) introduced the first bill.

A. *Threshold Legal Question*

The question quickly arose whether the agency already had sufficient statutory authority to approve biosimilars or at least abbreviated applications under the PHSa. Some members of Congress, including for example Representative Rosa DeLauro (D-CT) in 2004, suggested FDA already had the authority to approve biosimilars under the PHSa.²¹⁵ The generic industry, to the extent it addressed this question directly, took the same position.²¹⁶ By and large the argument appeared to be that the agency had the authority to approve and had already approved abbreviated packages under the PHSa. It also argued that because the PHSa states that nothing in it affects FDA's jurisdiction under the FDCA, FDA "clear[ly]" could regulate biological drugs under section 505, which — as noted — contained both the ANDA pathway and the 505(b)(2) pathway.²¹⁷ The proposition that FDA could approve BLAs in reliance on preclinical and clinical safety and effectiveness data submitted in other BLAs was controversial and, in the view of the authors, inconsistent with the agency's prior statements, the Federal Trade Secrets Act, FDCA section 301(j), and the U.S. Constitution. Moreover, there was a very real question whether the agency could rely on these data without also reviewing the first applicant's manufacturing process, which raised additional and arguably insurmountable legal obstacles.²¹⁸ The Generic Pharmaceutical Association (GPhA)

²¹⁵ See DeLauro Urges FDA to Move Forward with Generic Biologics, *Eyes Bill*, FDA WEEK, Mar. 5, 2004.

²¹⁶ See, e.g., Letter from Christine J. Siwik, Rakoczy Molino Mazzochi, Siwik, to FDA, Docket Nos. FDA-2004-P-0214, FDA-2004-P-0339, FDA-2003-P-0003 (formerly 2004P-0171, 2004P-0231, and 2003P-176), at 5 (Nov. 12, 2004) (Under section 351(a), FDA "can approve a biologic product based upon data on 'comparable' drugs, and [the statute] does not require each applicant to complete clinical trials.")

²¹⁷ *The Law of Biologic Medicine: Hearing Before the S. Comm. on the Judiciary*, 108th Cong. 153 (2004) (statement of William B. Schultz, for GPhA). Some also argued that the regulation of some proteins (such as insulin) under the FDA supported the notion that the agency had the authority to regulate all biologics under the statute. The innovator industry pointed out, among other things, that whatever FDA's pre-1997 authority and past practice with respect to dossier size for innovative biological products, section 123 of FDAMA directed the agency to harmonize its approaches to review and approval of drugs and biological products and arguably codified the FDCA "substantial evidence" standard with respect to PHSa products. The innovator industry has also argued that the BLA requirement for biological products is mandatory and that the provisions addressing overlap simply exempt products with BLAs from the NDA requirement that would otherwise also apply.

²¹⁸ The threshold question whether FDA could lawfully approve a biosimilar product on the basis of trade secrets and confidential commercial information owned and submitted by another applicant were explored in submissions to FDA as well as Congress, and discussed in a hearing before the Senate Judiciary Committee. The question was never resolved. Expansive discussions of this issue can be found in an October 2004 letter to the Senate Judiciary Committee from Professor John Yoo, of the University of California, Berkeley, and a July 2005 submission to FDA drafted by Robert Long, of Covington & Burling, on behalf of the generic and research-based industries, respectively. Letter from John C. Yoo, Professor of Law, University of California, Berkeley, to Senator Orrin G. Hatch (Oct. 21, 2004); Letter from Robert A. Long, Jr., *supra* note 148.

also argued at one point that FDA should create a “paper BLA” process, *i.e.*, a literature based pathway, comparable to the “paper NDA” process that it had created in the late 1980s for FDCA products.²¹⁹ FDA, however, took the position that legislative authority was required.²²⁰ The question was also mooted by the bipartisan decision in 2007 to proceed with legislative amendment.²²¹ There were also a few who argued that FDA could approve applications under section 505(b)(2) that were based on biological products licensed under the PHSA,²²² but this position never gained much traction.

In some cases discussion of the agency’s authority to move forward with biosimilars related not to the PHSA but to the FDCA. Specifically, since at least the early 2000s FDA had suggested that it could approve 505(b)(2) applications that relied on safety and effectiveness data submitted in — or at least prior approval of — a full application submitted under section 505(b)(1). Genentech, then the Biotechnology Industry Organization (BIO), and then Pfizer filed citizen petitions arguing that this was not lawful,²²³ and many in the innovative industry supported their views. A judicial challenge brought by Pfizer might have resolved the issue, but never reached a final decision on the merits.²²⁴ FDA responded at length to the petitions and legal argument, when it approved Omnitrope,²²⁵ which had been the subject of an application under section 505(b)(2). Introduction of legislation to amend the PHSA followed shortly thereafter, and this diverted attention from the 505(b)(2) issue. Many continue to believe that the agency’s interpretation of section 505(b)(2) is incorrect and would be vulnerable in a court challenge.

B. Mixed Signals from FDA

Over time, various persons at FDA indicated that the agency was working on product-specific guidance documents for insulin and human growth hormone, as

²¹⁹ *GPhA: FDA Has Authority to Institute Generic Biologics Approvals*, FDA WEEK, Feb. 8, 2002, at 1, 14.

²²⁰ See *The Law of Biologic Medicine*, *supra* note 217, at 134 (statement of Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of Food and Drugs). Dr. Crawford stated “we do not believe such authority exists for [a] 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.” Some undoubtedly took the view that litigation would be inevitable if the agency proceeded without legislation; this may have made legislation attractive even to those who thought it unnecessary.

²²¹ See *infra* section III.B.

²²² See, e.g., WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RL 33901, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES (2007).

²²³ Pfizer and Pharmacia filed a joint petition in July 2001, arguing that section 505(b)(2) of the FDCA codified the agency’s prior paper NDA policy. They asked that FDA amend its draft guidance and regulations to make it clear that it could not rely on nonpublic proprietary information in an NDA to approve an application submitted under section 505(b)(2), and that it not rely on or otherwise use nonpublic proprietary information in an NDA to approve an application submitted under section 505(b)(2). Letter from Kathleen M. Sanzo and Lawrence S. Ganslaw, Morgan, Lewis & Bockius, LLP, to FDA, Docket No. FDA-2001-P-0369 (formerly 2001P-0323) (July 27, 2001). BIO’s April 2003 citizen petition asked (among other things) that the agency refrain from preparing, circulating, or issuing any new guidance for industry concerning follow-on therapeutic protein products and that it withdraw the draft guidance on applications under section 505(b)(2). BIO, Citizen Petition, Docket No. FDA-2003-P-0003 (formerly 2003P-0176) (Apr. 23, 2003). Genentech filed a petition in April 2004 asking that FDA (1) refrain from issuing a draft guidance on the “similarity” or “sameness” of recombinant protein based products, (2) refrain from approving a biotechnology-derived product characterized as “similar to” or “the same as” a Genentech product, where the application relied in whole or in part on trade secrets or confidential commercial information belonging to Genentech, and (3) develop a process whereby Genentech would receive notice of any proposed use of its trade secrets or confidential commercial information and an opportunity to prevent that use or disclosure. Letter from Stephen G. Juelsgaard, Genentech, Inc. to FDA, Docket No. FDA-2004-P-0214 (formerly 2004P-0171) (Apr. 8, 2004).

²²⁴ Complaint, *Pfizer Inc. v. FDA*, 1:03CV02346 (D.D.C. filed Nov. 13, 2003).

²²⁵ Letter from FDA to Kathleen M. Sanzo, Stephan E. Lawton, and Stephen G. Juelsgaard, *supra* note 79.

well as either guidance documents or white papers on the history of protein product regulation, policy issues, immunogenicity issues, and characterization issues relating to biosimilars. The agency's comments on the drafts — both whether they were still being pursued and whether and when they would be released — shifted repeatedly, and in some cases fairly high level agency officials contradicted each other within the same month. Nothing was published by the agency prior to enactment of the BPCIA, although the historical work was probably the basis for an article published by Janet Woodcock and other FDA personnel in April 2007.²²⁶

As early as 1997, scientists from the agency signaled that it was considering issues such as the sameness and pharmaceutical equivalence of biological, or at least biotechnology derived, products.²²⁷ These comments continued in 1999,²²⁸ and in 2001 a scientist indicated that the agency was working on a guidance document that would address the scientific requirements for approval of section 505(b)(2) applications for human growth hormone products.²²⁹ The technical drafting of this document had apparently been completed in April 2001.²³⁰ She described the contents of this document in general terms repeatedly over the next few years. Also in April 2001, however, the head of the biologics center at FDA expressed a fair amount of caution about the scientific basis for approval of generic biologics, citing — among other things — the heterogeneous nature of biological products and the difficulty of characterizing biological molecules.²³¹

In July 2001, Pfizer and Pharmacia filed a joint citizen petition with FDA arguing that section 505(b)(2) codified the agency's earlier paper NDA policy and that the agency may not rely on nonpublic proprietary information in an NDA to approve an application filed under section 505(b)(2).²³² Nor, they argued, could the agency assign an A rating to drugs approved under section 505(b)(2).²³³ GPhA filed a response, disagreeing entirely.²³⁴ In 2003, BIO continued the discussion and made the connection to follow-on biologics explicit. Its April 2003 citizen petition not only asked that FDA withdraw its draft guidance on section 505(b)(2) but also that the agency initiate a public process before proceeding with consideration of follow-on biologics (including general policy relating to these products).²³⁵ It also asked that the agency refrain from approving any application for a therapeutic protein product that did not contain a full complement of original non-clinical and clinical data and that relied on information in another company's application.²³⁶ In May, the

²²⁶ Janet Woodcock et al., *The FDA's Assessment of Follow-on Protein Products: a Historical Perspective*, 6 NATURE REVIEWS DRUG DISCOVERY 437 (2007) (advance online publication was available April 13, 2007).

²²⁷ See, e.g., Transcript, Meeting of the CDER Pharmaceutical Science Advisory Committee, at 18-22 (May 8, 1997).

²²⁸ *Generic Recombinant Protein 'Paper' NDA Approval Process Outlined by FDA*, THE PINK SHEET, Apr. 5, 1999, at 32; *FDA Generic Recombinant Protein Approval Process Will Use 'Paper' NDAs*, HEALTH NEWS DAILY, Mar. 30, 1999, at 1-2.

²²⁹ *FDA Accepts Data Sets on Therapeutic Equivalence of Biotech Drugs*, FDA WEEK, Mar. 23, 2001, at 6.

²³⁰ *Generic Somatropin NDAs Would Require Human Immunogenicity Tests — FDA*, THE PINK SHEET, Apr. 22, 2002.

²³¹ *CBER Chief: Generic Biologics A Problem From Scientific Standpoint*, FDA WEEK, Apr. 20, 2001, at 18.

²³² Letter from Kathleen M. Sanzo and Lawrence S. Ganslaw, *supra* note 223, at 12-14 (July 27, 2001).

²³³ *Id.* at 25-29.

²³⁴ Letter from Steve Bende, GPhA, to FDA, Docket No. FDA-2001-P-0369 (formerly 2001P-0323 (Dec. 10, 2001)).

²³⁵ BIO, Citizen Petition, *supra* note 223, at 1-2.

²³⁶ *Id.*

director of CDER stated that there was no AB rating system for biologics, that data requirements for follow-on biologics under section 505(b)(2) would be taken up by the agency shortly, and that there were outstanding “legal and clinical questions” relating to the issue of “absolute therapeutic interchangeability.”²³⁷ Also in 2003, the U.S. Pharmacopeia (USP) announced the goal of publishing official reference standards for biological products,²³⁸ although it would later disclaim the inference that these monographs would themselves make biosimilar applications feasible.²³⁹

In September 2003, FDA issued a draft guidance on comparability protocols for a manufacturer’s changes to the chemistry, manufacturing, or controls of a licensed protein drug or biological product.²⁴⁰ The agency had released a comparability guidance for human biological products more generally in 1996.²⁴¹ Although these guidances focused on changes made by a manufacturer to its own manufacturing process, some took the position that they were an “attractive regulatory precedent” for generic biologics, insofar as it made clear that full clinical trials are not always required for these changes.²⁴² Others responded, however, that these changes are made with full knowledge of in-process tests and other trade secrets relating to the manufacturing process, to which a second company would not have access. Genentech’s April 2004 citizen petition, for example, made this argument.²⁴³ In October 2003, FDA responded to the Pfizer petition, focusing exclusively on the question whether the agency could assign an “A” therapeutic equivalence code to a drug product that — because it differs in salt — is a pharmaceutical alternative to, and not a therapeutic equivalent of, the reference product. With the argument thus construed, the agency agreed with Pfizer. By this time, as noted, BIO had filed its citizen petition on follow-on biologics. In its response to Pfizer, FDA also stated that “the unique scientific issues associated with biologically derived products present a separate set of challenges that will be addressed in a response to be issued later.” Some took this as an explicit commitment to proceed with the guidance documents.²⁴⁴

Throughout 2004, stakeholders heard mixed signals about the timing of, and even likelihood of, release of draft guidance documents. For example, in January 2004, Janet Woodcock — then Acting Deputy Commissioner for Operations — suggested to BIO that a draft guidance on scientific issues would not be released

²³⁷ *Generic Biologics on FDA Fast Track?: ‘Follow-on’ Process Under Debate*, THE PINK SHEET, May 26, 2003, at 9.

²³⁸ Roger Williams, M.D., Executive Vice President and Chief Executive Officer, USP, “US Pharmacopeia (USP) Creates Process to Consider the Science of Equivalence for Biologics and Biotechnology Ingredients and Products,” in *National Organization for Rare Disorders, National Organization for Rare Disorders (NORD®) Conference on Exploring the Pathway to Generic Biologics: Are Therapeutically Equivalent Biologics Feasible and Desirable?* at 14-16 (2003), available at http://www.rarediseases.org/pdf/GB_White_Paper_0114_2.pdf.

²³⁹ *USP: HGH Standards Do Not Aid Biogeneric Argument*, BIOWORLD TODAY, May 12, 2005.

²⁴⁰ 68 Fed. Reg. 52776 (Sept. 5, 2003); see FDA, *Draft Guidance for Industry, Comparability Protocols—Protein Drug Products and Biological Products—Chemistry, Manufacturing, and Controls Information* (Sept. 2003).

²⁴¹ FDA, *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products* (April 1996).

²⁴² James N. Czaban and Natasha Leskovsek, *Trying to Sell Same*, LEGAL TIMES, May 17, 2004, at 38, 39.

²⁴³ Letter from Stephen G. Juelsgaard, *supra* note 223.

²⁴⁴ See Steve Usdin, *FDA Timetable for Biogenics Framework*, BIOCENTURY, Jan. 19, 2004, at A13 (“The [spring 2004] draft will fulfill a commitment FDA made in an October 2003 response to citizen petitions challenging its authority to approve biogeneric versions of biologics that are regulated as drugs.”).

before April 2004,²⁴⁵ and she told the trade press that the agency hoped to release the document in the spring.²⁴⁶ She also indicated that product class guidances might follow. In June, however, she told BIO that the agency no longer planned to issue draft guidance in the summer of 2004, and she indicated that the first document would likely describe the history of protein regulation at the agency.²⁴⁷ As discussed below, the first meaningful Congressional hearing also occurred in June 2004; some at the agency may have taken this as a signal to wait for legislative action, although others probably did not. Steven Galson — then Acting Director of CDER — also stated in the summer of 2004 that the guidances would allow use of only data in the public domain.²⁴⁸ It is conceivable that the BIO citizen petition, which had been filed in 2003 and which questioned FDA's authority to approve FDCA biosimilars under section 505(b)(2), had given the agency pause. The Genentech citizen petition from April 2004 and a second Pfizer citizen petition filed in May 2004 likely contributed.²⁴⁹ There may also have been differences of opinion within the agency about the scientific and legal issues associated with biosimilars. And the absence of a confirmed Commissioner from March 2004 to July 2005 and from September 2005 to December 2006 no doubt contributed to the agency's pace.

At the end of the summer of 2004, FDA informed Sandoz that it was unable to approve the company's application for Omnitrope under section 505(b)(2) because of "uncertainty regarding scientific and legal issues."²⁵⁰ The agency conceded that it had completed its review of the application, and its letter did not identify any deficiencies with the application. In September 2005, Sandoz would sue FDA for failing to approve the application.²⁵¹ The company would argue, among other things, that section 505(c) of the FDCA compels the agency to take action on an application within 180 days of its filing date.²⁵²

By late 2004, the agency appeared to have settled on releasing a paper that would provide only background, specifically a history of the regulatory treatment

²⁴⁵ *BIO Met with FDA's Woodcock to Discuss 'Generic' Biologics Plans*, FDA WEEK, Feb. 20, 2004, at 1, 12.

²⁴⁶ *FDA Crafts Guide Detailing Follow-on Biologics Scientific Framework*, FDA WEEK, Jan. 30, 2004, at 1, 10 (reporting that Dr. Woodcock indicated the guidance would address PHSA and FDCA proteins and that the agency might later issue product class guidances); see also *McClellan Outlines 'Generic' Biologics Proposal*, DICKINSON'S FDA REVIEW, Mar. 2004, at 5 (noting that agency was preparing draft guidance outlining "scientific issues involved in evaluating the similarity of simple and complex proteins and the sameness of peptides").

²⁴⁷ *FDA Won't OK Generics of Biologic It Doesn't Fully Understand*, FDA WEEK, June 11, 2004, at 3.

²⁴⁸ *Generic Biologics Will Not Be Approved For At Least Three Years — Barr CEO*, THE PINK SHEET, May 24, 2004, at 30 ("FDA is expected to permit the use of existing data for generic biologics submissions. The upcoming draft guidance will allow use of data from the public domain. Center for Drug Evaluation & Research Acting Director Steven Galson, MD, told a recent Schwab healthcare conference."). Dr. Galson's speech was pre-scripted, read, and released publicly, and in some senses it represents the first written document from FDA concerning its views in the area. Among other things, he observed that "FDA does not have the legal authority to reference information in an innovator company's BLA submission." "Follow-On" Biologics Guidance Will Limit Use of Data to "Public Domain," THE PINK SHEET, May 10, 2004, at 3.

²⁴⁹ The second Pfizer petition requested that FDA immediately deny approval of the pending Omnitrope application because it was "scientifically and legally improper for FDA to rely on, reference, or otherwise use the clinical and manufacturing information establishing the safety and effectiveness of GENOTROPIN® (somatotropin [rDNA origin] for injection) to approve Omnitrop™." Letter from Kathleen M. Sanzo, Morgan, Lewis & Bockius LLP, to FDA, Docket No. FDA-2004-P-0339 (formerly 2004P-0231), at 1 (May 13, 2004).

²⁵⁰ *FDA Deals Blow to "Sandoz" Follow-On Biologic*, FDA WEBVIEW, Sept. 2, 2004.

²⁵¹ *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006).

²⁵² Complaint at 33, *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29 (D.D.C. 2006) (No. 1:05-cv-01810).

of protein products.²⁵³ And it projected the document would be released by the end of the year.²⁵⁴ The director of the Office of Pharmaceutical Science suggested that, by way of contrast, a scientific concept paper (e.g., on manufacturing and characterization issues) would *not* be released before the end of the year.²⁵⁵ And she noted that agency lawyers had been working through legal (intellectual property) issues. GPhA responded in November 2004 by writing to the Acting Commissioner expressing concern that the agency was delaying access to biosimilars.²⁵⁶

The agency's next step was to sponsor or co-sponsor workshops to consider the scientific issues associated with biosimilars. These took place in September 2004, February 2005, and December 2005.²⁵⁷ At the February workshop, FDA representatives indicated that before the agency would issue guidance on approval of biosimilars, it would issue a series of background documents, the first of which would describe the history of protein product regulation. In June, the director of the Office of Pharmaceutical Science stated that a white paper on the "issues" involved in approving biosimilars would be published in August 2005 and that guidance documents would follow shortly thereafter.²⁵⁸ In October 2005, Dr. Galson again indicated that the agency was working on guidance and expected to issue it "soon,"²⁵⁹ although the Deputy Commissioner for Medical & Scientific Affairs commented

²⁵³ *Follow-on Biologics Guidance Delayed, FDA Dispels Misconceptions*, GENERIC LINE, June 16, 2004 at 1 ("The FDA will not release its draft guidance detailing the scientific issues on follow-on biologics this summer as originally announced, according to a top agency official who also said the FDA will not approve generic biologics for products that can't be characterized. The agency is still assembling, in the guidance, an inventory of all the protein products it approved as drugs under various FDA regulatory mechanisms, which go back decades, Janet Woodcock, acting FDA deputy commissioner for operations, said at the Biotechnology Industry Organization convention in San Francisco June 7.").

²⁵⁴ *FDA Follow-On Biologics Background Document To Be Released by Year-End*, THE PINK SHEET, Nov. 1, 2004, at 16.

²⁵⁵ *FDA May Work with Mexico on Biogenics Regulatory System*, FDA WEEK, Nov. 5, 2004 ("[Office of Pharmaceutical Science director Helen] Winkle added that she doubts the agency will issue by December a biogenics concept paper that officials had hoped to finish by that date. The concept paper will cover such scientific issues as manufacturing, characterization, and potency under a potential biogenics regulatory system. Agency officials hope to start combining the scientific and legal issues of biogenics into a draft guidance following the FDA public workshop in February on the science of biogenics, Winkle said.").

²⁵⁶ See Letter from Kathleen D. Jaeger, President & CEO, GPhA, to Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner, FDA (Nov. 10, 2004).

²⁵⁷ There were three public workshops: "Scientific Considerations Related to Developing Follow-on Protein Products" (September 2004); "Follow-on Protein Pharmaceuticals" (co-sponsored with the Drug Information Association, February 2005); and "Scientific Issues in Assessing the Similarity of Follow-on Protein Products" (co-sponsored with the National Institute for Standards and Technology and the New York Academy of Sciences, December 2005). Each workshop consisted of a series of presentations and panel discussions by members of academia, industry (innovator and follow-on companies and trade organizations), and FDA. The slide presentations, transcripts, and comments submitted to the docket (Docket No. FDA-2004-N-0059 (formerly 2004N-0355)) can be accessed on the FDA's web site. See *FDA, Follow-On Protein Products: Regulatory and Scientific Issues Related to Developing*, <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm085854.htm>.

²⁵⁸ Ben Hirschler, *FDA Aims to Issue Guidance on Biogenics in Fall*, REUTERS NEWS, June 21, 2005 ("[FDA] is pushing ahead with preparation for regulating copycat forms of expensive biotech drugs, although the legal basis for so-called biogenics remains unclear. Helen Winkle, director of the agency's Office of Pharmaceutical Science, said on Tuesday that a white paper outlining the issues involved would be published in August and guidance documents should follow in September or October."); see also Kathleen Michael, *Follow-On Biologics White Paper From FDA Could Be Delayed Till Fall*, HEALTH NEWS DAILY, Aug. 3, 2005 ("The white paper is to be followed by a series of guidance documents. Three subsequent guidances are planned: one on policy and two technical guidances on characterization and immunogenicity, FDA said.").

²⁵⁹ *Guidance from FDA on Generic Biologics Delayed, But Expected 'Soon,' Official Says*, PHARM. LAW & IND. R. 2005, at 1119.

the same month that he was “not sure” the agency would “have much more to say” on the issue in the near future.²⁶⁰ Senate staff suggested the next month that the agency was unlikely to move forward without a permanent Commissioner.²⁶¹

In January 2006, the trade press reported that the white paper was “nowhere close to being released” and was “in bits and pieces filtering throughout FDA within the different review divisions” with jurisdiction over biologics.²⁶² The agency’s 2007 annual guidance agenda, released in September 2006, indicated FDA planned to develop guidance on immunogenicity for follow-protein products, but included no other planned guidances on related topics.²⁶³ At that time, the trade press reported that the immunogenicity guidance was being circulated among top CDER officials.²⁶⁴ Also in September, as discussed in Section III, Representative Waxman introduced the first biosimilar bill.

C. Preliminary Discussions on the Hill

Discussions on the Hill did not always differentiate clearly between approval of biosimilar versions of FDCA proteins (such as insulin and human growth hormone), on the one hand, and approval of biosimilar versions of PHSA proteins, on the other hand. Some of the legal issues (such as whether reliance on innovator data constituted a taking) were the same, and some (such as whether an abbreviated pathway existed) were different. The scientific question (*i.e.*, whether the science was “ready”) was the same, although many thought the answer to that question might be different for different products. From 2002 to 2006, some members of Congress urged FDA to proceed with FDCA products, some focused on crafting legislation to address PHSA products, and some apparently believed that FDA already had the authority to act with respect to PHSA products. From time to time individual members of Congress urged FDA to proceed and may have meant both with respect to FDCA proteins and with respect to PHSA proteins.

Senator Rockefeller (D-WV) introduced legislation in 2002 to start the process with a study by the Institute of Medicine (IOM) of the feasibility of “generic versions” of biological products.²⁶⁵ In 2002 and 2003, key members of Congress openly discussed the need for legislation.²⁶⁶ And immediately after Congress enacted Medicare reform in December 2003, Senator Hatch stated that the new law would put pressure on Congress and FDA “to find new ways to bring new biotechnology

²⁶⁰ *Follow-Ons Off? FDA Shelves Near-Term Plans for Biologics Documents*, THE PINK SHEET, Oct. 10, 2005, at 14.

²⁶¹ *Follow-On Biologics Pathway Unlikely Without Confirmed Commissioner*, THE PINK SHEET, Nov. 28, 2005, at 13.

²⁶² Ramsey Baghdadi, *Biogenics Are Happening Slowly, Product-by-Product*, RPM REPORT, Jan. 2006, at 17, 18.

²⁶³ 71 Fed. Reg. 52125, 52127 (Sept. 1, 2006).

²⁶⁴ *FDA Guidance Agenda Silent on Biogeneric Papers, Except Immunogenicity*, FDA WEEK, Sept. 15, 2006, at 4.

²⁶⁵ S. 2677, 107th Cong. § 103 (2002) (introduced by Senator Jay Rockefeller) (directing IOM to consider “the feasibility of producing generic versions of biological products” and “the relevance of the source materials and the manufacturing process to the production of the generic versions” and directing FDA to promulgate regulations within three years if IOM concluded an approval system was feasible).

²⁶⁶ See 148 Cong. Rec. 15,678 (2002) (Sen. Hatch) (“Sooner or later, we must face up to the generic biologics challenge.”); see also *FDA, USP Should Set Generic Biologics Standards, Sen. Hatch Proposes*, THE PINK SHEET, Aug. 12, 2002, at 16 (“Hatch has been talking about generic biologics as a concept since 1999, when he held a series of meetings with industry and consumer groups to discuss Waxman/Hatch reform.”).

products to the public when patents expire.”²⁶⁷ And as FDA’s guidance development process began to falter, some members of Congress responded by putting pressure on the agency to move forward. For example, in March 2004, Representative DeLauro stated at a GPhA meeting that FDA had authority to move forward with biosimilars; she urged the agency to move forward.²⁶⁸

The Senate Judiciary Committee held a hearing in early summer 2004. Representatives of the generic and innovative industries took very differing views on not only the scientific issues but also questions of precedent and legal authority.²⁶⁹ These views are discussed in subsection D. Other Judiciary Committee hearings were expected,²⁷⁰ but none occurred. In October, Senator Hatch — the Chair of the committee — was rumored to be considering introduction of a legislation modeled on the European approach, including with respect to data exclusivity (*i.e.*, a ten-year period).²⁷¹ Within a few months, however, he would signal that he was not prepared to introduce this legislation in the immediate term.²⁷²

By the end of 2004 and early 2005, following the various FDA workshops and the Senate hearing, it became clear that stakeholders would need more time to consider at least the scientific issues, and possibly the legal issues, associated with biosimilars. Indeed, in December 2004, Representative Waxman noted disagreement on how similarity could be established and expressed at least some concern that allowing “biogenerics” on the market “too soon could undermine consumer confidence.”²⁷³ By May, staff indicated that the push for legislation was “cooling off,” suggesting that general concerns about drug safety (which would lead to enactment of the Food and Drug Administration Amendments Act of 2007) as well as European rejection of the Omnitrop application²⁷⁴ had “helped take the steam out of the issue on Capitol Hill.”²⁷⁵

²⁶⁷ 149 Cong. Rec. 32290 (2003); see Steve Usdin, *FDA Timetable for Biogenerics Framework*, BIOCENTURY, Jan. 19, 2004, at A13. Indeed, during consideration of Medicare reform, members were apparently mindful that biosimilar legislation might soon be passed. The House conference report accompanying Medicare prescription drug legislation (H.R. 1) specified that certain reimbursement rules “would not apply to a drug or biological where a generic version of that drug or biological first enters the market on or after January 1, 2004.” H.R. Rep. No. 108-391, at 589 (2003) (Conf. Rep.); see also *Senator Hatch Again Urges Lawmakers to Take Up Generic Biologics*, FDA WEEK, Dec. 12, 2003, at 10. The 2003 reform legislation created a new Medicare Part D for coverage of outpatient prescription drugs, however, and in general biological products had already been reimbursed under Part B. Thus while the legislation may have made the pricing of drugs a higher priority issue for the federal government generally speaking, it should not have made the pricing of biological drugs in particular more of a priority than it already had been. The 2003 reform legislation created a new Medicare Part D for coverage of outpatient prescription drugs. In addition, the 2003 reform legislation established Average Sales Price as the basis of reimbursement for most separately reimbursable Part B drugs, and in general biological products are reimbursed under Part B. Thus while the legislation may have made the pricing of drugs a higher priority issue for the federal government generally speaking, it should not have made the pricing of biological drugs in particular more of a priority than it already had been.

²⁶⁸ *DeLauro Urges FDA to Move Forward with Generic Biologics, Eyes Bill*, FDA WEEK, March 5, 2004.

²⁶⁹ *The Law of Biologic Medicine*, *supra* note 217.

²⁷⁰ See *EU and US prepare for ‘biogenerics,’ SCRIP*, June 2, 2004 at 4 (“Hatch is to announce at the end of June that hearings will take place on the science, law, and policies for regulating ‘biogeneric’ products on the US market, a European generics conference heard.”).

²⁷¹ *Hatch Meets with Industry As He Crafts Generic Biologics Bill*, FDA WEEK, Oct. 8, 2004.

²⁷² *Hatch: Science on Biogenerics Not Ready, Will Not Drop Bill Soon*, FDA WEEK, Jan. 21, 2005, at 1, 6.

²⁷³ *Waxman: Biogeneric Safety Key to Avoid Loss of Faith in Generics*, FDA WEEK, Dec. 3, 2004 (discussing Waxman’s statements at a conference on the Hatch-Waxman amendments).

²⁷⁴ See *supra* section I.C.2.

²⁷⁵ *Generic Biologics Legislation Unlikely, But Issue Not Going Away*, THE PINK SHEET, May 16, 2005, at 4. (Citing comments from Senate Aging Committee majority counsel Steve Irizarry at a conference of the Stanford Washington Research Group).

In short, just as the agency's process stalled in early 2004, some of the preliminary Congressional interest in amendment of the PHSA to permit biosimilar versions of biologics subject to BLAs appeared to wane in late 2004 and 2005. There were even reports that at least one Senate appropriator considered adding language to the agricultural appropriations language for fiscal year 2006 to prevent FDA even from moving forward with approval of biosimilar applications under section 505(b)(2).²⁷⁶ Others, however, still urged FDA to move forward, either with FDCA proteins or more generally. For example, Congressman Waxman told attendees at a generic drug conference in September 2005 that the agency should not wait for legislation and should make decisions on a case-by-case basis.²⁷⁷

On January 26, 2006, the EMEA recommended approval of Omnitrope.²⁷⁸ In February, Senator Hatch and Representative Waxman wrote to the Acting Commissioner of Food and Drugs urging the agency to issue the long awaited insulin and human growth hormone generic approval guidance documents.²⁷⁹ (The states of Kansas, Minnesota, Vermont, and Wisconsin would file a citizen petition in August asking the same thing.²⁸⁰) In March, FDA responded to Senator Hatch and Representative Waxman, indicating that "FDA has decided it would be more appropriate to publish guidances that are more broadly applicable to [follow-on protein products] in general," but declining to provide a time frame for release of this guidance.²⁸¹ In April 2006, the District Court ruled that FDA had violated its statutory obligation under section 505(c) to act on the Sandoz application, and on May 30, FDA approved Omnitrope. At the same time, the agency denied the citizen petitions filed by Pfizer, BIO, and Genentech. Although the agency drafted the citizen petition response narrowly, limiting its scientific and legal conclusions to the product and application before it, many believed that this signaled to Congress that the agency was prepared to begin approvals of biosimilars.

D. Key Issues

1. Scientific Issues

Stakeholders considered many scientific issues relating to biosimilars between 2002 and 2006. Key issues included the following. First, is it possible for a biosimilar manufacturer to duplicate an innovator's therapeutic protein product using a different manufacturing process, or does the manufacturing process for each protein determine its structural and clinical characteristics? Second, are current analytical techniques for characterizing protein structure and biological activity sufficient to allow FDA to declare with confidence that a biosimilar is the same as, or highly

²⁷⁶ *Senate Appropriators Eye Provision to Stop Biogeneric Approvals*, FDA WEEK, Sept. 16, 2005 ("It is unclear which lawmaker is behind the proposal, and one industry source says it may never see the light of day.").

²⁷⁷ *Act on Generic Biologics Before New Law, FDA Urged*, DICKINSON'S FDA REVIEW, Oct. 2005, at 14.

²⁷⁸ EMEA, Background Information on the Procedure (2006), available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_before_authorisation/human/000607/WC500043693.pdf.

²⁷⁹ Letter from Rep. Henry A. Waxman & Sen. Orrin G. Hatch to Andrew C. Von Eschenbach, M.D., Acting Commissioner of Food and Drugs (Feb. 10, 2006).

²⁸⁰ States of Kansas, Minnesota, Vermont, and Wisconsin, Citizen Petition, Docket No. FDA-2006-P-0282 (Aug. 3, 2006).

²⁸¹ Letter from Patrick Roman, Associate Commissioner for Legislation, FDA, to Sen. Hatch, at 1 (Mar. 17, 2006). FDA also stated that it was continuing to move forward with review and approval of follow-on protein products. *Id.*

similar to, an innovator protein? Third, is it possible to determine that two complex proteins will have the same clinical efficacy and safety profiles, *i.e.*, are interchangeable, without conducting head-to-head clinical trials? Fourth, can current analytical and preclinical testing methods be used in lieu of full clinical trials to accurately predict the potentially serious immunological effects of a biosimilar, or is clinical testing always required to predict immunogenicity? (And relatedly, is clinical testing prior to approval sufficient to assess immunogenicity, or must steps be taken in the postmarketing phase to further assess or manage the risk?)

a. *Whether the process is the product*

The first scientific question was whether it continued to be the case that “the process is the product” – *i.e.*, whether a therapeutic protein must be defined as the substance that results from a particular manufacturing process, so that companies using different manufacturing processes by definition generate different substances.

1) *Generic Industry*

The generic industry generally argued that the manufacturing process no longer determined the characteristics of the product.²⁸² They also pointed out that FDA permitted (and other ICH regulators permitted) innovators to make some manufacturing changes without performing clinical trials of the changed product.²⁸³ Specifically, innovators use “comparability protocols” to evaluate changes made to their own manufacturing processes, and these protocols may, or may not, involve clinical testing. When making a change to its process, a manufacturer “evaluates the quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product.”²⁸⁴ These quality attributes include the physicochemical properties of the protein product, its biological activity, its purity, impurities, contaminants, its quantity, and its immunochemical properties (if any).²⁸⁵ A manufacturer may demonstrate the comparability of the pre-change product and the post-change product solely through analytical studies, if appropriate, but “[t]he extent and nature of nonclinical and clinical studies should be determined on a case-by-case basis” depending, in part, on the nature and level of knowledge of the product.²⁸⁶ The generic industry argued that FDA’s willingness to apply a flexible comparability approach demonstrated that the agency believed the manufacturing process of a particular product does not necessarily determine its safety and effectiveness in humans.²⁸⁷ Thus, the generic companies argued, a company may be able to produce a biosimilar protein product with comparable clinical effects through an alternative manufacturing process.²⁸⁸

²⁸² See, e.g., Letter from Suzanne M. Sensabaugh, SICOR, Inc., to FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), at 2 (Nov. 12, 2004) (“Specific aspects and parts of the manufacturing process do not determine the characteristics of a protein product.”).

²⁸³ See, e.g., *id.*, at 7 (Nov. 12, 2004).

²⁸⁴ ICH, ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, at 2 Nov. 13, 2003.

²⁸⁵ *Id.*, at 6-7.

²⁸⁶ *Id.*, at 10, 11.

²⁸⁷ *The Law of Biologic Medicine*, *supra* note 217, at 115 (statement of Carole Ben-Maimon, M.D., President and Chief Operating Officer, Barr Research, Inc.).

²⁸⁸ See, e.g., Letter from Christine J. Siwik, *supra* note 216, Attachment at 4 (Nov. 12, 2004) (“The manufacturing processes Genentech and others seek to protect as trade secrets merely represent one way in which a particular safe and effective biotechnology-derived pharmaceutical can be produced. Indeed, even if these processes represent the ‘best’ way to manufacture the product in terms of yield and cost, Genentech offers the Agency no reason to believe that alternative methods necessarily would fail to produce the same or a sufficiently similar product.”); Letter from Kathleen Jaeger, GPhA, to FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), Attachment at 17 (Dec. 8, 2004) (“Any reproducible process that yields a final product that matches the desired composition (based on comparability to the reference product) should, therefore, be equally acceptable.”).

2) *Innovator Industry*

Both PhRMA and BIO took the position that the manufacturing process has a significant effect on the characteristics of the final protein product. According to BIO, even seemingly minor process changes can have a “potentially profound clinical impact.”²⁸⁹ BIO emphasized that all aspects of the manufacturing process (e.g., cell lines, production system, and purification techniques) could affect the structural and clinical characteristics of the final protein product.²⁹⁰ PhRMA similarly argued that “the identity of each biological product — whether innovator or follow-on — is inseparable from the process used to manufacture it.”²⁹¹

Some individual companies argued that the end product of a recombinant protein manufacturing process is not a single protein species, but instead a family of closely related variants of the target protein product.²⁹² The specific ratio of variant proteins present in the final protein product is determined by several aspects of the manufacturing process, including the source materials (cell line, DNA, source nutrients), the fermentation or cell culture conditions, the isolation and purification methods, and the formulation process.²⁹³ Each innovator company has studied and refined its own manufacturing process so that it can consistently produce a final product containing a specific mixture of protein variants.²⁹⁴

PhRMA responded to the generic industry argument about comparability protocols by noting that a biosimilar manufacturer does not have the innovator’s “complete knowledge of the entire manufacturing process . . . , as well as significant historical experience with manufacturing the product and validating manufacturing changes.” These are critical to the innovator’s evaluation of the comparability of its own product after a change.²⁹⁵ Individual companies made the same point.²⁹⁶ The comparability approach works for intra-manufacturer process changes, one company argued, only because the manufacturers have the detailed process history, proprietary references standards, and analytical tools needed to prove that the pre-

²⁸⁹ Letter from Sara Radcliffe, BIO, to FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), at 18 (Dec. 13, 2004).

²⁹⁰ *Id.* at 19-29.

²⁹¹ Letter from Caroline J. Loew, PhRMA, to FDA, Comments, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), Attachment B at 12 (Nov. 12, 2004).

²⁹² See, e.g., *The Law of Biologic Medicine*, *supra* note 217, at 84 (statement of David Beier, Senior Vice President, Global Government Affairs, Amgen) (“The end product of [a] biotechnology manufacturing process is, most often, a complex mixture of heterogeneous proteins and impurities. Each of the closely-related proteins in this mixture contributes to the biological activity, efficacy, and safety of the product.”); *id.* at 72-73 (statement of William Hancock, M.D., Department of Bioanalytical Chemistry, Northeastern University) (“[A] batch of the product may contain a mixture of molecules that vary in important ways even though they have the same basic structure.”); Letter from Robert L. Garnick, Genentech, Inc. to Steven Galson, M.D., FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), at 3 (Nov. 11, 2004) (“[L]arger and more complex protein products, in particular glycoproteins, are generally produced and purified not as single species but as entire families of related variants of the primary protein sequence and/or carbohydrate structure.”).

²⁹³ See, e.g., Letter from Frederick W. Telling, Pfizer, Inc., to FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), Attachment at 3-5 (Nov. 12, 2004).

²⁹⁴ See, e.g., *id.* at 2; Letter from Robert L. Garnick, *supra* note 292, at 7-8 (Nov. 11, 2004). Genentech reaffirmed its position in an amicus brief submitted in *Merck KGaA v. Integra LifeSciences*, stating that “each biologic manufacturing process will result in a unique product.” Brief of Amici Curiae Genentech, Inc. and Biogen IDEC, Inc. in Support of Petitioner at 9, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 545 U.S. 193 (No. 03-1237).

²⁹⁵ Letter from Caroline J. Loew, *supra* note 291, Attachment B, at 14 n.35.

²⁹⁶ See Letter from Kenneth Seamon, Amgen, Inc., to FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), at 8-9 (Nov. 12, 2004); Letter from Michael Doherty, F. Hoffmann-LaRoche AG, to FDA, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), at 3 (Feb. 7, 2005).

change and post-change protein products will have comparable effects.²⁹⁷ Innovators also pointed out that FDA may require a manufacturer to conduct clinical trials on a post-change protein product if the manufacturer has made a fundamental change to the process (e.g., changed cell banks or transferred production to a new site).²⁹⁸

3) FDA

Much of the history of biological products and biotechnology products at FDA suggests the agency at least historically agreed that the process defined the product. But the agency rejected the argument that a comparison of the manufacturing processes for Sandoz's Omnitrope and Pfizer's Genotropin would be required in order to determine that the Sandoz product was similar to the Pfizer product. It commented that "for this relatively simple recombinant protein, it is possible to determine that the end products of different manufacturing processes are highly similar, without having to compare or otherwise refer to the processes."²⁹⁹ It also rejected both the argument that Omnitrope could not be considered similar to Genotropin unless the agency could determine that Omnitrope shared Genotropin's specific impurity and molecular variant profiles³⁰⁰ and the argument that it would need to compare the manufacturing processes for Omnitrope and Genotropin in order to ensure that Sandoz satisfied current good manufacturing (cGMP) requirements.³⁰¹

b. *Whether biotechnology-derived proteins can be fully characterized*

A second issue was whether current analytical methods can fully characterize complex proteins. Characterization in this context meant both characterization of the molecule's structure and characterization of the molecule's biological activity.

1) *Generic Industry*

Generic companies and GPhA took the position that current analytical techniques allow manufacturers to adequately characterize the physicochemical structure and biological activity of many proteins.³⁰² Barr commented, for example, that "[t]he state of the art today allows biologics to be characterized and compared analytically." Generic companies also argued that absolute characterization of a biosimilar should not be required. Instead, a biosimilar manufacturer should be required to compare only the "meaningful" characteristics of its product to those of the innovator's product.³⁰³ The generic industry also pointed to publication of

²⁹⁷ Letter from Kenneth Seamon, *supra* note 296, at 9.

²⁹⁸ *Id.* at 8; Letter from Michael Doherty, *supra* note 296, at 6.

²⁹⁹ Letter from Steven K. Galson, *supra* note 79, at 15; Letter from Michael Doherty, *supra* note 299.

³⁰⁰ *Id.* at 17 ("[W]e need not compare the impurities or molecular variants in one product to those in another to determine the products' similarity for purposes of approval under section 505(b)(2) of the [FDCA]."); *id.* ("Differences in the impurities and molecular variants for [Omnitrope and Genotropin] do not preclude the approval of Omnitrope under section 505(b)(2) of the Act.")

³⁰¹ *Id.* at 19.

³⁰² See *The Law of Biologic Medicine*, *supra* note 217, at 24 (statement of Carole Ben-Maimon, M.D., President and Chief Operating Officer, Barr Research, Inc.) ("[A]dvances over the past 20 years in analytical methods and validation techniques have allowed companies to characterize their biological drug products such that the impact of changes in processes and cell lines can be evaluated, and biologic drug products can be kept constant."); Letter from Suzanne M. Sensabaugh, *supra* note 282, at 13 ("Analytical methods are available today to adequately characterize certain protein products.")

³⁰³ See Letter from Kathleen Jaeger, *supra* note 288, Attachment at 2 (Dec. 8, 2004) ("A comparative characterization need not fully elucidate all aspects of both products in absolute terms – in contrast, it need only compare the two products in all meaningful ways.")

a United States Pharmacopoeia (USP) monograph for human growth hormone, which it argued suggested that at least some recombinant protein products could be easily characterized.³⁰⁴ SICOR, a subsidiary of Teva Pharmaceuticals, disputed claims that current scientific analytical techniques were incapable of fully characterizing proteins.³⁰⁵ Indeed, it stated, “the results of analytical characterization are often more sensitive to product changes than are clinical studies.”³⁰⁶

2) *Innovator Industry*

PhRMA and BIO took the position that current analytical techniques were not capable of detecting subtle differences in protein structure that could cause a significant difference in clinical impact. In support of its argument that proteins could be difficult to fully characterize, PhRMA noted that some biological products that had been on the market for “decades and rigorously studied generally do not have a fully characterized active ingredient.”³⁰⁷ Amgen stated that current analytical techniques provide, at most, an incomplete snapshot of a protein product.³⁰⁸ Pfizer argued that analytical techniques used to characterize small molecules are “generally insufficient to fully characterize most protein products.”³⁰⁹ Innovators also disputed the argument that analytical studies are better predictors of safety and efficacy than are clinical studies. The Plasma Protein Therapeutics Association, for example, noted that characterization techniques may be useful for determining product equivalence, but not safety and effectiveness.³¹⁰

3) *FDA*

Prior to its approval of Omnitrope, FDA gave stakeholders little insight into its views on the characterization of biosimilars. It had issued guidance on characterization of biotechnology derived and biological products, and it had noted (for example, in labeling) that some protein products were difficult to characterize. But it had not addressed the biosimilar issue squarely.

The 1999 guidance document discussed general considerations for the characterization of biotechnology-derived and biological products.³¹¹ It addressed four aspects of protein characterization: physicochemical characterization; biological activity; immunological properties; and purity, impurities, and contaminants. FDA acknowledged that recombinant proteins have an “inherent degree of structural heterogeneity” due to post-translational modifications and suggested that each manufacturer can adequately characterize its protein product by demonstrating “a consistent pattern of product heterogeneity.”³¹² The guidance document also

³⁰⁴ *HGH Monograph Proves Follow-On Viability, GPhA Says*, THE FOOD & DRUG LETTER, May 20, 2005, at 5; *GPhA: HGH Monograph Proves Biogenics Can Be Characterized*, WASHINGTON DRUG LETTER, May 16, 2005, at 8; see Press Release, USP, USP Announces Creation of Human Growth Hormone Monographs (May 5, 2005); The United States Pharmacopoeia and National Formulary (28th Revision, Supp. No. 1) (2005), at 3272-74.

³⁰⁵ Letter from Suzanne M. Sensabaugh, *supra* note 282, at 12.

³⁰⁶ *Id.* at 11.

³⁰⁷ Letter from Caroline J. Loew, *supra* note 291, Attachment B, at 10.

³⁰⁸ See *The Law of Biologic Medicine*, *supra* note 217, at 84 (statement of David Beier, Senior Vice President, Global Government Affairs, Amgen Inc.).

³⁰⁹ Letter from Frederick W. Telling, *supra* note 293, at 7.

³¹⁰ Letter from Mary Eustafson, to FDA, Plasma Protein Therapeutics Association, Docket No. FDA-2004-N-0059 (formerly 2004N-0355), at 7 (Nov. 12, 2004).

³¹¹ See FDA, *Guidance for Industry, Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* (Aug. 1999).

³¹² See *id.* at 3-5.

affirmed the importance of an accurate assessment of a protein's biological activity through animal-based assays, cell-based assays, biochemical assays, and ligand and receptor binding assays.³¹³ FDA stated that a manufacturer should establish a correlation between the expected clinical response and the activity measured by a biological assay either through pharmacodynamic or clinical studies.³¹⁴ It also stated that physicochemical tests may replace biological assays only when "[s]ufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated [and] [t]here exists a well-established manufacturing history."³¹⁵

At the same time, FDA had acknowledged that some proteins are difficult to characterize. These would presumably include Amphadase (hyaluronidase), the approved labeling of which states that the product is a "preparation of purified bovine testicular hyaluronidase, a protein enzyme," the "exact chemical structure" of which "is unknown." Other examples are Vitrase (ovine-derived hyaluronidase) and naturally-derived conjugated estrogens such as Premarin.³¹⁶ When it approved Omnitrope, however, FDA effectively endorsed the analytical methods used by Sandoz to compare the active ingredient in Omnitrope to the international reference standards provided by the WHO and the European Pharmacopoeia as well as the active ingredient in Genotropin.

c. *Whether complex proteins can be deemed interchangeable*

A third issue was whether, and on what basis, complex proteins could be deemed "interchangeable" by FDA. The question, ultimately, was whether it would be possible to deem two proteins interchangeable on the strength of analytical testing or whether it would instead be necessary to conduct some sort of clinical testing (e.g., head-to-head comparative trials). This in turn depended in part on the extent to which complex proteins could be fully characterized and the extent to which small changes in the manufacturing process could lead to differences in clinical effect that could not be detected through analytical testing.

1) *Generic Industry*

Most generic stakeholders argued that the therapeutic equivalence model could be applied to biosimilars. Representatives of generic companies stated that therapeutic equivalence can be determined by using less than full clinical studies (e.g., in vitro testing, pharmacokinetics, and surrogate markers).³¹⁷ In comments to FDA, GPhA stated that innovative and biosimilar protein products should be "treated as if they were therapeutically interchangeable" if the biosimilar manufacturer can demonstrate comparability through a comprehensive side-by-side comparative analytical characterization. If analytical tests yield sufficient comparability,

³¹³ *Id.* at 4.

³¹⁴ *Id.*

³¹⁵ *Id.* at 4-5.

³¹⁶ FDA's position on conjugated estrogens was that "the reference listed drug Premarin [was] not adequately characterized," in part because "the quantitative composition of Premarin with respect to potentially pharmacologically active components has not been defined. Without this information, it is not possible to define the active ingredients of Premarin." FDA, *FDA Backgrounder on Conjugated Estrogens* (July 7, 2005).

³¹⁷ See Carole Ben-Maimon, M.D., Duramed Research, General Panel Discussion, Scientific Considerations Related to Developing Follow-On Protein Products Public Workshop (Sept. 14-15, 2004) (remarks made during discussion).

GPhA contended, the need for preclinical, pharmacokinetic, pharmacodynamic, and clinical studies can be reduced or eliminated.³¹⁸

2) *Innovator Industry*

Many innovator companies argued that the therapeutic equivalence model used for chemically synthesized drugs under the FDCA could not be applied to biosimilars. The existing “therapeutic equivalence” definition would not work, because a biosimilar could not be shown to be pharmaceutically equivalent to the reference product. Amgen took the position, for example, that the concept of “therapeutic equivalence” could not apply, because “proteins cannot be characterized and duplicated in the same way as small molecule drugs.”³¹⁹

Innovators also addressed the larger question: whether and on what basis it would be possible for FDA to deem two complex proteins interchangeable. Genentech, for example, stated that the “full complement of critical animal and clinical studies” must be required to justify approval, because the safety and efficacy profile of the biosimilar cannot be established by only analytical comparison to the innovator product.³²⁰ Pfizer similarly rejected the adoption of a therapeutic equivalence model for biosimilars because “current analytical technology cannot adequately characterize protein products,” and small changes in a protein product can have clinical effects incapable of prediction based solely on analytical testing.³²¹ In their final joint position statement on the naming of biotechnology-derived therapeutic proteins, presented to the WHO in November 2006, PhRMA and BIO argued for the use of different nonproprietary names for any two products that may not contain the identical drug substance (e.g., for two biotechnology-derived therapeutic proteins) in order to ensure that interchangeability determinations “rest exclusively and unambiguously with regulatory authorities.”³²² This, they argued, would prevent “inappropriate substitutions.”³²³ Implicit in this statement was the argument that a biosimilar is not necessarily interchangeable, i.e., that the showing necessary for some degree of reliance on another company’s data (or use of an abbreviated pathway with submission of comparative data) might not support the conclusion that the products are in fact therapeutically interchangeable.

³¹⁸ Letter from Kathleen Jaeger, *supra* note 288, Attachment at 8.

³¹⁹ Letter from Kenneth Seamon, *supra* note 296, at 9-10; *The Law of Biologic Medicine*, *supra* note 217, at 85 (statement of David Beier, Senior Vice President, Global Government Affairs, Amgen) (“[T]he chemical characterization of active ingredients in these products is inadequate to ensure sameness of efficacy (i.e., ‘biological activity’) and sameness of safety (i.e., no unexpected adverse reactions, including immunogenic response.”); *id.* at 91 (“[I]t is impossible to determine – with only analytical and bioequivalence testing – that a follow-on biological product will be just as safe and effective as the pioneer product.”); *id.* at 101 (“[F]ollow-on biologics cannot be considered therapeutically equivalent to the innovator product.”).

³²⁰ Letter from Robert L. Garnick, *supra* note 292, at 5; see also Brief of Amici Curiae Genentech, Inc. and Biogen IDEC, Inc. in Support of Petitioner at 9-10, *Merck KGaA v. Integra LifeSciences I, Ltd.*, 545 U.S. 193(No. 03-1237) (“[E]ven if the physical, chemical, and biological properties of the process and the resulting product are carefully defined or characterized, that does not ensure clinical or therapeutic equivalence of two biologics produced in different conditions of manufacture.”).

³²¹ See Letter from Frederick W. Telling, *supra* note 293, Attachment at 11.

³²² BIO, EuropaBIO, EBE, EFPIA, IFPMA, PhRMA, *Policy Position on Naming of Biotechnology-Derived Therapeutic Proteins* (Oct. 31, 2006), at 5.

³²³ *Id.* at 6. Some stakeholders took the position that biosimilars should have distinctive non-proprietary names (or, barring that, some other distinguishing feature, such as a trade name) even if interchangeability determinations were not permitted. They argued that because reference products and biosimilars are not identical, pharmacovigilance systems will work effectively only if adverse events can be traced to the specific manufacturer, product, and lot number with which they are associated.

3) *FDA*

FDA's position on the interchangeability of complex proteins was difficult to discern. From 1999 to 2003, the agency was considering ways to rate as therapeutically equivalent recombinant proteins approved under the FDCA (i.e., insulin and human growth hormone). For example, in 1999 the Director of the Office of Pharmaceutical Science, Roger Williams (later the Chief Executive Officer of USP), told the Generic Pharmaceutical Industry Association (GPIA) that to get this "AB" rating, a biosimilar manufacturer "will show that the molecules are pharmaceutically equivalent . . . [but] not identical."³²⁴ Bioequivalence, he claimed, was "easy because a lot of these recombinant products are in solution." Specifically, "[a]s long as your excipients remain qualitatively and quantitatively the same, you don't have to struggle with the issue of bioequivalence. We would just say that it is self-evident." To demonstrate pharmaceutical equivalence, however, would require chemistry, manufacturing, and control (CMC) tests comparing the biosimilar protein to the reference protein, as well as "very complicated physiochemical tests," and in some cases — if tertiary structure was hard to determine from physiochemical tests — human PK and PD studies. In some cases, clinical studies and additional safety studies for antigenicity would be required.

In March 2001, the Director of the Office of New Drug Chemistry told the National Association of Pharmaceutical Manufacturers that the agency was willing to accept data sets from applicants seeking to prove the therapeutic equivalence of biological drugs.³²⁵ The data necessary to demonstrate therapeutic equivalence, she explained, must be "scientifically based, technology driven, and product dependent." She added that the issue in general for biotechnology-derived proteins would be pharmaceutical equivalence, not bioequivalence. Trade press explain that she attributed this to "difficulties with biotech proteins," which include "the complicated chemical structure, the limitations of physiochemical tests, the fact that biological activity assays are imprecise and unable to detect small chemical changes, [the fact that] the potency assay is not always clinically relevant," and the fact that "the same solution with the same formulation from the same protein can end up having different pharmacokinetics / pharmacodynamic profiles when produced by different manufacturers or different processes." Her description of the agency's general approach to pharmaceutical equivalence did not differ substantially from Williams's statements two years earlier, although she did add that "clinical efficacy" would need to be shown "in the absence of meaningful bioassays and/or in-vivo biomarkers."³²⁶ She gave subsequent talks — including a talk in 2002 to the International Generic Pharmaceutical Alliance — suggesting that FDA was open to interchangeability showings for somatropin and insulin.³²⁷

³²⁴ *FDA Generic Recombinant Protein Approval Process Will Use 'Paper' NDAs*, HEALTH NEWS DAILY, Mar. 30, 1999, at 1-2; see also *Generic Recombinant Protein 'Paper' NDA Approval Process Outlined by FDA*, THE PINK SHEET, Apr. 5, 1999, at 33.

³²⁵ *FDA Accepts Data Sets on Therapeutic Equivalence of Biotech Drugs*, FDA WEEK, Mar. 23, 2001.

³²⁶ *Id.*

³²⁷ *Generic Somatropin NDAs Would Require Human Immunogenicity Data – FDA*, THE PINK SHEET, Apr. 22, 2002; Steve Usdin, *Countdown to biogenerics*, BIOCENTURY, Apr. 15, 2002. The press later reported that FDA had at this time completed draft guidance on interchangeability of human growth hormone products. See *FDA Won't OK Generic of Biologic It Doesn't Fully Understand*, FDA WEEK, June 11, 2004 ("Two years ago in a draft guidance on growth hormones, FDA had outlined studies a manufacturer would have to conduct to receive an interchangeability rating for follow-on products, the source says.").

After 2003, however, the agency's signals became more mixed. In 2003, CDER Director Janet Woodcock noted "outstanding legal and clinical questions" relating to the issue of "absolute therapeutic interchangeability" for biosimilars. One reporter wrote that she implied the "jury was still out" on whether biologics may be AB-rated.³²⁸ When speaking to BIO in June 2004, she expressed some concern about approving "interchangeable" versions of biologic products "if the brand products are not fully characterized."³²⁹ A scientist in CDER's Office of Pharmaceutical Science noted the same year that while "certain biotech products" could be shown "interchangeable and pharmaceutically equivalent without the need for clinical study," this was "highly product dependent" and that "[f]or the majority of biotech products, identity [could not] be truly determined just by physicochemical biological and PK characterization."³³⁰ And at a September 2004 workshop, "FDA scientists said the safety of a generic may differ from a branded biologic, and they indicated that it would be difficult to assign 'therapeutic equivalence' to a product that has not yet been proven equivalent."³³¹ Nevertheless, a scientist in the Clinical Pharmacology and Biopharmaceutics Office in CDER outlined in a presentation at the February 2005 FDA/DIA scientific workshop the criteria that would need to be met for a follow-on biologic to be deemed interchangeable with its reference product.³³² In a September 2006 written statement to the World Health Organization, FDA stated that "[a]s of today, FDA has not determined how interchangeability can be established for complex proteins."³³³

d. *Whether it is possible to predict immunogenicity*

A fourth scientific question was whether current analytical and preclinical testing methods can accurately predict the immunogenicity of a biosimilar product. If they cannot, a related question was whether pre-approval clinical trials can detect extremely rare immunogenic reactions.

1) *Generic Industry*

Some members of the generic industry took the position that the potential immunogenicity of a biosimilar could be adequately predicted by measurement of protein characteristics and comparison to the innovator product. GPhA and SICOR both suggested identifying and monitoring factors — specifically, protein aggregation — known to correlate with increased product immunogenicity.³³⁴ If analytical

³²⁸ *Generic Biologics on FDA Fast Track?: 'Follow-On' Process Under Debate*, THE PINK SHEET, May 26, 2003.

³²⁹ See *supra* note 327.

³³⁰ *Some Follow-On Biologics May Get 'AB' Rating Without Clinical Study*, FDA WEEK, June 20, 2003.

³³¹ *FDA Says It Would be Difficult to Assign 'Equivalence' to Biogenerics*, FDA WEEK, Sept. 17, 2004.

³³² Follow-On Protein Pharmaceuticals, Plenary Session (Feb. 14, 2005), Tr. at 157. This person stated that if two products satisfy the following criteria, they may be deemed interchangeable: (1) they are highly purified; (2) their primary structure is proven; (3) physicochemical tests are available to determine their secondary and tertiary structure; (4) there are clinically relevant bioassays; (5) the mechanism of drug "interaction" (possibly "action") is known; (6) there are validated biomarkers available; and (7) there are extensive experience and human data available from multiple manufacturers. *Id.* at 158-59; see also *Follow-on Protein 505(b)(2) Applications Do Not Require Pharm/Tox Studies*, THE PINK SHEET, Feb. 21, 2005.

³³³ U.S. FDA, *Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) on Possible International Non-proprietary Name (INN) Policies for Biosimilars* (Sept. 1, 2006).

³³⁴ GPhA, Comments, Docket No. 2004N-0355, at 23-34 (Dec. 8, 2004); SICOR, Comments, Docket No. 2004N-0355, at 20-22 (Nov. 12, 2004).

tests demonstrated an unusual level of aggregation in a batch of protein product, then pre-approval clinical testing might be required to address immunogenicity concerns.³³⁵ A question asked by Senator Schumer (D-NY) during the 2004 Senate Judiciary Hearing implied that pre-approval clinical trials would not be sufficiently large to allow detection of rare immunogenic reactions resulting from manufacturing changes.³³⁶ The implication was that pre-approval clinical trials should not be required simply on account of the risk of immunogenicity.

2) *Innovator Industry*

The innovator industry generally contended that the immunogenicity of a protein must be assessed in pre-approval clinical studies and should also be monitored after approval, for example through patient registries or phase IV commitments. Although PhRMA and BIO noted that analytical studies of product characteristics such as aggregation provide some useful information, both groups firmly stated that immunogenicity cannot be predicted solely through analytical or preclinical testing.³³⁷ The Plasma Protein Therapeutics Association also took the position that “[q]uestions regarding immunogenicity cannot be identified solely with current analytical technology.”³³⁸

Individual companies took similar positions. Genentech, for example, stated that “immunogenicity cannot be reliably assessed until extensive patient studies (Phase III or IV) are conducted, in which patients are treated and followed over a number of years” and that “[e]xtensive comparative immunogenicity studies should be conducted for every follow-on protein product.”³³⁹ Biogen Idec and Pfizer made similar arguments.³⁴⁰ In its Citizen Petition urging rejection of Sandoz’s NDA for Omnitrope, Pfizer emphasized the unpredictability and potential severity of immune responses to therapeutic protein products, noting that “[b]ecause the reasons for induction of an immune response are not well understood, however, immunogenicity can not be predicted theoretically and can only be determined directly by clinical trials.”³⁴¹ Amgen argued that “neither analytical testing nor testing in animals can predict whether, or at what rate, a biological product may trigger a serious immune response in humans.”³⁴²

³³⁵ See GPhA, Comments, Docket No. 2004N-0355, at 25 (Dec. 8, 2004) (suggesting that if characterization of the follow-on product demonstrates comparability to the reference product and no unusual levels of “impurities, aggregates, or other objectionable characteristics,” immunogenicity studies should not be required).

³³⁶ *The Law of Biologic Medicine*, *supra* note 217, at 57-58 (question from Senator Schumer to David Beier).

³³⁷ BIO, Comments, Docket No. 2004N-0355, at 35 (Dec. 13, 2004) (“[A]lthough analytical correlation studies and animal studies will be useful and will provide some information about immunogenic responses in humans, they should not be substitutes for clinical studies.”); PhRMA, Comments, Docket No. 2004N-0355, Attachment A, at 11 (Nov. 12, 2004) (“There is broad scientific consensus that problems with immunogenicity cannot be dependably predicted from physicochemical characterization, epitope analysis, or animal studies.”).

³³⁸ Plasma Protein Therapeutics Association, Comments, Docket No. 2004N-0355, at 9 (Nov. 12, 2004).

³³⁹ Genentech, Comments, Docket No. 2004N-0355, at 19, 20 (Nov. 11, 2004).

³⁴⁰ Biogen Idec, Presentation at FDA Public Workshop on Scientific Considerations of Follow-On Protein Products (Sept. 14-15 2004) (slide presentation); Pfizer, Comments, Docket No. 2004N-0355, at 9 (Nov. 12, 2004).

³⁴¹ Pfizer, Citizen Petition, Docket No. 2004P-0231, at 17 (May 13, 2004).

³⁴² *The Law of Biologic Medicine*, *supra* note 217, at 93-94 (statement of David Beier, Senior Vice President, Global Government Affairs, Amgen); *see also* Amgen, Comments, Docket No. 2004N-0355, at 5 (Nov. 12, 2004) (“[I]t is essential to investigate the safety and immunogenicity of any protein product with appropriate preclinical and clinical testing pre-approval, and robust pharmacovigilance post-approval.”).

3) FDA

FDA did not make any official statements about immunogenicity of biosimilars prior to introduction of the first bill in 2006, although a guidance document on the issue was slated for release in 2007.³⁴³ Two actions indicated that FDA would take a case-by-case approach to the immunogenicity of biosimilars. First, in its May 2006 explanation of its decision to approve Omnitrope, FDA stated that “clinical data establish that the active ingredient in Omnitrope and Liquid Omnitrope is not unacceptably immunogenic and has an immunogenicity level that is similar to Genotropin or other approved rhGH products.”³⁴⁴ Although “a significant number of patients who were administered Early Omnitrope developed anti-GH antibodies during the first and second phase 3 clinical trials,” the agency concluded that “Sandoz implemented changes to the drug product to address this immunogenicity.”³⁴⁵ Second, FDA issued a not-approvable letter to Natestch Pharmaceutical for its follow-on version of Novartis’s Miacalcin (calcitonin-salmon nasal spray).³⁴⁶ The letter cited concerns about potential immunogenicity resulting from interactions of the calcitonin and the chlorobutanol preservative in Natestch’s nasal spray.³⁴⁷

III. PROPOSED LEGISLATION AND OTHER DEVELOPMENTS, 2006-2010

A. 109th Congress, Second Session (2006)

During the 109th Congress, Democrats in the House and Senate launched the legislative debate on biosimilars in earnest. In September 2006, Representative Waxman introduced the first biosimilars bill in the House, H.R. 6257, and Senator Schumer introduced almost identical legislation in the Senate.³⁴⁸ The authors refer to these as H.R. 6257 or the “first Waxman bill.” It was not expected that the bill would pass during the 109th Congress.³⁴⁹ Instead, stakeholders generally understood that Representative Waxman intended the bill to start discussion of the issues related to biosimilars legislation.³⁵⁰ The trade press reported that Representative Waxman planned to collect cosponsors and make the bill a legislative priority in 2007.³⁵¹

The first Waxman bill would have permitted a case-by-case approach with respect to clinical and other data supporting licensure of the biosimilar. This approach contrasted sharply with section 505(j) of the FDCA which, as noted above, specifies the data and information that may be required in an ANDA. It was more like the approach of section 505(b)(2), as interpreted by FDA. In other respects, the bill proposed a framework that differed substantially from the generic drug approval

³⁴³ FDA Guidance Agenda Silent on Biogeneric Papers, Except Immunogenicity, FDA WEEK, Sept. 15, 2006.

³⁴⁴ FDA, Response to Citizen Petition, Docket No. 2004P-0231, at 34 (May 30, 2006).

³⁴⁵ *Id.*

³⁴⁶ Press Release, Natestch Pharmaceutical Company, Inc., Natestch Pharmaceutical Company Receives FDA Communication Concerning Calcitonin-Salmon Nasal Spray (July 13, 2006).

³⁴⁷ *Id.*

³⁴⁸ The bills differed in substance in only one way: the Waxman bill contained a tax credit for certain clinical testing expenses for demonstrating interchangeability, and the Schumer bill did not. Compare H.R. 6257, 109th Cong. § 3(b) (2006) with S. 4016, 109th Cong. § 3(b) (2006).

³⁴⁹ Catherine Hollingsworth, *First-Ever Generic Biotech Drugs Bill Introduced by Congressional Democrats*, 4(39) PHARM. L. & INDUSTRY REPORT 1064 (Oct. 6, 2006).

³⁵⁰ U.S. biosimilars legislation mulls “comparability” and “interchangeability,” SCRIP NEWS, (Oct. 4, 2006); Waxman to Unveil Biogenics Bill by Year’s End, Senators May Too, FDA WEEK, Sept. 22, 2006.

³⁵¹ U.S. biosimilars legislation mulls “comparability” and “interchangeability,” SCRIP NEWS, Oct. 4, 2006; Waxman to Unveil Biogenics Bill by Year’s End, Senators May Too, FDA WEEK, Sept. 22, 2006.

framework of the Hatch-Waxman amendments. For example, the bill would have provided no data exclusivity for innovative products, and it proposed a very different patent litigation scheme. At the time of the bill's introduction, the trade press commented that it contained "many elements that will please the generics industry but which the innovator companies are likely to find unsettling and unacceptable."³⁵² As Representative Waxman apparently intended, the bill ignited debate, particularly on the issues of clinical data requirements, data exclusivity, and the system for resolving patent issues between biosimilar applicants and patent owners.

1. *Regulatory Provisions of H.R. 6257*

The first Waxman bill would have created two pathways for licensure of biosimilars. First, under section 351(k)(1) of the PHSa, FDA could have licensed "comparable" biological products.³⁵³ As noted above, the term "comparable" has been used in guidance describing the requirements for supporting changes to the chemistry, manufacturing, or controls of approved drugs and biological products.³⁵⁴ Second, under section 351(k)(2), the agency could have licensed biological products "differ[ing] from, or incorporat[ing] a change to" a licensed reference product, even if the products were not comparable, so long as the proposed product's safety, purity, and potency "relative to the reference product" was shown.³⁵⁵ Section 351(k)(2) seems to have been modeled on FDA's interpretation of section 505(b)(2) of the FDCA.

a. *Scope of Reference Products*

The first Waxman bill would have permitted applicants to cite, as reference products, both innovative products and products licensed under the new pathway. This is because it defined "reference product" to include biological products licensed under section 351(a) of the PHSa (innovative biological products) and those licensed under section 351(k) (biosimilars).³⁵⁶ Under the Hatch-Waxman amendments, a generic drug approved under section 505(j) may not serve as a reference product for a generic drug, but a drug approved under section 505(b)(2) may. Unlike the BPCIA, the bill would not have changed the definition of "biological product" in section 351(i) of the PHSa.³⁵⁷ Nor did it address proteins approved under the FDCA. The new pathway would have been available only for applications citing a PHSa-licensed product as a reference product.³⁵⁸

b. *Comparability*

As noted, to obtain licensure under proposed section 351(k)(1), an applicant would have needed to show that the reference product and its proposed product were "comparable." Comparability would not require sameness in active ingredi-

³⁵² *U.S. biosimilars legislation mulls "comparability" and "interchangeability,"* SCRIP NEWS, Oct. 4, 2006; *see also New Democrats Support Brand-Backed Follow-on Biologic Bill,* FDA WEEK, May 25, 2007.

³⁵³ H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSa § 351(k)(1)).

³⁵⁴ *See supra* note 240 and accompanying text.

³⁵⁵ H.R. 6257 § 3(a)(2) (proposed PHSa § 351(k)(2)). As noted below, the BPCIA uses the words "highly similar" and "biosimilar" instead of "comparable."

³⁵⁶ H.R. 6257, § 2(2) (2006) (proposed PHSa § 351(i)(3)).

³⁵⁷ *See id.* § 2(1).

³⁵⁸ *See id.* § 2(1) (proposed PHSa § 351(i)(2) & (3)).

ent, as is required under section 505(j) for generic FDCA products.³⁵⁹ Instead, a product would be “comparable” to its reference product if there was an “absence of clinically meaningful differences . . . in terms of the safety, purity, and potency of the product.” This showing was to be based on: (1) data from biological, chemical, and physical assays and “other non-clinical laboratory studies”; and (2) data generated in “any necessary clinical study or studies sufficient to confirm safety, purity and potency in one or more appropriate conditions of use.”³⁶⁰ Any clinical studies required were to be “designed to avoid duplicative and unethical clinical testing.”³⁶¹ FDA could not require postmarketing studies as a condition of approval.³⁶²

Separately, a section 351(k)(1) applicant would have had to show that the products contained “comparable principal molecular structural features . . . notwithstanding minor differences in heterogeneity profile, impurities or degradation patterns.”³⁶³ This showing was to be based on “thorough characterization,” i.e., “appropriate analytical and functional testing sufficient to identify differences between [the products] relevant to safety, purity, or potency.”³⁶⁴ The bill would have directed FDA to find various products, including proteins with minor differences in amino acid sequence, to have “comparable principle molecular structural features.”³⁶⁵ The list of examples seems to have been drawn from a similar list in FDA’s regulations implementing the Orphan Drug Act.³⁶⁶ The list was not exhaustive; FDA would have had discretion with respect to other drugs to determine the data and information “necessary” to show comparability of the principal molecular structural features.³⁶⁷ This provision drew criticism from innovators, who believed it would “forc[e] the agency to say something is comparable that scientifically is not.”³⁶⁸

³⁵⁹ FDCA § 505(j)(4)(C). Section 505(b)(2), as interpreted by FDA, does not require sameness.

³⁶⁰ *Id.* § 2(2) (proposed PHSA § 351(i)(4)).

³⁶¹ *Id.*

³⁶² *Id.* (proposed PHSA § 351(k)(3)). The agency could, however, “agree” that the applicant would conduct a postmarketing study in situations where such a study was being performed for the reference product and a “reasonable showing” was made that a separate study of the comparable biological product would “provide relevant information not available from the studies of the reference product.” *Id.*

³⁶³ *Id.* (proposed PHSA § 351(k)(1)(B)).

³⁶⁴ *Id.* § 2(2) (proposed PHSA § 351(i)(5)).

³⁶⁵ *Id.* (proposed PHSA § 351(k)(1)(B)). The list was: (1) two proteins with structural differences “solely due to post-translational events, infidelity of translation or transcription, minor differences in amino acid sequence”; (2) two polysaccharides with similar saccharide repeating units, even if there were differences in the number of units and polymerization modifications; (3) two glycosylated proteins, if the differences between them had been due solely to post-translational events, infidelity of transcription or translation, or “minor differences in amino acid sequence,” and, in cases where the proteins had similar saccharide repeating units, even if there were differences in the number of units and post-polymerization modifications; (4) two polynucleotide products having an identical sequence of purine and pyrimidine bases or their derivatives and an identical sugar backbone; and (5) “[c]losely related, complex partly definable drugs with similar therapeutic intent, such as two live viral products for the same indication.” *Id.* (proposed PHSA § 351(k)(1)(B)(i)-(v)).

³⁶⁶ See 21 C.F.R. § 316.3(b)(13)(ii). The Orphan Drug Act provides seven years of market exclusivity for drugs and biologics intended to treat rare diseases or conditions. Pub. L. No. 97-414 § 2(a), 96 Stat. 2049, 2050-51 (1983) (creating FDCA § 527). FDA may not approve a subsequent product during the exclusivity period if it is the same drug and intended for the same condition. The agency’s regulations and the accompanying preambles describe drugs that are deemed the same for this purpose, make it clear that the examples are to be understood within the context of the aims of the Orphan Drug Act, and imply that the drugs in this case might not have the same clinical profile. See 57 Fed. Reg. 62076, 62077-79 (Dec. 29, 1992); 56 Fed. Reg. 3338, 3342 (Jan. 29, 1991) (“Overall, the approach embodied in [this language] would . . . tend to increase the likelihood that a potential competitor would be barred by the Orphan Drug Act from marketing a variant of an already marketed orphan drug.”). By way of contrast, the first Waxman bill would have permitted the clinical data supporting licensure of one of these drugs to support licensure of the other. H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(1)(B)(i)-(v)).

³⁶⁷ H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(1)(B)).

³⁶⁸ *Timing Is Everything: Biotech Pioneers Push Follow-On Biologics Bill*, RPM REPORT, Apr. 1, 2007, at 10 (commenting on same language in subsequent Waxman bill).

If an applicant showed comparability to a reference product for one condition of use, FDA would have been required to license the proposed product for all other conditions of use of the reference product sharing the same mechanism of action.³⁶⁹ Where the mechanism of action was unknown, FDA would have licensed the proposed product only for the condition(s) of use for which comparability had been established with data.³⁷⁰ Although this approach of permitting “extrapolation” from data for one indication was used by FDA in the Omnitrope approval,³⁷¹ the first Waxman bill would have permitted extrapolation in situations where less substantial data packages were submitted.

The notion of comparability in the first Waxman bill also diverged from FDA’s apparent view of biosimilarity under section 505(b)(2). When the agency approved Omnitrope in 2006, it found the product “highly similar” to the reference product Genotropin, on the basis of physicochemical, pharmacokinetic, pharmacodynamic, and clinical data comparing the products, as well as safety data from a 24-month, long-term safety and immunogenicity study.³⁷² The first Waxman bill apparently contemplated much smaller data packages. (In addition, as discussed in the next subsection, the first Waxman bill required interchangeability decisions. The Hatch-Waxman amendments do not, and FDA did not give Omnitrope an AB rating.)

Many of the other requirements for section 351(k) applications would have been similar to those in the Hatch-Waxman amendments for ANDAs. These included: (1) the requirement that the products use the same mechanism(s) of action (if known) for the proposed conditions of use and have the same route of administration, dosage form, and strength; (2) the requirement that the sought conditions of use be previously approved for the reference product; and (3) the requirement that the manufacturing facilities comply with cGMP.³⁷³ The grounds for disapproval were similar to those for disapproval of ANDAs and would have included the failure of the applicant to make any of the showings described above.³⁷⁴ Unlike the Hatch-Waxman amendments, however, the first Waxman bill provided that the applicant could submit “any additional data and information in support of the application, including publicly available information with respect to the reference product or another biological product.”³⁷⁵ No equivalent language is found in section 505(j) of the FDCA.

³⁶⁹ H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(5)).

³⁷⁰ *Id.*

³⁷¹ Woodcock et al., *supra* note 226, at 440.

³⁷² Woodcock et al., *supra* note 226, at 440.

³⁷³ H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(1)); *see also* FDCA § 505(j)(2)(A). A cGMP requirement would have followed from section 501(a)(2)(B) of the FDCA even without inclusion of this provision.

³⁷⁴ *Compare* H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(5)) (including as grounds for disapproval that the inactive ingredients or composition of the proposed product were unsafe, the application contains an untrue, materials statement of fact, and that the reference product was or had been proposed to be withdrawn for safety or effectiveness reasons). Under section 505(j)(4) of the FDCA, FDA generally must approve an ANDA (absent a suitability petition) unless the manufacturing facilities do not satisfy cGMP; the application does not show that the proposed conditions of use were approved for the reference listed drug; the application fails to show the active ingredient(s) are the same as those of the reference listed drug; the drug’s route of administration, dosage form, or strength are not the same as those for the reference listed drug; the application is insufficient to show that the proposed product is bioequivalent to the reference listed drug; the labeling for the proposed product is not the same as that for the reference listed drug except for differences due to the fact that the products are produced or distributed by different manufacturers; the inactive ingredients or composition of the drug are unsafe; the approval for the reference listed drug has been withdrawn, suspended, or proposed for withdrawal for certain specified reasons (including reasons of safety or effectiveness); the applicant did not contain all the required contents (e.g. drug samples); or the application contained an untrue statement of material fact. FDCA § 505(j)(4).

³⁷⁵ H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(1)(H)).

c. *Interchangeability*

The standards and process for interchangeability designations were both similar to and different from those in the Hatch-Waxman setting. Under the bill, a comparable biological product would have been “interchangeable” with the reference product if: (1) its active ingredient(s) had “principal molecular structural features” comparable to those of the reference product; and (2) it could have been “expected to produce the same clinical result as the reference product in any given patient in the condition or conditions of use for which both products [we]re labeled.”³⁷⁶ An applicant could have requested an interchangeability determination as part of its initial application or a later supplement. In either case, FDA would have been required to publish a “therapeutic comparability evaluation code” for the product.³⁷⁷ Upon a finding of interchangeability, the applicant could have requested that the labeling of its product include a statement that it was interchangeable with the reference product for all conditions of use for which comparability had been demonstrated.³⁷⁸

The most important difference between the first Waxman approach and the approach in the Hatch-Waxman setting is that the Waxman bill would have specified, by statute, the criteria for a finding of interchangeability. As noted in section I, the agency created therapeutic equivalence codes for generic drugs in the 1970s after extensive rulemaking on pharmaceutical equivalence and bioequivalence, and Congress did not address the issue in its legislation. In addition, the criteria in H.R. 6257 for an interchangeability designation are different from those in the *Orange Book* for drugs approved under the FDCA. First, a generic drug product must contain the “same” active ingredient in order to be deemed therapeutically equivalent in the *Orange Book*, whereas a biological product’s active ingredient needed to be only “comparable” under the first Waxman bill.³⁷⁹ Second, H.R. 6257 would have required the products to have the same clinical profile, while FDA’s therapeutic equivalence determinations are meant to signify the agency’s belief that the generic drug “can be substituted with the full expectation that [it] will produce the same clinical effect and safety profile as the [RLD].”³⁸⁰ In other words, FDA has defined the scientific showing necessary to support the inference, and the first Waxman bill specified that the showing should be that inference.

The process for interchangeability designations under H.R. 6257 was also different from the process used by FDA for drugs approved under the FDCA. Generic drugs approved under section 505(j), with the exception of those approved following grant of a suitability petition, are automatically deemed therapeutically equivalent. Generic drugs that are the basis of approved suitability petitions do not receive therapeutic equivalence ratings, and generally products that are the subject of 505(b)(2) applications do not receive these AB ratings.³⁸¹ Omnitrope did not receive an AB rating.³⁸²

³⁷⁶ *Id.* § 2(2) (proposed PHSA § 351(i)(6)).

³⁷⁷ *Id.* § 3(a)(2) (proposed PHSA § 351(k)(7)).

³⁷⁸ *Id.* (proposed PHSA § 351(k)(8)).

³⁷⁹ Compare *id.* with FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS iii-iv (30th ed. 2010).

³⁸⁰ FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS iv (30th ed. 2010).

³⁸¹ Products with approved 505(b)(2) applications and AB ratings include Prinivil (lisinopril), various levothyroxine products, and Humegon (menotropins), which is no longer marketed. Steven Kozlowski, Acting Director of Monoclonal Antibodies, Follow-On Protein Workshop Background Concepts and Definitions (Feb. 16, 2005), at slide 5; FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 32 (14th ed., Cum. Supp. No. 10, 1994)(showing Humegon approved Sept. 1, 1994 and given AB rating).

³⁸² Letter from Steven K. Galson to Kathleen M. Sanzo, Stephan E. Lawton, and Stephen J. Juelsgaard, Esq., *supra* note 79, at 4.

2. Exclusivity Provisions of H.R. 6257

In contrast to the scheme for new drugs in the FDCA and the European approach for new medicines, H.R. 6257 would have provided no data exclusivity to biological product innovators. Biosimilar applicants who made interchangeability showings, however, would have been eligible for exclusivity.³⁸³ This exclusivity would have blocked “approv[al] [of] a second or subsequent comparable biological product application.”³⁸⁴ This period of exclusivity would have terminated on the earlier of: (1) the day 180 days after first commercial marketing of the first interchangeable product, or (2) various other dates dependent on the pendency and outcome of patent litigation in accordance with H.R. 6257.³⁸⁵ It appears to have been modeled on the provision in the Hatch-Waxman amendments governing 180-day exclusivity for first generic applicants.

3. Patent Provisions of H.R. 6257

Like the BPCIA, H.R. 6257 would have created a scheme for identification and resolution of patent issues related to market entry of comparable biological products. Just as the BPCIA provisions do, the patent litigation provisions in the first Waxman bill differed significantly from the Hatch-Waxman litigation provisions. For example, the patent resolution process would have begun at the applicant’s option. Also, the bill would have created a private process for identification of patents relevant to launch of the comparable biological product. Finally, the bill would have limited the remedies available for patent infringement where the holder of the reference product BLA failed to comply with certain provisions.

First, the bill called for the patent resolution process to be “left entirely to the discretion of the applicant or prospective applicant.”³⁸⁶ The applicant could not have been compelled, “by court order or otherwise,” to begin the patent resolution process described in the bill. Although the Hatch-Waxman amendments permit a generic or 505(b)(2) applicant to file a paragraph III certification and thereby avoid the FDCA’s special litigation process, in that case approval of its application may not be effective until expiry of the patent. The first Waxman bill imposed no such requirement. The Waxman approach also contrasted with that of the BPCIA, which is described in Section IV and which requires the patent resolution procedure to begin within twenty days of filing of the biosimilar application.

³⁸³ H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(9)(A)).

³⁸⁴ *Id.* The exclusivity also would have prevented the reference product sponsor or anyone authorized by it from marketing, selling, manufacturing, or distributing a “rebranded interchangeable biologic,” defined as “any rebranded interchangeable version of a reference product that the holder of the biological product license approved under subsection (a) for that reference product seeks to commence marketing, selling, or distributing, directly or indirectly.” *Id.* (proposed PHSA § 351(k)(9) (A) & (B)). This provision appears to have been modeled on prior legislative proposals that would have blocked marketing of authorized generics during the 180-day exclusivity period for the first generic applicant to file an ANDA with a paragraph IV certification. *See, e.g.*, S. 3695, 109th Cong. § 1 (2006); H.R. 5993, 109th Cong. § 1 (2006).

³⁸⁵ *Id.* (proposed PHSA § 351(k)(9)(A)). Other potential end dates for the exclusivity included: (1) one year after a final court decision as to all patents in suit in, or dismissal of, patent litigation commenced pursuant the bill’s special litigation procedure; (2) thirty-six months after approval of the first interchangeable product, if such patent litigation was ongoing; or (3) one year after approval of the first interchangeable product, if no such patent litigation was initiated. “Final court decision” was defined to mean “a final decision of a court from which no appeal (other than a petition to the United States Supreme Court for a writ of certiorari) has been or can be taken.” *Id.*

³⁸⁶ *Id.* (proposed PHSA § 351(k)(16)(E)).

Second, the bill would have created a private process for identification of relevant patents rather than a public listing process as in the Hatch-Waxman context. Under the first Waxman bill, an applicant could have elected to request patent information from the holder of the reference product BLA.³⁸⁷ This request could have been made during “the initial stages of development” of the comparable biological product, and the applicant could have submitted additional requests “at any time.”³⁸⁸ The BLA holder would have been required to respond with a list of all owned or licensed patents that it “in good faith believe[d] relate[d]” to the reference product, including product, method, component, and process patents, without confidential access to the biosimilar application or information regarding the manufacturing process.³⁸⁹ The BLA holder would have had to update this list within thirty days of issuance or licensure of a new relevant patent.³⁹⁰

Then, “at any time” after the submitting its application to FDA and as many times as desired, the applicant could have provided a “notice” to the BLA holder and the patent owner challenging the validity or enforceability of a listed patent or claiming that the patent would not be infringed by commercial sale of the biosimilar.³⁹¹ The notice provision differed from the provision requiring paragraph IV certifications under the Hatch-Waxman amendments. Specifically, the applicant could have selected the patents it wished to challenge and could have excluded any others it did not desire to litigate.³⁹² As under the Hatch-Waxman amendments, however, providing the notice would have constituted an act of patent infringement as to patents identified in it,³⁹³ creating federal court jurisdiction for a patent infringement case. In the notice, the applicant would have been required to specify at least one judicial district in which it would consent to being sued.³⁹⁴

The BLA holder or patent owner could have brought an infringement suit within forty-five days of receiving the notice.³⁹⁵ Failure to do so would have had the consequences described in the next paragraph. This litigation could have been brought with respect to only those patents identified by the applicant in its notice and only in the judicial district(s) it had identified.³⁹⁶ In contrast, under the Hatch-Waxman amendments, an innovator bringing suit during the forty-five-day period provided by the statute selects the forum and may sue on any patent for which jurisdiction is established. Under the first Waxman bill, neither the BLA holder nor the patent owner could have brought suit for a declaratory judgment of infringement regarding any other patent before commercial marketing of the comparable biological product.³⁹⁷

³⁸⁷ *Id.* (proposed PHSA § 351(k)(16)(A)(i)).

³⁸⁸ *Id.* (proposed PHSA § 351(k)(16)(A)(iv)).

³⁸⁹ *Id.* This contrasts with the approach taken in the BPCIA, under which the reference product sponsor receives confidential access to the biosimilar application and information about its manufacturing process. *See* BPCIA § 7002(a)(2) (PHSA § 351(l)(2)(A)). Also, under the BPCIA, the reference product sponsor must assemble a list of patents as to which it believes a claim of infringement “could reasonably be asserted”—presumably a different standard than the “relate to” standard of the Waxman bill. *Compare* BPCIA § 7002(a)(2) (PHSA § 351(l)(3)(A)) *with* H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(16)(B)).

³⁹⁰ H.R. 6257, § 3(a)(2) (proposed PHSA § 351(k)(16)(A)(iii)).

³⁹¹ *Id.* (proposed PHSA § 351(k)(16)(B)(i) & (ii)). If the applicant opted to provide a notice, it would have been required to provide the notice to both the BLA holder and the patent owner. *Id.* (proposed PHSA § 351(k)(16)(B)(i)).

³⁹² The Waxman approach also differs from that of the BPCIA, under which the applicant must address each patent the reference product sponsor identifies.

³⁹³ H.R. 6257, § 3(a)(2) § 3(b)(1)(A)(iii) & (iv) (proposed 35 U.S.C. § 271(e)(2)(C)); 35 U.S.C. § 271(e)(2)(A).

³⁹⁴ *Id.* (proposed PHSA § 351(k)(16)(B)(iii)).

³⁹⁵ *Id.* (proposed PHSA § 351(k)(16)(C)(i)).

³⁹⁶ *Id.* (proposed PHSA § 351(k)(16)(C)(ii)).

³⁹⁷ *Id.* (proposed PHSA § 351(k)(16)(D)).

Finally, unlike the Hatch-Waxman amendments, the bill would have limited remedies available for patent infringement in two situations. First, rather than staying approval of the comparable biological product application if the innovator brought timely premarket patent litigation, which is the approach taken in the Hatch-Waxman amendments, H.R. 6257 would have penalized innovators for failure to bring suit. If the innovator did not initiate suit within forty-five days or did not “maintain[] [the suit] through a final court decision or a dismissal with prejudice” on validity, enforceability, or infringement,³⁹⁸ it could have recovered only a “reasonable royalty” from the infringing applicant or a person found to have induced or contributed to the infringement.³⁹⁹ Second, if the BLA holder failed to include in its list of patents a patent that should have been disclosed, the patent owner (whether or not also the BLA holder) would have been barred from bringing an infringement suit against the applicant.⁴⁰⁰ This bar was not limited to infringement suits related to the omitted patent or the product to which it related. These provisions appeared to be modeled on previous legislative proposals to amend the Hatch-Waxman provisions, which would have limited remedies based on failure to list patents and bring suit within the forty-five-day period.⁴⁰¹

Unlike the Hatch-Waxman amendments, H.R. 6257 also would have limited the circumstances in which an innovator could have obtained an injunction staying approval of the comparable biological product application. The bill provided that “no court shall enjoin [FDA]” from licensing a biosimilar, “except by issuance of a permanent injunction” where clear and convincing evidence showed that the requestor: (1) had prevailed on the merits; (2) would have suffered “imminent and actual irreparable injury” (other than irrevocable monetary losses) that would threaten the person’s business; and (3) had an interest outweighing the “overwhelming” public interest in licensure of the comparable biological product.⁴⁰²

B. 110th Congress, First Session

The mid-term elections in November 2006 gave Democrats control of Congress. Discussions during the first six months of the 110th Congress were fueled, in part, by the interest of stakeholders and Members of Congress — including GPhA and Senator Schumer — in rolling biosimilars into legislation slated for enactment during 2007, the re-authorization of the Prescription Drug User Fee Act (PDUFA).⁴⁰³ FDA and BIO opposed inclusion of biosimilars in PDUFA.⁴⁰⁴ FDA called for

³⁹⁸ *Id.* § 3(b)(1)(B) (proposed 35 U.S.C. § 271(e)(5)(A)). “Final court decision” was not defined for purposes of this subparagraph.

³⁹⁹ *Id.* A variation of this language survived in the BPCIA. *See infra* note 1303 and accompanying text.

⁴⁰⁰ H.R. 6257, § 3(b)(1)(B) (proposed 35 U.S.C. § 271(e)(5)(B)). This concept of barring third party patent owners if the BLA holder fails to identify a relevant patent survived in the BPCIA. *See infra* note 1304.

⁴⁰¹ *See, e.g.*, S. 812, 107th Cong. §§ 103(a)(1) (proposed FDCA § 505(c)(2)(F)); 104(a)(2) (proposed FDCA § 505(j)(5)(C)); 104(b) (proposed FDCA § 505(c)(4)).

⁴⁰² H.R. 6257 § 3(a)(2) (proposed PHSA § 351(k)(12)). *Compare* 35 U.S.C. § 271(e)(4) (requiring a court that finds patent infringement in a Hatch-Waxman case to stay approval of the generic drug until patent expiry).

⁴⁰³ FDA “Failure” to Approve Generic Biologics Questioned by Commerce Cmte, THE PINK SHEET, Feb. 5, 2007; *Generic Biologics Bill’s Key Battleground May Be Senate Health Committee*, THE PINK SHEET, Feb. 19, 2007; *FDA Opposes Using PDUFA as Vehicle for Biogenics Legislation*, FDA WEEK, Jan. 19, 2007.

⁴⁰⁴ *FDA Opposes Using PDUFA as Vehicle for Biogenics Legislation*, FDA WEEK, Jan. 19, 2007.

Congress to pass the critical funding legislation “as unencumbered as possible,” while BIO took the position that the time frame in which PDUFA needed to be passed was too short for stakeholders to consider “an issue of such complexity.”⁴⁰⁵

Members of Congress introduced three biosimilars bills between February and May 2007, and both the House and Senate held hearings on the topic. The bills included a re-introduced version of the first Waxman bill with minor substantive changes (H.R. 1038, with identical companion legislation in the Senate, S. 623, introduced by Senator Schumer and cosponsored by Senator Clinton (D-NY) and others); H.R. 1956, introduced by Representative Inslee (D-WA); and S. 1505, introduced by Senator Gregg (R-NH). During this same time period, as discussed in section III.B.3, then FDA Deputy Commissioner and Chief Medical Officer Janet Woodcock and other FDA personnel published an article providing insight into the agency’s views on biosimilars.

In early May 2007, Senator Kennedy committed to Senators Schumer and Clinton that the PDUFA legislation would include a follow-on biologics pathway and that this legislation would be marked up on June 13, 2007.⁴⁰⁶ When the PDUFA legislation passed the Senate in May 2007, it included a placeholder for insertion of text on follow-on biologics.⁴⁰⁷ At the same time, four members of the Senate Committee on Health, Education, Labor, and Pensions (HELP) — Senators Kennedy, Hatch, Enzi (R-WY), and Clinton — were developing a legislative proposal on biosimilars⁴⁰⁸ and working with both the generic industry and the innovative industry in the hopes of crafting a compromise that would have wide support like the Hatch-Waxman amendments had had. These efforts culminated in introduction of S. 1695 in June 2007. Amendments to S. 1695 were proposed shortly thereafter in the draft known as the “7721” draft because of its file path stamp.⁴⁰⁹ The HELP Committee voted to pass the bill.⁴¹⁰ Nevertheless, the bill was not attached to PDUFA in conference in part because there was disagreement about what were described by some as “technical” amendments to the as-passed bill and in part because House legislators indicated they believed further consideration of the legislation was necessary. Because discussion continued regarding amendments to the bill and in particular its data exclusivity provisions, the bill was not formally reported until November 2008.

Consensus was reached early with respect to a general approach to the regulatory provisions, although there were disagreements over details.⁴¹¹ The patent litigation process and the data exclusivity term proved more troublesome. The patent litigation provisions eventually placed in S. 1695 were enacted in essentially their introduced form in the BPCIA. Congress also retained the initially agreed-upon data exclusivity term of twelve years. As discussed in more detail below, however, there was a debate before enactment regarding application of the agreed-upon

⁴⁰⁵ *Generic Biologics Bill's Key Battleground May Be Senate Health Committee*, THE PINK SHEET, Feb. 19, 2007; see also Steve Usdin, *Firing up for FOBs*, BIOCENTURY, Jan. 29, 2007, at A16, A18.

⁴⁰⁶ Press Release, Clinton Press Office, Senators Schumer and Clinton Secure Commitment on Generic Version of Biologic Medications (May 3, 2007).

⁴⁰⁷ 153 Cong. Rec. S5759, S5803 (daily ed. May 7, 2007).

⁴⁰⁸ *Generic Biologics May See Life After PDUFA; Senate Mark-Up Possible in May*, THE PINK SHEET, Apr. 23, 2007, at 6.

⁴⁰⁹ Draft Amendment in the Nature of a Substitute to S. 1695, stamped O:\KERAKER07721.xml (the 7721 Draft).

⁴¹⁰ Press Release, U.S. Senate Committee on Health, Education, Labor & Pension, Lawmakers Praise Committee Passage of Biologics Legislation (June 27, 2007).

⁴¹¹ *Follow-On Biologics Alternative Bill Progresses; IP Issues Remain Sticking Point*, THE PINK SHEET, Apr. 16, 2007.

twelve-year period to supplemental BLAs and new BLAs that were filed by the same company and that related in some fashion to a previously approved BLA. Some would seek to prohibit a practice they called “evergreening” (discussed below), and others would argue that an agreement even with respect to subsequent applications had already been reached, that evergreening was a fiction, and that the discussion really related to second generation products, which should receive their own periods of data protection. This disagreement caused the legislative negotiations on biosimilars to fall apart during 2007, but — as noted below — the exclusivity language in the BPCIA ultimately took the same form as the language proposed in the 7721 draft in June 2007.

1. *The Second Waxman Bill*

Representative Waxman and Senator Schumer introduced H.R. 1038 and S. 623, respectively, in the 110th Congress. These bills were identical, and this article refers to them as H.R. 1038 or the “second Waxman bill.”⁴¹² The second Waxman bill was different in several respects from the first Waxman bill. These differences primarily related to the required analytical comparison between the products; the definition of interchangeability; the mechanics of obtaining an interchangeability determination; and the naming of biosimilars.

H.R. 1038 would have required biosimilar applicants to demonstrate that the biosimilar and reference product “contain[ed] highly similar principal molecular structural features.”⁴¹³ This version of the bill substituted “highly similar” where “comparable” had previously been used. H.R. 1038 would have required this structural comparison to be made “based upon such data and other information characterizing the two products as [FDA] deem[ed] necessary.”⁴¹⁴ As noted, the first Waxman bill (H.R. 6257) had called for this comparison to be based on “thorough characterization,” a phrase defined in that bill. The definition of “thorough characterization” remained in H.R. 1038 but the phrase was not used in the analytical data provision or anywhere else.

Representative Waxman had also modified the definition of “interchangeability.” The earlier definition had required the active ingredients of the biosimilar and reference product to have comparable principle molecular structural features. The new bill substituted a requirement that the biosimilar be “comparable” to the reference product.⁴¹⁵ Thus, under the second Waxman bill, a biological product would have been interchangeable with the reference product if it was comparable to the reference product and if it could have been expected to product the same clinical result in a given patient.⁴¹⁶ The concept of “therapeutic comparability codes” from the first bill was omitted.

Representative Waxman also addressed the question whether biosimilars should have nonproprietary names that differed from those of their corresponding reference products. The provision on naming on the second Waxman bill was informed by discussions of the issue at the November 2006 World Health Organization (WHO)

⁴¹² H.R. 1038, 110th Cong. (2007); S. 623, 110th Cong. (2007).

⁴¹³ H.R. 1038, § 3(a)(2) (proposed PHSA § 351(k)(1)(B)). The corresponding disapproval condition also was modified to provide that FDA would be required to approve an application unless information in it was insufficient to show the products had highly similar principal molecular structural features. *Id.* (proposed PHSA § 351(k)(4)(A)(ii)).

⁴¹⁴ *Id.*

⁴¹⁵ *Id.* § 2(a)(2) (proposed PHSA § 351(i)(5)).

⁴¹⁶ *Id.*

meeting regarding the International Nonproprietary Name (INN) Program. GPhA had argued that biosimilars should have the same nonproprietary names as their reference products, stating that this approach would foster competition in the biotechnology sphere, avoid prescriber and consumer confusion, and be consistent with the practice of not requiring a new name when an innovator changes its own product and supports the change with a comparability showing.⁴¹⁷ Others argued that identical nonproprietary names would inappropriately “imply that these products are pharmacologically interchangeable when they are not” and would undermine pharmacovigilance efforts by making it difficult to determine whether an adverse event was associated with the biosimilar or reference product.⁴¹⁸ Under the naming provision of the second Waxman bill, FDA could designate an official name for a biosimilar using its existing authority under section 508 of the FDCA, which authorizes FDA to designate an official name for a drug if it “determines that such action is necessary or desirable in the interests of usefulness or simplicity.”⁴¹⁹ Under the second Waxman bill, if FDA made this determination, it would have been required to designate the same official name for the biosimilar as for the reference product.⁴²⁰ This requirement would not have applied to products incorporating a change from the reference product, *i.e.*, 351(k)(2) applications.⁴²¹

The second Waxman bill was praised by GPhA as providing a “safe, clear, and efficient” pathway and granting FDA “the authority and flexibility it needs to request from generic companies the necessary data and tests on a product-by-product basis.”⁴²² In contrast, BIO issued a press release stating that “strongly oppose[d]” the second Waxman bill because the bill “would restrict” FDA’s ability to require “clinical testing it believes appropriate to determine the safety and efficacy” of biosimilars, “would prohibit the FDA from requesting postmarketing studies,” and “would improperly dictate scientific conclusions that the FDA should reach about . . . comparability.”⁴²³ BIO also objected to the bill’s “one-sided” changes to patent law and its lack of data exclusivity provisions.⁴²⁴

BIO subsequently released a paper supporting its conclusion that the data exclusivity “period should be no less than 14 years,” which “would run concurrently with the patent term for the product.”⁴²⁵ According to BIO, there would be a “gap in

⁴¹⁷ See GPhA, Letter to World Health Organization Regarding the International Nonproprietary Name Programme (Aug. 10, 2006), at 1-2, available at <http://www.gphaonline.org/sites/default/files/GPhA%20Letter%20to%20World%20Health%20Organization%20Regarding%20the%20International%20Nonproprietary%20Name%20Programme.pdf>.

⁴¹⁸ BIO, BIO Position Statement: Naming and Labeling Requirements for Biological Medicines 2 (Nov. 2006), available at <http://www.bio.org/healthcare/followon/position20061106.pdf>.

⁴¹⁹ H.R. 1038, § 3(a)(2) (proposed PHSA § 351(k)(6)); FDCA § 508(a). An official name designated by FDA must appear on the drug labeling and is the only name for the drug that can be used in any official compendium. FDCA §§ 502(e)(1)(A) & (3)(A); 508(a).

⁴²⁰ *Id.*

⁴²¹ *Id.* Other changes made in the second Waxman bill included a change to the bill’s postmarketing study provisions to provide that these requirements would have applied only to section 351(k)(1) applications (not to those filed under section 351(k)(2)), and a change providing that a rebranded interchangeable biological product could not have been marketed for any condition of use during the exclusivity period for the first interchangeable biologic. *Id.* (proposed PHSA § 351(k)(5) & (10)).

⁴²² Press Release, GPhA, GPhA Endorses Access to Life Saving Medicine Act—Legislation Would Create Safe, Abbreviated FDA Approval Pathway for Biogenerics (Feb. 14, 2007).

⁴²³ Press Release, BIO, BIO Restates Opposition to H.R. 1038 (Mar. 26, 2007), available at http://www.bio.org/news/pressreleases/newsitem.asp?id=2007_0326_01.

⁴²⁴ *Id.*

⁴²⁵ BIO, *A Follow-On Biologics Regime Without Strong Data Exclusivity Will Stifle the Development of New Medicines* 1, 4 (May 3, 2007) (BIO Data Exclusivity Paper).

patent protection for biologics” for several reasons.⁴²⁶ First, a biosimilar would “only have to be ‘highly similar’ to [rather than the ‘same as’] the innovator product.”⁴²⁷ Thus, according to BIO, “there is a very real potential that the manufacturer of a [biosimilar] may be able to secure abbreviated regulatory approval based at least in part on the innovator’s prior approval, and, at the same time, avoid infringing patents that protect the innovator’s biotech product.”⁴²⁸ Second, BIO stated, “[b]ecause of the nature of biologic products — produced by living cells and organisms — patent protection is different from and may be weaker than that afforded to small medicinal molecules.”⁴²⁹ According to BIO, “[t]his is because” several requirements for obtaining a patent “are interpreted more stringently for biotechnology inventions than for most other technologies.”⁴³⁰ BIO also stated that, as a result of “current limitations of patentability of naturally occurring substances, many biologics are protected only by process patents that may be easier to ‘design around.’”⁴³¹

According to BIO, exclusivity would provide an “insurance policy” for “instances where the [biosimilar] manufacturer is able to work around the patents held by the innovator but still gain approval of its [biosimilar].”⁴³² Moreover, BIO stated, Congress “concluded that 14 years of patent protection is appropriate for drugs and biological products” when it “created a mechanism allowing for the extension of patents on innovator drugs and biologics for up to 14 years following approval of the product.”⁴³³ According to BIO, as a result, “any statutory formula that allows for [biosimilars] should at least guarantee that same degree of effective market protection — and . . . that protection can be accomplished most predictably through data exclusivity.”⁴³⁴ The month after BIO released its position paper, Duke University Professor Henry Grabowski released a working paper concluding that biotechnology companies typically recover their investments in an innovative product between 12.9 and 16.2 years after approval.⁴³⁵ BIO updated the paper to cite this finding.⁴³⁶

The pathway issues raised by the Waxman bill and, to a lesser extent, the data exclusivity and patent issues, were the focus of hearings in 2007.

2. Hearings

Three hearings were held on issues related to biosimilars legislation between March and May 2007. On March 8, 2007, the Senate HELP Committee held a

⁴²⁶ *Id.* at 1.

⁴²⁷ *Id.* at 2.

⁴²⁸ *Id.* at 1.

⁴²⁹ *Id.* at 2.

⁴³⁰ *Id.* 2-3 n.2.

⁴³¹ *Id.* at 3.

⁴³² *Id.* at 4.

⁴³³ *Id.* at 3. Title II of the Hatch-Waxman amendments permits restoration of the patent term lost when commercial marketing of a drug is delayed due to premarket clinical trials and regulatory review. Under these provisions, a maximum of five years of the patent term may be restored. The restored period equals half of the IND review period and all of the NDA review period. The total effective patent life — i.e., patent term remaining after product approval plus the extension — cannot exceed 14 years after the regulatory approval of the claimed product or method. 35 U.S.C. § 156(g)(6). If the remaining patent life already exceeds 14 years, no restoration is available. The House Report accompanying the Hatch-Waxman amendments stated: “by providing for up to fourteen years of market exclusivity, the Committee expects that research intensive companies will have the necessary incentive to increase their research and development activities.” H.R. Rep. No. 98-857, at 41 (1984).

⁴³⁴ BIO Data Exclusivity Paper, at 3-4.

⁴³⁵ Henry Grabowski, *Data Exclusivity for New Biological Entities*, (Duke University Department of Economics Working Paper No. 2., June 2007).

⁴³⁶ BIO, *A Follow-On Biologics Regime Without Strong Data Exclusivity Will Stifle the Development of New Medicines* 4 (Sept. 26, 2007).

hearing.⁴³⁷ This was followed by a March 26 hearing before the House Committee on Oversight and Government Reform⁴³⁸ and a May 2 hearing before the Subcommittee on Health of the House Energy and Commerce Committee.⁴³⁹ The trade press reported that the Senate HELP hearing was set up “‘by design’ to make several key points: the value of the European model, the critical need for clinical demonstration of safety and effectiveness . . . and the difficulty of establishing interchangeability.”⁴⁴⁰

The testimony and member questions at these hearings focused on five questions: (1) whether FDA’s comparability guidance for changes to the manufacturing process of a licensed biologic was relevant to the appropriate framework for licensing biosimilars; (2) how well protein products could be characterized and the implications of this for the type and amount of clinical data (including immunogenicity data) that should be required in a biosimilar application; (3) whether FDA should issue guidance documents prior to licensing biosimilars; (4) the appropriateness of the provision in the Waxman bills deeming certain types of products comparable including, for example, products with differences in amino acid sequence; and (5) whether biosimilars could be deemed interchangeable with the corresponding reference products, and if so, the criteria that should govern these determinations. In addition, several witnesses discussed data exclusivity and patent provisions. These issues would become the central focus of the 2009 hearing, discussed in section III.D.6.

One of the witnesses at the HELP hearing was Nicolas Rossignol, Administrator of the European Commission Pharmaceuticals Unit. Mr. Rossignol commented that “there is no reason why, in principle, scientific requirements should be different on one side of the Atlantic than on the other.”⁴⁴¹ Many witnesses advocated approaches consistent with the European model, particularly regarding clinical data requirements and the issuance of guidance. Mr. Rossignol’s testimony was sufficiently influential that one trade press article called him the “star witness” for the HELP Committee hearing.⁴⁴²

a. *Relevance of Comparability Guidance to Biosimilars*

Most witnesses agreed that FDA’s experience with comparability assessments would be valuable in reviewing biosimilars. Nonetheless, there was disagreement on the extent to which the principles of FDA’s comparability guidance should be used in the licensure of biosimilars. On the one hand, witnesses such as Theresa L. Gerrard, Ph.D., President of TLG Consulting, Inc., stated that “[t]he underlying scientific principles that guided comparability policy . . . can and should be adopted” for

⁴³⁷ *Examining Food and Drug Administration Follow-On Biologics, Generally Referred to as a Biotechnology-Derived Protein Drug (or Biologic) that is Comparable to a Novel, Previously Approved Biologic and that is Approved with Less Supporting Data than the Innovator Biologic: Hearing Before the S. Comm. on Health, Labor, and Pensions*, 110th Cong. (2007).

⁴³⁸ *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. (2007).

⁴³⁹ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 110th Cong. (2007).

⁴⁴⁰ *Timing is Everything: Biotech Pioneers Push Follow-On Biologics Bill*, RPM REPORT, Apr. 2007, at 9.

⁴⁴¹ *Examining Food and Drug Administration Follow-On Biologics*, *supra* note 437, at 39 (statement of Nicolas Rossignol, Administrator of the European Commission Pharmaceuticals Unit) (Rossignol Testimony).

⁴⁴² *Timing is Everything: Biotech Pioneers Push Follow-On Biologics Bill*, RPM REPORT, Apr. 2007, at 9.

biosimilars.⁴⁴³ Then House Oversight and Reform Committee Chairman Waxman stated that, in his view, the comparability guidance “seems to undercut the brand name industry argument that changes in manufacturing processes can affect safety and effectiveness in ways that can only be assessed through clinical trials.”⁴⁴⁴ On the other hand, some witnesses, including Dr. Woodcock, then FDA Deputy Commissioner and Chief Medical Officer, pointed out the differences between evaluating a new biosimilar and evaluating changes to a licensed biologic.⁴⁴⁵ Dr. Woodcock noted that “demonstrating the similarity of a follow-on protein product to a reference product will typically be more complex, and thus require more new data, than assessing the similarity of products before and after manufacturing changes made by the licensed product’s sponsor.”⁴⁴⁶ The manufacturer of an already-licensed product has access to trade secret information about its own prior manufacturing process (including information about intermediate steps in the manufacturing and purification processes), while a biosimilar manufacturer will not.⁴⁴⁷ According to Jay P. Siegel, M.D., Group President, Biotechnology, Immunology, and Oncology, Research & Development, Johnson & Johnson, access to this information is very important: an innovator changing its own process can “compare not only final product but also various components and intermediates that are produced during various stages of the new and old manufacturing process.”⁴⁴⁸ This may allow for “detect[ion] [of] the presence of new variants or contaminants that, after purification and/or formulation, may be reduced or masked such that they are still present but undetectable in final product.”⁴⁴⁹

b. *Clinical Data Requirements*

The consensus was that clinical data — and in particular an immunogenicity assessment — would be required for most biosimilars for the foreseeable future.⁴⁵⁰ According to most witnesses, the types of clinical data required for a biosimilar would depend on factors such as the complexity of the product, the degree to which it can be characterized, the history of the product’s clinical use, and the level of demonstrated structural similarity between the biosimilar and reference product.⁴⁵¹

⁴⁴³ *Safe and Affordable Biotech Drugs*, *supra* note 438, at 63 (statement of Theresa L. Gerrard, Ph.D., President, TLG Consulting, Inc.) (Gerrard Testimony); *accord id.* at 73 (statement of William Schwieterman, M.D., President, Tekgenics Corp.) (First Schwieterman Testimony); *Examining Food and Drug Administration Follow-On Biologics*, *supra* note 437, at 32 (statement of Ajaz S. Hussain, Ph.D., Vice President and Global Head of Biopharmaceutical Development, Sandoz) (Hussain Testimony).

⁴⁴⁴ *Safe and Affordable Biotech Drugs*, *supra* note 438, at 117 (statement of Rep. Waxman).

⁴⁴⁵ *Safe and Affordable Biotech Drugs*, *supra* note 438, at 41 (statement of Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer, FDA) (First Woodcock Testimony); *Examining Food and Drug Administration Follow-On Biologics*, *supra* note 437, at 15 (statement of Jay P. Siegel, M.D., Group President, Biotechnology, Immunology, and Oncology, Research & Development, Johnson & Johnson) (Siegel Testimony).

⁴⁴⁶ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 31 (statement of Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer, FDA) (Second Woodcock Testimony).

⁴⁴⁷ First Woodcock Testimony, at 41.

⁴⁴⁸ Siegel Testimony, at 17-18.

⁴⁴⁹ *Id.* at 63.

⁴⁵⁰ *See, e.g.*, Siegel Testimony, at 15, 18; Hussain Testimony, at 54; First Woodcock Testimony, at 43; *Safe and Affordable Biotech Drugs*, *supra* note 438, at 84 (statement of Inger Mollerup, Ph.D., Vice President for Regulatory Affairs, Novo Nordisk A/S) (Mollerup Testimony); *Safe and Affordable Biotech Drugs*, *supra* note 438, at 103 (statement of Ganesh Venkataraman, Ph.D., Senior Vice President, Research, Momenta Pharmaceuticals, Inc.) (Venkataraman Testimony).

⁴⁵¹ *See, e.g.*, Hussain Testimony, at 54; First Woodcock Testimony, at 45; Gerrard Testimony, at 64.

For example, Dr. Woodcock noted, “[i]n some instances the manufacturer may not be able to show enough similarity and [it] may have to repeat much of the clinical program. In other instances [it] may be able to show an extreme amount of similarity, a very great similarity to prior product, and therefore would have very much smaller clinical trials needed, perhaps of immunogenicity.”⁴⁵²

In addition, Dr. Woodcock testified that “[r]ight now . . . for proteins, we believe we will need immunogenicity trials in people because we cannot predict the immunogenicity answers without doing human trials.”⁴⁵³ Although a few witnesses stated that other methods would be more sensitive for detecting immunogenicity and that clinical immunogenicity studies would not be required in all cases,⁴⁵⁴ others concurred with Dr. Woodcock’s assessment.⁴⁵⁵

A consensus was reached that FDA should have the authority and flexibility to determine the appropriate clinical requirements for biosimilars on a case-by-case basis.⁴⁵⁶ Dr. Siegel emphasized that “any proposed pathway . . . should not constrain the FDA’s ability to request data and studies in support of sound scientific decisions.”⁴⁵⁷ Dr. Gerrard agreed, stating “[w]e want FDA to have the ability to request any additional data they need to make sure the product is safe.”⁴⁵⁸ Nevertheless, witnesses disagreed about whether biosimilars legislation should mandate clinical studies. For instance, Dr. Siegel stated that he “believe[d] that there will always be a need (in the foreseeable future) for some amount of clinical testing.”⁴⁵⁹ In his opinion, the legislation should require clinical trials to provide a “floor” to give “guidance to industry,” FDA, and the court system.⁴⁶⁰ He noted there was precedent for a statutory requirement of clinical trials in the FDCA provision requiring adequate and well-controlled clinical investigations for new drugs.⁴⁶¹ Representative Gene Green (D-TX) stated that “it would be disingenuous for [Congress] to point out . . . why we need drug safety reform at FDA and in the next breath give FDA carte blanche authority to approve any follow-on biologic without some sort of clinical trials . . .”⁴⁶²

Dr. William Schwieterman, President of the consulting firm Tekgenics Corp., disagreed, stating that “[m]andated clinical trials . . . is not something that is scientific, but rather political.”⁴⁶³ Bruce L. Downey, testifying on behalf of Barr Pharma-

⁴⁵² First Woodcock Testimony, at 47.

⁴⁵³ Second Woodcock Testimony, at 47.

⁴⁵⁴ See, e.g., First Schwieterman Testimony, at 118.

⁴⁵⁵ See, e.g., Siegel Testimony, at 18; Mollerup Testimony, at 84.

⁴⁵⁶ See, e.g., Siegel Testimony, at 15 (noting clinical testing “will be needed” but that “the types and extent of clinical testing will need to be determined on a case-by-case basis . . .”); Hussain Testimony, at 32 (noting FDA should be empowered to determine the specific clinical requirements applicable to a given product); *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, supra note 439, at 118 (statement of Bruce L. Downey, Chairman and Chief Executive Officer, Barr Pharmaceuticals, Inc. & Chairman of the Board, GPhA) (Downey Testimony); *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, supra note 439, at 129 (statement of Richard F. Kingham, Partner, Covington & Burling LLP) (Kingham Testimony).

⁴⁵⁷ Siegel Testimony, at 15.

⁴⁵⁸ Gerrard Testimony, at 126; see also Downey Testimony, at 118 (noting the legislation should include “provisions giving FDA discretion to require the needed tests—and only the needed tests—to make safety and effectiveness determinations”).

⁴⁵⁹ Siegel Testimony, at 18.

⁴⁶⁰ *Id.* at 48.

⁴⁶¹ *Id.*

⁴⁶² *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, supra note 439, at 6 (statement of Rep. Green).

⁴⁶³ First Schwieterman Testimony, at 125.

ceuticals, Inc. for which he then served as Chairman and Chief Executive Officer, stated that the PHSA does not mandate clinical trials for innovative biologics.⁴⁶⁴ Representative Waxman also expressed concern that statutory language requiring clinical trials would “freeze science as of the date of enactment.”⁴⁶⁵ When Representative Inslee asked Dr. Woodcock whether a clinical trial requirement would slow the pace of scientific inquiry, she responded, “it would depend on how specific or how prescriptive you were.”⁴⁶⁶ The final legislation generally requires clinical testing, including an assessment of immunogenicity, but gives FDA discretion to waive the requirements upon a finding they are unnecessary.⁴⁶⁷

Most witnesses argued for an approach consistent with the European model, where clinical data are required but the amount and type vary depending on the complexity of the product, and where the “legislation . . . is relatively . . . flexible and supplemented . . . by guidance.”⁴⁶⁸ Dr. Woodcock’s testimony was consistent with Mr. Rossignol’s statement that “a biosimilar application could . . . range from being almost as abridged as a generic application . . . to being nearly as complete as a full, stand-alone application.”⁴⁶⁹

A few witnesses also expressed reservations about the second Waxman bill’s language that any needed clinical trials must be designed to avoid duplicative and unethical clinical testing. For example, Dr. Siegel considered this language to have “potential to inhibit appropriate regulatory activity.”⁴⁷⁰ According to Dr. Siegel, “replication of results is a basic scientific approach to ensure validity, admonition to avoid duplicative testing, depending on how the term is interpreted, could lead to inadequate testing. Regarding unethical testing, the language is unnecessary and could, depending on how it is interpreted, discourage appropriate testing requirements.”⁴⁷¹ Dr. Woodcock stated, however, that “[w]here trials aren’t needed, it is . . . of questionable ethics to repeat them. So use of human subjects for trials that are not needed or done simply to check a box on a regulatory requirement are not desirable.”⁴⁷² The final legislation does not contain the Waxman language.

c. *Deemed Comparable Provision of Waxman Bills*

Representative Anna Eshoo (D-CA) and several witnesses expressed concern about the provision in the Waxman bills seemingly modeled on the orphan drug regulations, deeming certain proposed products comparable despite differences in, for example, amino acid sequence or post-translational modifications. Representative Eshoo said, “I think it is up to the FDA to make the call on defining [what products are highly similar in structure]—we shouldn’t get into statutory language and be prescribing this.”⁴⁷³ Inger Mollerup, Ph.D., Vice President of Regulatory Affairs at Novo Nordisk A/S, added that the provision “go[es] far beyond the science.”⁴⁷⁴ Dr. Mollerup explained that Novo Nordisk had studied two fast-acting

⁴⁶⁴ Downey Testimony, at 115, 138.

⁴⁶⁵ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 110th Cong. 45 (statement of Rep. Waxman).

⁴⁶⁶ Second Woodcock Testimony, at 62.

⁴⁶⁷ *See infra* note 1232.

⁴⁶⁸ Rossignol Testimony, at 27, 29, 44.

⁴⁶⁹ *Id.* at 29.

⁴⁷⁰ Siegel Testimony, at 25; *see also* Kingham Testimony, at 129-130.

⁴⁷¹ Siegel Testimony, at 25.

⁴⁷² Second Woodcock Testimony, at 53.

⁴⁷³ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 54 (statement of Rep. Eshoo).

⁴⁷⁴ Mollerup Testimony, at 84.

insulin analogs differing each by one amino acid from human insulin, and only one of the two significantly elevated tumor potential in rats.⁴⁷⁵ Although not commenting directly on the wisdom of the provision, Dr. Woodcock noted that “a change in even a single amino acid is not a trivial change whatsoever.”⁴⁷⁶

Dr. Siegel expressed significant concerns about the provision. He stated that “there is no scientific basis for allowing abbreviated testing of a new biologic on the basis of it being only distantly related to an existing one.”⁴⁷⁷ He also took issue with the application of concepts from the orphan drug regulations — which he noted that he had helped write and implement — to biosimilars: “[FDA] established a broad regulatory definition ensuring that orphan drug exclusivity would block the marketing of similar molecules,” but this does not “provide any significant assurance of a similar safety and efficacy profile.”⁴⁷⁸ In Dr. Siegel’s view, “there is no basis for taking the definitions that FDA developed to preclude approval of products supported by complete data and using them to identify products that can be approved through an abbreviated application with partial data.”⁴⁷⁹

Representative Waxman defended the “deemed comparable” language, noting that it “is from an FDA reg[ulation] and it is . . . narrowing the universe of possible follow-through drugs, and then once you narrow it, then they have to meet the second standard in the legislation . . . no clinically significant differences in terms of safety.”⁴⁸⁰ The final legislation does not contain the language taken from the orphan drug regulations.

In addition, Dr. Siegel objected to the section 351(k)(2) pathway (the “(k)(2) pathway”) proposed in the first and second Waxman bills, stating that this pathway was “not only unnecessary (as the differences [between the products] are avoidable), and risky (the presence of such differences leaves little or no basis for abbreviated testing), it also discourages innovation by allowing follow-ons to design around patents and undermine the incentives for innovation.”⁴⁸¹ In contrast, Ajaz S. Hussain, Ph.D., Vice President and Global Head of Biopharmaceutical Development, Sandoz, praised the (k)(2) pathway “as a second generation pathway for innovators to facilitate their improvements to their own and each others already-licensed biologic products.”⁴⁸² The final legislation does not contain the (k)(2) pathway.

d. *Guidance Documents*

Many witnesses testified that development of scientific and product class-specific guidance, as had been done in Europe, would be helpful.⁴⁸³ Most, however, stated that issuance of product class-specific guidance should not be a prerequisite to licensure of biosimilars.⁴⁸⁴ For example, Mr. Downey stated that requiring guidance prior to biosimilar licensure “is not consistent with FDA policy today” for BLAs, NDAs, and ANDAs, where the sponsors “propose their own product and

⁴⁷⁵ *Id.*

⁴⁷⁶ Second Woodcock Testimony, at 48.

⁴⁷⁷ Siegel Testimony, at 21.

⁴⁷⁸ *Id.* at 22.

⁴⁷⁹ *Id.*

⁴⁸⁰ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 55 (statement of Rep. Waxman).

⁴⁸¹ Siegel Testimony, at 68.

⁴⁸² Hussain Testimony, at 74.

⁴⁸³ *See supra* notes 178-179 and accompanying text.

⁴⁸⁴ *See, e.g.*, Hussain Testimony, at 73; *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 91 (statement of Geoffrey Allan, President & CEO, Insmad Inc.).

their own guidelines, and the FDA comments.”⁴⁸⁵ In his written testimony, Mr. Downey referred to a guidance prerequisite as an “unnecessary barrier[].”⁴⁸⁶ In response to follow-up questions from Senators Kennedy, Enzi, Burr (R-NC), and Bingamen (D-NM), Mr. Rossignol noted that, in Europe, applicants are able to submit an application for a biosimilar for which a product class guideline has not yet been issued.⁴⁸⁷

Dr. Woodcock indicated a preference for a case-by-case approach. When Representative Waxman asked whether FDA typically issues guidance prior to taking action on a 505(b)(2) application, she responded “[w]e have not done that . . . [I]t is going to depend on the situation. In some cases, it might be desirable to have a public process because of so many open questions. In other cases, obviously the path will be very clear.”⁴⁸⁸ In addition, Dr. Woodcock indicated that FDA was, at the time, “preparing a guidance document on the general scientific framework for preparation of abbreviated applications for follow-on proteins under 505(b)(2)” and “expect[ed] to follow this with guidance on technical issues such as immunogenicity, dealing with immunogenicity of proteins and physical characterization methods.”⁴⁸⁹

e. *Interchangeability*

Interchangeability was one of the most contentious issues in the hearings. Witnesses gave contradictory testimony as to whether a finding of interchangeability between a biosimilar and its reference product was scientifically feasible and appropriate. Europe’s approach was an important consideration: biosimilar approvals in the EU “do[] not lead to a scientific conclusion on interchangeability.”⁴⁹⁰ Instead, Mr. Rossignol explained, Member States make substitution decisions, and European guidance notes that “biosimilars are not generics.”⁴⁹¹

On one side of the issue, Dr. Schwieterman stated “without hesitation, that adequate scientific tools currently exist to assess and deem certain products interchangeable.”⁴⁹² Other witnesses agreed that scientific methods were sufficient to permit these designations.⁴⁹³ Dr. Hussain stated that “FDA already uses comparability data for manufacturing changes and there, interchangeability is presumed,” and that interchangeability designations for biosimilars were “a natural next step.”⁴⁹⁴

⁴⁸⁵ Downey Testimony, at 134.

⁴⁸⁶ *Id.* at 118.

⁴⁸⁷ Although both biosimilar applications approved in Europe at the time — for Omnitrope and Valtropin — had been submitted prior to issuance of a guideline, a final guideline had been adopted before their approval. According to Mr. Rossignol’s testimony, work on the somatropin product class-specific guideline began in early 2005, whereas the applications for Omnitrope and Valtropin had been submitted in July and June 2004, respectively. Rossignol Testimony, at 70. The final guideline was released on February 22, 2006 and became effective on June 1 of that year. CHMP, Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Somatropin (EMEA/CHMP/BMWP/94528/2005), adopted Feb. 22, 2006. The Omnitrope and Valtropin applications were approved in April 2006, Rossignol Testimony, at 70; *see also supra* notes 184-185. Thus, these products were approved after adoption of the final guidance but before it went into effect. It is generally understood that the CHMP has prioritized for guidance product classes as to which applicants have expressed an interest or asked questions.

⁴⁸⁸ First Woodcock Testimony, at 45.

⁴⁸⁹ *Id.* at 20.

⁴⁹⁰ Rossignol Testimony, at 27.

⁴⁹¹ *Id.*

⁴⁹² First Schwieterman Testimony, at 81.

⁴⁹³ *See, e.g.*, Hussain Testimony, at 32.

⁴⁹⁴ *Id.* at 33.

Although recognizing that the EMA and CHMP do not make interchangeability decisions, Dr. Hussain said that “the history of generic drugs in the United States makes it much more fitting that FDA recommend the designation.”⁴⁹⁵ Dr. Hussain stated that interchangeability could be shown in either an initial biosimilar application or a later supplement after the biosimilar had been marketed.⁴⁹⁶ He also suggested that “switching clinical studies” or postmarketing data from the already-marketed biosimilar could be used to support interchangeability.⁴⁹⁷ Ganesh Venkataraman, Ph.D. Senior Vice President, Research, Momenta Pharmaceuticals, agreed that interchangeability designations were possible and stated that they “can be done through total characterization and/or through a proper combination of characterization and clinical trials.”⁴⁹⁸

On the other side of the issue, Dr. Siegel testified that interchangeability designations should not be permitted. He stated that, “in the foreseeable future, there is no realistic potential for scientifically valid determination of interchangeability” because biosimilars “can be shown to be similar but never identical to” the reference product.⁴⁹⁹ Dr. Siegel expressed concern that interchangeability designations “could lead to inappropriate assumptions of sameness and substitution . . . [that could] have potentially serious health consequences.”⁵⁰⁰ Dr. Mollerup agreed, emphasizing the lack of sameness and “the potential difference in immunogenicity and other drug-specific adverse events” between biosimilars and reference products.⁵⁰¹

Dr. Woodcock expressed concerns about interchangeability and switching, particularly with respect to products with different immunogenicity.⁵⁰² Nevertheless, she agreed with Representative Waxman that it might be possible to demonstrate that a biosimilar version of a well-understood protein was interchangeable with the reference protein if there were no limits on the studies that could be required.⁵⁰³ To establish substitutability, she explained, the biosimilar applicant would need to “demonstrate through additional clinical data that repeated switches from the follow-on product to the referenced product (and vice-versa) would have no negative effect on the safety and/or effectiveness of the products as a result of immunogenicity.”⁵⁰⁴ She noted, however, that these studies could present “ethical issues” requiring careful assessment.⁵⁰⁵ Moreover, according to Dr. Woodcock, the agency’s ability to make these interchangeability designations might be “limited” because of the “significant potential” for switches to have a negative effect on safety and effectiveness.⁵⁰⁶ Under the final legislation, to demonstrate interchangeability of a product administered more than once to an individual, the applicant must show that the risk in terms of safety or diminished efficacy of alternating or switching between the products is no greater than the risk of using the reference product without alternating or switching.⁵⁰⁷

⁴⁹⁵ *Id.* at 36.

⁴⁹⁶ *See id.* at 45.

⁴⁹⁷ *Id.*

⁴⁹⁸ Venkataraman Testimony, at 103.

⁴⁹⁹ Siegel Testimony, at 15.

⁵⁰⁰ *Id.*

⁵⁰¹ Mollerup Testimony, at 85.

⁵⁰² First Woodcock Testimony, at 54.

⁵⁰³ *Id.*

⁵⁰⁴ *Id.* at 33.

⁵⁰⁵ *Id.* at 55.

⁵⁰⁶ *Id.* at 33-34.

⁵⁰⁷ PHSA § 351(k)(4).

f. *Intellectual Property Provisions*

Although data exclusivity and patent issues were not the central focus of these three hearings, several witnesses spoke to them. Some witnesses took the position that the European model was less informative on intellectual property issues than it was on scientific and regulatory issues. Two witnesses expressed approval of aspects of the European data exclusivity provisions. For example, Henry Grabowski, Ph.D., Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics at Duke University, stated that the United States should offer at least ten years of data exclusivity because “[b]reak-even returns on R&D for the average . . . biological product now exceed more than a decade.”⁵⁰⁸ Dr. Hussain indicated that “Novartis support[ed] a non-patent research incentive such as may be achieved through modeling on EU data exclusivity provisions,”⁵⁰⁹ but did not clarify whether he was referring to the structure or the term of these provisions. Mr. Rossignol noted that while “science should be the same everywhere . . . protection of innovation . . . is something, in our opinion, that has to be seen in the context, in a specific national context.”⁵¹⁰

David Schenkein, M.D. Vice President of Clinical Hematology and Oncology at Genentech, Inc. — testifying on behalf of BIO — and Richard F. Kingham, Partner at Covington & Burling, agreed that the legislation should provide a fourteen-year data exclusivity period.⁵¹¹ “[S]ociety has a profound interest,” Mr. Kingham explained, in ensuring adequate incentives for investment in biotechnology.⁵¹² He stressed that patents reward innovation typically accomplished at the beginning of the pharmaceutical research and development process, whereas data exclusivity rewards the investment made in translating the invention into a marketed product.⁵¹³ This process takes about fifteen years, costs about \$1.2 billion, and is subject to substantial risks that the costs will never be recovered. Mr. Kingham expressed concern that patents would provide inadequate protection for this substantial investment due to “special issues posed by biotechnology [patents].”⁵¹⁴ He stated that there is “real potential for patents not to serve the same protective market purpose that is served by patents for small molecule drugs under Hatch-Waxman.”⁵¹⁵ According to Mr. Kingham, in the Hatch-Waxman setting, when there is a valid patent for the reference product, “it is likely that the applicant will run head on into the patent . . . and the referenced product will enjoy a period of effective market exclusivity equal to the life of that patent.”⁵¹⁶ This cannot be expected in the biosimilars context, because biosimilars will not be required to be the same as their reference products, and because biotechnology patents are “more narrowly drawn than in the past” due to recent court decisions and United States Patent and Trademark

⁵⁰⁸ *Safe and Affordable Biotech Drugs*, *supra* note 438, at 162 (statement of Henry Grabowski, Ph.D., Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics, Duke Univ.).

⁵⁰⁹ Hussain Testimony, at 36.

⁵¹⁰ Rossignol Testimony, at 39.

⁵¹¹ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 183 (statement of David Schenkein, M.D. Vice President of Clinical Hematology and Oncology at Genentech, Inc.) (Schenkein Testimony) (“As such, we believe that the same 14 years should be applicable to innovator biologics; however, the only true way to guarantee such time is through data exclusivity.”); *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 99 (2007) (statement of Richard F. Kingham, Partner, Covington & Burling) (Kingham Testimony).

⁵¹² Kingham Testimony, at 92.

⁵¹³ *Id.*

⁵¹⁴ *Id.*

⁵¹⁵ *Id.*

⁵¹⁶ *Id.*

Office (PTO) requirements.⁵¹⁷ Mr. Kingham then stated his belief that the exclusivity period should “equal the period of market exclusivity that was contemplated by Congress under the patent term restoration provisions of the Hatch-Waxman [amendments].”⁵¹⁸ Dr. Schenkein agreed with this position.⁵¹⁹ In response to these statements, Representative Waxman emphasized that “[t]he law didn’t guarantee 14 years, it said up to 14 years. That was the maximum.”⁵²⁰

In contrast, Mr. Downey opposed a fourteen-year period of exclusivity. He emphasized that biologics already benefit from patent term restoration under the Hatch-Waxman amendments even though they were not subjected to generic competition by those amendments.⁵²¹ They can also receive orphan drug exclusivity and various tax credits associated with orphan designation. Thus, according to Mr. Downey, “the law currently provides more than enough incentive to continue innovating.”⁵²² He said that brand companies “have not yet come forward with any concrete data that would suggest additional incentives are necessary.”⁵²³ Nonetheless, Mr. Downey said he could support a five-year exclusivity period.⁵²⁴

Mr. Downey also proposed a mechanism for resolution of patent infringement issues between biosimilar applicants and reference product sponsors, a topic not addressed in depth by most witnesses. According to Mr. Downey, the legislation should allow resolution of patent issues while FDA is reviewing the biosimilar application.⁵²⁵ It should not “force[]” biosimilar companies “to litigate every patent relating to the brand product in order to obtain the patent certainty needed to launch.”⁵²⁶ In other words, the legislation should contain “a mechanism for litigating only those patent disputes that the generic company believes would delay its launch,” because litigation of other patents would cause “unnecessary delay” and could be done later.⁵²⁷ It should not provide for a stay of FDA approval of the biosimilar application based on initiation of patent litigation.⁵²⁸ It should allow the biosimilar applicant to choose the forum for litigation, so that the most expedient court can be selected.⁵²⁹ And it should provide that, “if a brand company refuses to participate in the patent process, as increasingly happens with small molecule applications, the generic company must be allowed to enter the market without risking potentially massive damages.”⁵³⁰

Although Dr. Schenkein also supported a scheme in which patent litigation would occur prior to approval of the biosimilar application, he stated that biosimilar applications should not be approved until all patent disputes had been resolved. He added that the legislation “should not create special patent litigation rules that favor [biosimilar] manufacturers.”⁵³¹ In contrast to both Mr. Downey and Dr.

⁵¹⁷ *Id.*

⁵¹⁸ *Id.* at 98.

⁵¹⁹ Schenkein Testimony, at 183.

⁵²⁰ *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States*, *supra* note 439, at 133 (statement of Rep. Waxman).

⁵²¹ Downey Testimony, at 115.

⁵²² *Id.* at 119.

⁵²³ *Id.* at 120.

⁵²⁴ *Id.* at 115.

⁵²⁵ *Id.* at 119.

⁵²⁶ *Id.*

⁵²⁷ *Id.*

⁵²⁸ *Id.*

⁵²⁹ *Id.*

⁵³⁰ *Id.*

⁵³¹ Schenkein Testimony, at 91.

Schenkein, Dr. Hussain called for a “decoupling” of the patent litigation process and the biosimilar licensure process, on the ground that patent estates associated with biotechnology-derived products are “complex” and that litigation could therefore take some time to resolve.⁵³² Dr. Hussain added, however, that Novartis would support a scheme in which the biosimilar manufacturer provided the reference product sponsor with forty-five days notice prior to launch of the biosimilar, after which the reference product sponsor could bring suit (*i.e.*, prior to launch if it wished).⁵³³

3. FDA Activity in Early 2007

In early 2007, FDA personnel made seemingly inconsistent statements regarding the agency’s capability to license biosimilars. As noted, Dr. Woodcock’s testimony reflected her belief that FDA had the scientific expertise to license these drugs. In April 2007, Dr. Woodcock and other agency personnel published a journal article in *Nature Reviews Drug Discovery* reaching similar conclusions. The trade press considered the article to constitute the long-awaited white paper.⁵³⁴ Dr. Woodcock gave an interview in late April 2007 to the same effect. In contrast, Commissioner of Food and Drugs Andrew von Eschenbach indicated he viewed biosimilars legislation as premature pending resolution of scientific issues, and the Administration issued a Statement of Administrative Policy stating that it opposed inclusion of biosimilars provisions in the legislation reauthorizing PDUFA.

The journal article stated that FDA had “more than 20 years” of “experience in analysing related protein products.”⁵³⁵ According to the authors, the agency addressed scientific challenges involved in these assessments — including, in particular, the determination of the type and quantity of data needed to establish similar clinical performance — using a “scientifically based, case-by-case approach” that was “consistent with its statutory authority and in a manner analogous to the approach the FDA has taken in ensuring safety and effectiveness in other contexts.”⁵³⁶ The authors stressed their view that this approach “provides flexibility . . . should the science support a reduction” in the required data package and that it accorded with FDA’s “longstanding policy of permitting appropriate reliance on what is already known about a drug.”⁵³⁷ The authors noted that “important factors” in assessing follow-on protein products include the robustness of the manufacturing process; the degree of structural similarity between the products; the extent to which the mechanism of action of the products is understood; comparative pharmacokinetic and pharmacodynamic data; comparative immunogenicity; and the extent to which existing clinical data and experience with the innovative product can be relied on.⁵³⁸ For recombinant proteins, establishing a high degree of structural similarity to the reference product was viewed as “crucial” by the authors.⁵³⁹ The authors noted their expectation that, as characterization technology improves, showing structural similarity “will become feasible for a wide range of products” and that FDA will

⁵³² Hussain Testimony, at 36.

⁵³³ *Id.*

⁵³⁴ *FDA Releases Long-Awaited ‘White Paper’ on Follow-On Biologics*, FDA WEEK, Apr. 27, 2007.

⁵³⁵ Woodcock et al., *supra* note 226, at 438.

⁵³⁶ *Id.* at 438, 441.

⁵³⁷ *Id.* at 438.

⁵³⁸ *Id.* at 438, 441.

⁵³⁹ *Id.* at 441.

integrate this new information into its review of proteins.⁵⁴⁰ With respect to the issue of interchangeability, the paper favorably cited Dr. Woodcock's testimony before Congress noting that "the ability to make determinations of substitutability for follow-on protein products may be limited" and that switching studies would be necessary to support such a determination.⁵⁴¹

Dr. Woodcock made similar points in a subsequent interview with *The Pink Sheet*. She emphasized that Congress needed to establish a clear biosimilars pathway for legislation.⁵⁴² She also described a number of guidance documents in development at the agency, including a guidance on use of the 505(b)(2) pathway for follow-on protein products covering characterization, clinical testing, and other "scientific underpinnings."⁵⁴³ While Dr. Woodcock stated her belief that comparability analyses required for changes to innovator products are relevant to the evaluation of biosimilars, she stressed that "they're not the whole universe," because a biosimilar manufacturer "does not have all the history, all the intermediate steps" or "all the experience" of the reference product sponsor.⁵⁴⁴ She also noted that FDA was preparing an immunogenicity guidance that would outline testing methodology, and she stated that immunogenicity data requirements for biosimilars would "vary a great deal" and could amount to the same data requirements as for innovative products; in any event significant human testing would be needed.⁵⁴⁵

Dr. Woodcock's testimony and interview, and the journal article, contrasted with nearly contemporaneous statements of the Commissioner and the Executive Office of the President. In March 2007, Dr. von Eschenbach indicated that FDA was considering the scientific framework regarding biosimilars as Congress was considering the legal framework, but that he opposed biosimilars legislation as "premature" at the time.⁵⁴⁶ Even if the legislation passed, according to Dr. von Eschenbach, FDA would not be able to implement it unless scientific issues were resolved.⁵⁴⁷ Then, on May 1, the Executive Office of the President released a statement indicating the Administration's view that biosimilars legislation should not be attached to re-authorization of PDUFA because "complex issues" regarding biosimilars had not yet been the subject of "[s]ufficient discussion," and a "robust scientific, regulatory, and legal" dialogue was needed.⁵⁴⁸ As discussed below, the Administration, through the Secretary of HHS, refined its approach and in June provided more specific feedback on biosimilars that reflected aspects of both lines of thinking.

⁵⁴⁰ *Id.* at 442.

⁵⁴¹ *Id.* at 440 (citing First Woodcock Testimony, *supra* note 445).

⁵⁴² *Follow-On Pathway Necessary for Industry To Be Invested, Woodcock Says*, THE PINK SHEET, Apr. 23, 2007.

⁵⁴³ *Id.*

⁵⁴⁴ *Id.*

⁵⁴⁵ *Id.*

⁵⁴⁶ *US FDA eyes "similarity" for follow-on biologics*, SCRIP NEWS, Mar. 23, 2007, at 13; *Von E opposes generic biologics legislation*, DICKINSON'S FDA REVIEW, Mar. 2007, at 10.

⁵⁴⁷ *FDA Developing Scientific Tools to Support Follow-on Biotech Rx, Agency Chief Says*, PHARM. L. & IND. REPORT, Mar. 23, 2007. Dr. von Eschenbach did seem to agree with Dr. Woodcock that biosimilars would have to be reviewed on a case-by-case basis due to varying scientific issues and knowledge regarding them, and could require clinical trials and immunogenicity studies, depending their complexity. *US FDA eyes "similarity" for follow-on biologics*, SCRIP NEWS, Mar. 23, 2007, at 13; *Von E opposes generic biologics legislation*, DICKINSON'S FDA REVIEW, Mar. 2007, at 10.

⁵⁴⁸ Executive Office of the President, Office of Management & Budget, Statement of Administration Policy on S. 1082—Food and Drug Administration Revitalization Act (May 1, 2007), at 2.

4. *Inslee and Gregg Bills*

Subsequent to the initial House and Senate hearings and to the release of the *Nature Reviews Drug Discovery* article, legislation supported by the innovative industry was introduced in the House and Senate.⁵⁴⁹ On April 19, 2007, Representative Jay Inslee introduced the “Patient Protection and Innovative Biologic Medicines Act of 2007,” otherwise known as H.R. 1956.⁵⁵⁰ The trade press referred to the Inslee bill and the second Waxman bill as “the major anchors for the different sides of the debate in the House.”⁵⁵¹ Just over a month later, Senator Gregg introduced a somewhat similar bill, known as the “Affordable Biologics for Consumers Act,” S. 1505.⁵⁵² Although the two bills bore a “strong resemblance” to each other and both shared elements with the EU model, the trade press reported that no one from the House had been consulted about S. 1505.⁵⁵³

Like the second Waxman bill, H.R. 1038, H.R. 1956 and S. 1505 would have added subsection (k) to PHSA section 351 to create a pathway for licensure of biosimilars.⁵⁵⁴ These bills differed from the second Waxman bill, however, with respect to the clinical data, interchangeability, data exclusivity, and patent provisions. Supporters of the second Waxman bill argued that the data exclusivity provisions of these bills were too generous and that the clinical data and interchangeability provisions effectively issued scientific mandates to FDA.⁵⁵⁵ In contrast, proponents of the Inslee/Gregg approach contended that the bills would promote innovation and investment in biotechnology through their data exclusivity provisions and would better protect patient safety (in light of recent concerns about FDA’s performance on drug safety issues) by not providing FDA “carte blanche” to set clinical trial requirements.⁵⁵⁶

a. *Regulatory Pathway Provisions*

1) *Scope and Terminology*

Under both the Gregg bill and the Inslee bill, the new pathway would have been available for biosimilar versions of biotechnology-derived therapeutic proteins licensed under section 351(a) or approved based on an application submitted under FDCA section 505(b)(1).⁵⁵⁷ This approach was broader than the approach in the first two Waxman bills, because it permitted FDCA approved products to serve as reference products, and in fact, biosimilar versions of these proteins would have been subject to the new pathway rather than sections 505(j) or 505(b)(2).⁵⁵⁸ The Waxman bill permitted only products with an approved BLA to serve as reference products, and would have left open section 505(b)(2) and (theoretically) section

⁵⁴⁹ *Follow-On Biologics Face Negotiation Slalom After Scaling Mount PDUFA*, THE PINK SHEET, May 7, 2007, at 5; *GOP Senators Introduce Brand-Friendly Biogenics Bill*, FDA WEEK, June 1, 2007.

⁵⁵⁰ H.R. 1956, 110th Cong. (2007).

⁵⁵¹ *Follow-On Biologics Face Negotiation Slalom After Scaling Mount PDUFA*, THE PINK SHEET, May 7, 2007, at 6.

⁵⁵² S. 1505, 110th Cong. (2007).

⁵⁵³ *GOP Senators Introduce Brand-Friendly Biogenics Bill*, FDA WEEK, June 1, 2007.

⁵⁵⁴ H.R. 1956 § 2(a)(2) (proposed PHSA § 351(k)); S. 1505 § 2(a)(2) (proposed PHSA § 351(k)).

⁵⁵⁵ *GOP Senators Introduce Brand-Friendly Biogenics Bill*, FDA WEEK, June 1, 2007; *FDA Signals Opposition to Mandatory Trials in Biogenics Bill*, FDA WEEK, May 4, 2007, at 4.

⁵⁵⁶ *FDA Signals Opposition to Mandatory Trials in Biogenics Bill*, FDA WEEK, May 4, 2007, at 4; Letter of Jim Greenwood, President & CEO, BIO, to Rep. Inslee (Aug. 27, 2007), available at http://www.bio.org/healthcare/followonbkg/Inslee_Support_Letter_20070827.pdf.

⁵⁵⁷ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(1)(B)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(1)(B)(ii)).

⁵⁵⁸ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(D)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(E)).

505(j) for approval of biosimilar versions of FDCA proteins. The approach of the Inslee and Gregg bills was narrower than the second Waxman bill insofar as it applied only to therapeutic proteins, not other PHSAs biologics, such as vaccines and blood products. Both the Inslee bill and the Gregg bill would have required FDA to report to Congress regarding whether the abbreviated pathway should be available for biosimilar versions of other biologics.⁵⁵⁹

The Inslee/Gregg bills were similar in some respects to the EU approach. In Europe, only products approved on the basis of a full dossier may serve as reference products.⁵⁶⁰ The over-arching CHMP biosimilars guideline provides that the biosimilars pathway generally is not appropriate for blood and blood products; that gene therapy and cell therapy will be evaluated in the future; and that biosimilar vaccines must be considered on a case-by-case basis.⁵⁶¹

2) *Scheme for Establishing Data Requirements*

Under the Waxman bill, FDA would have determined the necessary data for licensure of a comparable biological product on a case-by-case basis, through private negotiations with the applicant. The processes for formulating data requirements under H.R. 1956 and S. 1505 contrasted with this approach. Under both bills, the data requirements for a given "product class" of biosimilars would have been established through a public process. In the case of H.R. 1956, this process was guidance development, and in the case of S. 1505, the process was rulemaking. Both bills described minimum data requirements for biosimilar applications.

The Inslee bill would have established a procedure for adoption of product class-specific guidance: (1) a request for issuance of guidance; (2) publication of a concept paper on the issues to be addressed in the guidance, with a four-month period for public comments; (3) publication of a proposed guidance, with a six-month public comment period; (4) input on the proposed guidance from an Advisory Committee on similar biological products; and (5) publication of a final guidance or a determination that no guidance could ensure the safety, purity, and potency of similar biological products in the product class based on the current state of science.⁵⁶² Guidance documents could be developed during the data exclusivity period for the relevant products, and the entire process generally would have been required to be complete within twenty-four months of the initial request.⁵⁶³ The Inslee approach was consistent with the practice in Europe, where the process from issuance of a concept paper to adoption of a final guideline generally takes twelve to eighteen months.⁵⁶⁴

The Gregg bill set out a procedure for promulgation of product class-specific regulations. Any person could have requested that FDA issue a product class-specific rule.⁵⁶⁵ As in the Inslee bill, the subsequent stages of the process would have included publication of a concept paper; a four-month comment period; publication of the proposed rule, with a six-month comment period; input from an advisory committee; and publication, within two years of the initial request, of either a final rule or a statement that no such rule was possible given the current state of science.⁵⁶⁶

Under both bills, a product class-specific guidance or rule, as appropriate, would have been required to specify certain minimum data and information for inclusion

⁵⁵⁹ H.R. 1956, § 4(a); S. 1505, § 4.

⁵⁶⁰ CHMP, Guideline on Similar Biological Medicinal Products (CHMP/437/04) (adopted Sept. 2005), Paragraph 2.2.

⁵⁶¹ *Id.*, Paragraphs 3.3-3.5.

⁵⁶² H.R. 1956, § 2(a)(2) (proposed PHSAs § 351(k)(4)).

⁵⁶³ *Id.* (proposed PHSAs § 351(k)(4)(C)(vii)).

⁵⁶⁴ *See supra* Section 1.C.3.

⁵⁶⁵ S. 1505, § 2(a)(2) (proposed PHSAs § 351(k)(3)(A)).

⁵⁶⁶ *Id.* (proposed PHSAs § 351(k)(3)(C)(ii)).

in a biosimilar application. Under both bills, this would have included: (1) data showing “the consistency and robustness of the manufacturing process” for the biosimilar at both the active ingredient and finished formulation levels; (2) data demonstrating the stability and integrity of the biosimilar’s active ingredient and its compatibility with the excipients used; (3) a comparative characterization of the biosimilar and reference product at the active ingredient and finished product levels, based on data from physical, chemical, and biological assays; (4) data from comparative nonclinical studies showing the products “have similar profiles in terms of pharmacokinetics, pharmacodynamics, toxicity, immunogenicity and other relevant factors”; and (5) data from comparative clinical trials showing that the products have similar safety, purity, and potency profiles, including pharmacokinetic and pharmacodynamic studies and clinical trials “of sufficient size and duration” to show similar safety, purity, and potency profiles.⁵⁶⁷

These requirements would have been generally consistent with the data requirements that have been established in Europe through guidelines.⁵⁶⁸ FDA would have been required to update each guidance or rule, using the procedures that applied to adoption of that guidance or rule, upon licensure or approval of a reference product for a new condition of use.⁵⁶⁹

The Inslee bill also would have mandated that all product class-specific guidance documents call for inclusion of a postmarketing safety monitoring plan, whereas the Gregg bill would have required information about “postmarket assessment and monitoring” of the biosimilar’s safety, purity, and potency.⁵⁷⁰ Both approaches echoed the European approach, in which a biosimilar applicant must submit a pharmacovigilance plan and the “clinical safety of [biosimilars] must be monitored closely on an ongoing basis.”⁵⁷¹

Under H.R. 1956, FDA could have approved a section 351(k) application only if: (1) the applicant showed that the similar biological product met the requirements of the applicable product class-specific guidance; (2) the manufacturing facilities for the product satisfied cGMP; and (3) the applicant consented to an inspection of that facility.⁵⁷² S. 1505 would have required the first three conditions to be met (with the first condition referring to the product class-specific rule rather than guidance) and would have required the applicant to meet two additional conditions.⁵⁷³ First, the application would have needed to show that the biosimilar had the same strength, dosage form, route of administration, and mechanism of action as the reference product.⁵⁷⁴ Second, the applicant would have needed to demonstrate that “the biosimilar [wa]s as similar to the reference product as [could have been] achieved given the state of scientific knowledge and technology capabilities at the time of the [application’s] submission.”⁵⁷⁵

Under both bills, the 351(k) application could have been approved only for conditions of use: (1) for which the reference product was approved or licensed; (2) for which the applicant demonstrated conformance to the product class-specific guidance or rule; and (3) for which the applicant submitted nonclinical and clinical

⁵⁶⁷ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(5)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(5)).

⁵⁶⁸ See *supra* notes 180-183 and accompanying text.

⁵⁶⁹ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(6)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(6)).

⁵⁷⁰ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(5)(B)(vi)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(5)(B)(vi)).

⁵⁷¹ Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMA/CHMP/42832/05) (adopted February 2006), Paragraph 4.3.

⁵⁷² H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(2)(B)).

⁵⁷³ S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(2)(B)(i), (iv)-(v)).

⁵⁷⁴ *Id.* (proposed PHSA § 351(k)(2)(B)(iii)).

⁵⁷⁵ *Id.* (proposed PHSA § 351(k)(2)(B)(ii)).

data.⁵⁷⁶ In Europe, by way of contrast, although each indication must ordinarily be separately supported, the CHMP may permit extrapolation with appropriate justification.⁵⁷⁷ S. 1505 also would have required that the applicant agree to provide FDA all written documents it prepared “characteriz[ing] the difference between the biosimilar and the reference product.”⁵⁷⁸

Both bills would have prohibited FDA from designating biosimilars as therapeutically equivalent to their reference products.⁵⁷⁹ This approach was both similar to and different from the European approach. Interchangeability designations are not explicitly prohibited in Europe. European Commission approval decisions do not, however, include a determination of interchangeability. Substitution policy is developed at the Member State level.⁵⁸⁰ Both bills would have required FDA to assess, on a biennial basis, whether interchangeability determinations were feasible for particular product classes, and to report its conclusion to Congress including (if applicable) statutory criteria that should govern these determinations.⁵⁸¹

Both H.R. 1956 and S. 1505 would have amended section 351(j) of the PHSa to require that FDA maintain the confidentiality of information submitted under PHSa section 351 “to the same extent and in the same manner as” the agency maintains the confidentiality of information submitted under FDCA section 505.⁵⁸²

b. *Data Exclusivity*

In sharp contrast to the Waxman bill, H.R. 1956 and S. 1505 would have provided data exclusivity for innovative biological products. Neither bill would have permitted submission of a section 351(k) application until FDA had published the final product class-specific guidance or rule *and* twelve years had elapsed since licensure of the reference product.⁵⁸³ As previously noted, the EU does not have a requirement that guidance be issued before applications are approved, although to date the European Commission has not approved any biosimilar application prior to adoption of the relevant product class-specific guideline.⁵⁸⁴ Under both bills,

⁵⁷⁶ H.R. 1956, § 2(a)(2) (proposed PHSa § 351(k)(2)(C)); S. 1505, § 2(a)(2) (proposed PHSa § 351(k)(2)(C)(i) & (ii)).

⁵⁷⁷ See *supra* note 182 and accompanying text.

⁵⁷⁸ S. 1505, 110th Cong. § 2(a)(2) (proposed PHSa § 351(k)(2)(C)(iii)).

⁵⁷⁹ *Id.* (proposed PHSa § 351(m)(1)(A)); H.R. 1956, 110th Cong. § 2(a)(2) (proposed PHSa § 351(k)(2)(D)).

⁵⁸⁰ See *supra* note 491 and accompanying text.

⁵⁸¹ S. 1505, § 2(a)(2) (proposed PHSa § 351(m)(1)(B) & (2)); H.R. 1956, § 4(b).

⁵⁸² S. 1505, § 2(b); H.R. 1956, § 2(b).

⁵⁸³ H.R. 1956, § 2(a)(2) (proposed PHSa § 351(k)(3)(A)); S. 1505, § 2(a)(2) (proposed PHSa § 351(k)(7)(A)).

⁵⁸⁴ See *supra* note 487 and accompanying text (explaining the sequence of events for Omnitrope and Valtropin). The guideline applicable to filgrastim products was adopted in February 2006, and the filgrastim approvals did not occur until 2008. See *supra* notes 193-197; Annex Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues—Guidance on Similar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor (EMEA/CHMP/31329/2005) (adopted February 2006). The first guideline applicable to recombinant erythropoietins was adopted in March 2006, before approval of the first biosimilar in this class in August 2007. See *supra* notes 187-191; Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues; Guidance on Similar Medicinal Products containing Recombinant Erythropoietins (EMEA/CHMP/BMWP/94526/2005 Corr.) (adopted March 2006). The guideline applicable to recombinant erythropoietins was revised, beginning with release of a concept paper in July 2008 and adoption of a final guideline in March 2010. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision) (EMEA/CHMP/BMWP/301636/2008 Corr. *) (adopted March 2010).

approval of the section 351(k) application could not be made effective until fourteen years after approval or licensure of the reference product.⁵⁸⁵ This “12+2” data exclusivity structure was similar to the “8+2” structure in Europe discussed earlier.

H.R. 1956 contained no transition provisions for older biological products. In contrast, S. 1505 included a special provision for reference products approved or licensed more than fourteen years prior to enactment; section 351(k) applications referencing these products could be made effective on the later of: (1) the date on which the relevant product class-specific rule was published; or (2) one year after enactment of the bill.⁵⁸⁶

Both bills provided for extension of the fourteen-year exclusivity period if FDA approved a supplement for a new indication for the reference product during the first twelve years after licensure and if the new indication provided a “significant clinical benefit.”⁵⁸⁷ Under H.R. 1956, FDA would have had to determine whether the significant clinical benefit had been shown “in comparison with existing therapies.”⁵⁸⁸ This language tracks the supplemental exclusivity language used in Europe.⁵⁸⁹ S. 1505 did not contain the “in comparison with existing therapies” language and thus presumably would have granted FDA full discretion to determine when a new indication met the significant clinical benefit standard.⁵⁹⁰ The additional period of exclusivity for a new indication with significant clinical benefit would have been one year under H.R. 1956 and two years under S. 1505.⁵⁹¹ In Europe, the period is one year.⁵⁹²

A special provision governed supplemental exclusivity for reference products licensed prior to enactment under S. 1505. If, before publication of the rule for that class of products, the reference product sponsor obtained approval of a supplement for a new indication with a significant clinical benefit, a biosimilar could not be licensed until sixteen years elapsed from initial approval or licensure of the reference product.⁵⁹³ S. 1505 contained an additional supplemental exclusivity provision absent from H.R. 1956, modeled on three-year exclusivity under the Hatch-Waxman amendments.⁵⁹⁴ Under this provision, the reference product sponsor could have obtained an additional three years of exclusivity for a new use not meeting the significant clinical benefit standard, but the protection would have attached only to the data supporting the new use.⁵⁹⁵ To obtain this exclusivity, the innovator would have had to submit a supplement with new clinical data (other than bioavailability data) essential to the approval of the application.⁵⁹⁶ This exclusivity could have been obtained at any time after approval of the reference product application.⁵⁹⁷

The Gregg bill would have provided one year of exclusivity for the first biosimilar version of a particular reference product, during which no other biosimilar versions could have been licensed.⁵⁹⁸ The Inslee bill would have provided no such exclusivity.

⁵⁸⁵ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(B)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(B)).

⁵⁸⁶ S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(F)).

⁵⁸⁷ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(C)); S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(C)).

⁵⁸⁸ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(C)(ii)).

⁵⁸⁹ See *supra* note 169 and accompanying text.

⁵⁹⁰ See S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(C)(ii)).

⁵⁹¹ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(l)(1)); S. 1505, § 2(a)(2) (same).

⁵⁹² See *supra* note 169 and accompanying text.

⁵⁹³ S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(G)).

⁵⁹⁴ See *supra* note 90 and accompanying text.

⁵⁹⁵ S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(D)).

⁵⁹⁶ *Id.*

⁵⁹⁷ *Id.*

⁵⁹⁸ *Id.* (proposed PHSA § 351(k)(9)).

c. *Naming, Labeling, and Dispensing*

The Inslee and Gregg bills contained nearly identical provisions requiring unique nonproprietary names for biotechnology-derived therapeutic proteins made by different manufacturers. These provisions would have required a protein to be labeled with its "proper name,"⁵⁹⁹ which would have been defined to mean either: (1) the name adopted for it by the United States Adopted Names Council (its USAN); or (2) in the event that the USAN was not "unique," an official name designated by FDA.⁶⁰⁰ To be "unique," the USAN could not have been adopted for any protein manufactured by a different entity.⁶⁰¹ A recombinant therapeutic protein licensed after enactment would have been considered misbranded if not labeled with its unique proper name and a warning that it could not be dispensed in substitution for another protein unless the prescriber expressly authorized and supervised this substitution.⁶⁰² For biosimilars, this warning would have needed to explicitly identify the reference product, by proprietary and proper name, as a product for which the product could not be substituted without prescriber authorization and supervision.⁶⁰³

The bills also would have provided transition rules for proteins licensed prior to enactment. The proper names of these proteins would have been their USANs, even if not unique.⁶⁰⁴ Such a product would have been required to be labeled with a brand name or "phrasing . . . approved by [FDA] that adequately distinguish[ed] it from other approved . . . proteins with the same proper name."⁶⁰⁵ Within 180 days of enactment, the labeling of these proteins would have been required to bear a warning indicating that "[a]ny change in [insert the proper name of the product], including a change in manufacturer, should be made cautiously and only if authorized by and supervised by the prescribing health care professional."⁶⁰⁶ Both the Inslee and Gregg bills would have mandated that recombinant therapeutic proteins licensed under the PHSA be dispensed only upon a prescription specifying the product's proprietary name or (if it had no proprietary name) its proper name. The dispensing of a protein other than the one specified in the prescription would have constituted an act that resulted in the drug being misbranded while held for sale.⁶⁰⁷

These requirements have parallels in the European approach. The CHMP's overarching biosimilars guideline provides that, "in order to support pharmacovigilance monitoring, the specific medicinal product given to the patient should be clearly identified."⁶⁰⁸ In addition, Article 82 of Directive 2001/83/EC requires Member States to "take all appropriate measures" to ensure that pharmaceutical manufacturers "are able to provide information that makes it possible to trace the distribution path of every medicinal

⁵⁹⁹ H.R. 1956, 110th Cong. § 3(a) (proposed FDCA § 502(y)); S. 1505, § 3(a)(1) (same).

⁶⁰⁰ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(l)(1)(A)); S. 1505, § 2(a)(2) (same).

⁶⁰¹ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(l)(1)(B)); S. 1505, § 2(a)(2) (same).

⁶⁰² H.R. 1956, § 2(a)(2) (proposed FDCA § 502(z)); S. 1505, § 2(a)(2) (same).

⁶⁰³ H.R. 1956, § 2(a)(2) (proposed FDCA § 502(z)); S. 1505, § 2(a)(2) (same).

⁶⁰⁴ H.R. 1956, § 2(a)(2) (proposed PHSA § 351(l)(1)(D)); S. 1505, § 2(a)(2) (same). Under both bills, the proper name of a biological product that was not a recombinant therapeutic protein would have been the official name designated by FDA under FDCA section 508, unless there was none; in that case, it would have been the official title from a compendium or, if it was not listed in a compendium, the common or usual name. H.R. 1956, § 2(a)(2) (proposed PHSA § 351(l)(2)); S. 1505, § 2(a)(2) (same).

⁶⁰⁵ H.R. 1956, § 3(a) (proposed FDCA § 502(y)(ii)); S. 1505, § 3(a)(1) (same).

⁶⁰⁶ H.R. 1956, § 3(a) (proposed FDCA § 502(y)(iii)); S. 1505, § 3(a)(1) (same).

⁶⁰⁷ H.R. 1956, § 3(b) (proposed FDCA § 503(b)(6)); S. 1505, § 3(b) (same).

⁶⁰⁸ Guideline on Similar Biological Medicinal Products (CHMP/437/04), adopted September 2005, Paragraph 2.1.

product.”⁶⁰⁹ In addition, every biosimilar approved in the EU to date “bears a trademark or a name that incorporates a reference to the company responsible for the product.”⁶¹⁰

The Gregg bill would have added that a biosimilar would have been misbranded if its labeling: (1) was “inconsistent with” the reference product’s labeling; (2) did not “accurately characterize” the biosimilar product or “account for” differences between the biosimilar and reference product; (3) did not describe new data submitted in support of the biosimilar; (4) did not “disclose any special safety concerns” associated with the biosimilar; or (5) omitted safety information noted in the reference product labeling, unless the sponsor justified the omission to FDA.⁶¹¹

d. *Patent Provisions*

In contrast to both the Hatch-Waxman scheme and H.R. 1038, the Inslee bill contained no patent provisions. In this regard, the Inslee bill was similar to the European approach, where patent infringement issues must be litigated after generic and biosimilar market entry. Under the scheme in the Gregg bill, FDA would have been required to publish a notice in the *Federal Register* upon the filing of a biosimilar application, identifying the sponsor of the reference product and a contact person for the biosimilar applicant to whom communications about patents could be sent.⁶¹² A patent owner would have had the option to request information from the applicant to determine whether its patents might be infringed and to provide the applicant with a notice of patents that might be “infringed by the production or sale of the biosimilar,” including “patents on compound (protein sequence), composition, host cell, nucleic acid, process of production, and method of treatment patents.”⁶¹³ If the applicant sought approval prior to expiry of any identified patent, it would have had to provide a “written explanation” of its belief that the patent was invalid or would not be infringed by approval of the biosimilar application.⁶¹⁴ The act of providing the written explanation would have constituted an act of patent infringement, giving rise to federal court jurisdiction for litigation of the validity and infringement questions.⁶¹⁵

Under the Gregg bill, FDA could have approved the biosimilar application once the data exclusivity period expired, regardless of whether patent litigation had concluded.⁶¹⁶ Nevertheless, if a patent was found valid and infringed prior to biosimilar licensure (presumably by any court, though this was not specifically stated), FDA could not have approved the application until expiry of the patent.⁶¹⁷ The bill also provided that the biosimilar applicant could not initiate a declaratory judgment regarding a patent identified by the patent owner in its initial notice after: (1) the

⁶⁰⁹ European Parliament and Council Directive 2001/83/EC, of November 6, 2001 on the Community code relating to medicinal products for human use, 2001 O.J. (L 331) 67.

⁶¹⁰ R.F. Kingham and E. Lietzan, *Current Regulatory and Legal Considerations for Follow-On Biologics*, 84 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 633 (2008); see also *supra* notes 184-185, 187-191, 193-197.

⁶¹¹ S. 1505, § 3(a)(1) (proposed FDCA § 502(aa)).

⁶¹² *Id.* § 2(a)(2) (proposed PHSA § 351(k)(8)(A)).

⁶¹³ *Id.* (proposed PHSA § 351(k)(8)(B)(i)(I) & (II)). The patent owner could also indicate patents available for licensure; any such patent could not be the subject of a declaratory judgment action brought by the applicant prior to approval of the 351(k) application. *Id.* (proposed PHSA § 351(k)(8)(B)(i)(III) & (ii)).

⁶¹⁴ *Id.* (proposed PHSA § 351(k)(8)(C)(i)). The drafters probably meant “marketing of the biosimilar” and not “approval of the application for the biosimilar.”

⁶¹⁵ *Id.* § 2(c)(1) (proposed 35 U.S.C. § 271(e)(2)).

⁶¹⁶ *Id.* (proposed PHSA § 351(k)(8)(D)).

⁶¹⁷ *Id.*

date eighteen months prior to expiration of the data exclusivity period; or (2) the date sixty days after provision of the written explanation, if that occurred during the last eighteen months before data exclusivity expired.⁶¹⁸

5. *HELP Committee Negotiation and S. 1695*

Throughout April, May, and June of 2007, HELP Committee members Senators Kennedy, Clinton, Hatch, and Enzi, known as the “Gang of Four,” worked to develop a biosimilars bill.⁶¹⁹ Five key discussion drafts proposed legislative language.⁶²⁰ In chronological order and designated by their numbering in the file path stamp, these discussion drafts were: the 7574 Discussion Draft; the 7641 Discussion Draft; the 7645 Discussion Draft; the 7655 Discussion Draft; and the 7669 Discussion Draft.⁶²¹ These four Senators reached agreement on a bill on June 22, 2007,⁶²² and Senator Kennedy introduced the bill (S. 1695) on June 26, with Senators Clinton, Hatch, and Enzi as co-sponsors.⁶²³ The BPCIA largely tracks the language of this bill. The HELP committee passed the bill,⁶²⁴ but did not formally report it during 2007 due to a failure to agree on technical amendments.⁶²⁵ This section describes the key provisions of S. 1695 in detail, noting how they differed from the proposals set forth in the discussion drafts. It then describes the proposed amendments to the bill considered by the HELP Committee.

a. *S. 1695*

The bill would have created a pathway for licensure of “biosimilar biological products” in PHSA section 351(k).⁶²⁶ The terms “comparable,” “similar,” and “follow-on biologics” were considered in various discussion drafts,⁶²⁷ but the sponsors of the bill ultimately settled on “biosimilar,” the term used in Europe and the

⁶¹⁸ *Id.* (proposed PHSA § 351(k)(8)(E)).

⁶¹⁹ See, e.g. *Generic Biologics May See Life After PDUFA; Senate Mark-Up Possible in May*, THE PINK SHEET, Apr. 23, 2007.

⁶²⁰ The authors are aware of other discussion drafts with stamped file paths that were circulated throughout the legislative process. This article focuses on those drafts that are most relevant to the BPCIA as enacted.

⁶²¹ Staff Discussion Draft stamped O:\BAI\BASI07574 (Apr. 13, 2007), available at http://www.thepinksheet.com/nr/FDC/SupportingDocs/Pink/2007/Kennedy_Generic_Biologics_discussion_draft.pdf (7574 Discussion Draft); Discussion Draft stamped O:\BAI\BAI07641.xml (on file with authors) (7641 Discussion Draft); Discussion Draft stamped O:\KER\KER07645 (June 14, 2007) (on file with authors) (7645 Discussion Draft); Discussion Draft stamped O:\KER\KER07655.xml (June 16, 2007) (on file with authors) (7655 Discussion Draft); Discussion Draft stamped O:\KER\KER07669.xml (June 19, 2007) (7669 Discussion Draft). A draft stamped O:\KER\KER07692.xml is the same as the introduced version.

⁶²² Press Release, U.S. Senate Committee on Health, Education, Labor & Pensions, Senators Kennedy, Hatch, Clinton, Enzi Announce FDA Biologics Agreement (June 22, 2007).

⁶²³ S. 1695, 110th Cong. (2007). Senator Schumer was subsequently added as a co-sponsor. 153 Cong Rec S 8611, S 8612 (daily ed. June 27, 2007).

⁶²⁴ Press Release, U.S. Senate Committee on Health, Education, Labor & Pensions, Lawmakers Praise Committee Passage of Biologics Legislation (June 27, 2007).

⁶²⁵ On June 27, 2007, the Committee ordered the bill reported to the full Senate by a voice vote, but with the expectation that that staff would work on certain additional provisions in the bill. See Colby Itkowitz and Drew Armstrong, *Senate Committee Endorses Health Measures*, CONGRESSIONAL QUARTERLY, June 27, 2007; *Senate Panel Passes Biogenerics Bill; Still Working On Changes*, FDA WEEK, June 29, 2007. Chairman Kennedy, however, did not file the Committee’s report in the Senate, apparently because the Committee could not reach a conclusion on the additional changes.

⁶²⁶ S. 1695, § 2(a)(2) (proposed PHSA § 351(k)).

⁶²⁷ See, e.g. 7574 Discussion Draft § __ (a) (proposed PHSA § 351(a)(2)(C)(i)(I)(bb), using term “comparable”); 7645 Discussion Draft preamble and § 2(a)(2) (proposed PHSA § 351(i)(2)) (using “follow-on biological products,” and bracketing terms “similar” and “comparable”). The sections in the 7574 and 7641 Discussion Drafts were not numbered, but were instead shown with blanks (“Sec. ___”).

one that is used in the final legislation. No provision modeled on section 505(b)(2), as had appeared in the Waxman bills, was incorporated into S. 1695.

1) *Regulatory Pathway*

a) *Scope*

S. 1695 defined “reference product” as a single biological product licensed under section 351(a)—*i.e.*, based on a full application.⁶²⁸ In other words, the bill did not permit a biosimilar to serve as a reference product. All five discussion drafts had taken this approach,⁶²⁹ and it is the approach taken in Europe.⁶³⁰

Under S. 1695, FDA could have indicated, in a product class-specific guidance, that current science and experience did not allow approval of section 351(k) applications with respect to a particular product or product class (other than recombinant proteins). It could have modified or reversed this determination at any time.⁶³¹ “Product class” was not defined in the bill.⁶³² In Europe, as previously noted, the CHMP has concluded that biosimilar blood, blood products, and certain other biological medicines are not currently feasible, but it could theoretically change its mind at any time. European law does not prohibit such a conclusion with respect to recombinant proteins, but as also noted the European Commission has approved a number of biosimilar recombinant proteins.

The guidance provision was considered as an alternative to a five-year moratorium on licensure of biosimilar versions of antibodies, vaccines that are not recombinant proteins, live cells, viruses, and other micro-organisms.⁶³³ The moratorium approach was abandoned late in the process for the guidance provision.⁶³⁴ When the guidance provision was first circulated, it did not contain the recombinant protein exclusion; this was added in a June discussion draft.⁶³⁵

Unlike the Waxman, Inslee, and Gregg bills, S. 1695 contained transition provisions for FDCA proteins. Under these provisions — which were not to be codified — any application for a “biological product” generally would be required to be submitted under section 351 of the PHSa.⁶³⁶ S. 1695 also would have amended the statutory definition of “biological product” to include proteins, other than chemically synthesized polypeptides.⁶³⁷ Under an exception to the general requirement to use the PHSa pathway for biosimilars, a transition provision would have

⁶²⁸ S. 1695, § 2(b)(2) (proposed PHSa § 351(i)(4)). An early discussion draft would have included products approved based on a full BLA that were withdrawn from sale for reasons other than safety, purity, or potency, in the scope of “reference product.” 7574 Discussion Draft § __ (c) (proposed PHSa § 351(i)(2)(B)).

⁶²⁹ *See, e.g.*, 7574 Discussion Draft § __ (c) (proposed PHSa § 351(i)(2)).

⁶³⁰ *See supra* note 560 and accompanying text.

⁶³¹ S. 1695, § 2(a)(2) (proposed PHSa § 351(k)(8)(E)(i) & (ii)).

⁶³² The first discussion draft defined “product class” to mean “the class of biological products with the same or highly similar active ingredients.” 7574 Discussion Draft § __ (c) (proposed PHSa § 351(i)(3)).

⁶³³ *See, e.g.*, 7641 Discussion Draft § __ (c) (proposed PHSa § 351(k)(9)); *see also Generic Biologics May See Life After PDUFA; Senate Mark-Up Possible in May*, THE PINK SHEET, Apr. 23, 2007, at 6.

⁶³⁴ *Compare* 7655 Discussion Draft § 2(b)(2) (proposed PHSa § 351(k)(7)(C)) *with* 7669 Discussion Draft § 2(a)(2) (proposed PHSa § 351(k)(8)(E)).

⁶³⁵ 7645 Discussion Draft § 2(b)(2) (proposed PHSa § 351(k)(7)(C)(i)).

⁶³⁶ S. 1695, § 2(e)(1).

⁶³⁷ *Id.* § 2(b)(2) (proposed PHSa § 351(i)(1)). This approach was first suggested in the 7655 Discussion Draft, which proposed to add “recombinant protein” to the definition of biological product. The version eventually introduced was proposed in the next discussion draft. *See* 7655 Discussion Draft § 2(a)(1) (proposed PHSa § 351(i)(1)); 7669 Discussion Draft § 2(b)(1) (same).

allowed applications to be submitted under section 505 of the FDCA for a ten-year transition period, if: (1) the product belonged to “a product class” also containing a product subject to an application approved under the FDCA prior to enactment; and (2) there was not “another biological product” licensed under section 351(a) of the PHSA that could serve as the reference product.⁶³⁸ After the transition period, all biological products with approved applications under the FDCA would have been “[d]eemed approved” under section 351 of the PHSA.⁶³⁹

Several other approaches to transition of the FDCA proteins were considered. The first draft would have required use of section 351 unless the product contained an active ingredient previously approved under the FDCA. It also directed FDA to “conform the review and approval” of “biological protein product[]” applications submitted under section 505(b)(2) and section 351(k).⁶⁴⁰ This echoed section 123 of FDAMA, which had directed FDA to “take measures to minimize differences in the review and approval of products” subject to the BLA and NDA requirements.⁶⁴¹ A subsequent draft proposed a seven-year transition period during which an application for a biological product could be filed either under section 351 or section 505, apparently at the applicant’s option.⁶⁴² The next draft would have allowed applicants to choose either pathway for seven years, provided: (1) the proposed product was in a product class one product of which had already been approved under section 505, or (2) the application cited a reference product approved under section 505.⁶⁴³ In a subsequent discussion draft, the second condition was dropped, the transition period was extended to ten years, and the “deemed approved” provision was added.⁶⁴⁴ This was the approach taken in S. 1695.

b) *Application Contents*

i) *Core Data Requirements*

S. 1695 generally required a biosimilar application to contain three types of data showing the proposed product was “biosimilar”⁶⁴⁵ to the reference product: (1) data from analytical studies showing that the biosimilar was “highly similar to the reference product notwithstanding minor differences in clinically inactive components”; (2) data from animal studies; and (3) data from “a clinical study or studies.”⁶⁴⁶ The clinical data would have needed to include immunogenicity data and an assessment of either pharmacokinetics or pharmacodynamics.⁶⁴⁷ These data would have been required to be sufficient to show the biosimilar’s safety, purity, and potency “in 1 or more appropriate conditions of use” for which licensure was sought and for which the reference product was licensed.⁶⁴⁸ The clinical studies in question would also have been required to be “designed to avoid needlessly duplicative or unethi-

⁶³⁸ S. 1695, § 2(e)(2) & (3).

⁶³⁹ *Id.* § 2(e)(4).

⁶⁴⁰ 7574 Discussion Draft § __ (f).

⁶⁴¹ *See supra* note 143 and accompanying text.

⁶⁴² 7645 Discussion Draft § 2(c).

⁶⁴³ 7655 Discussion Draft § 2(c).

⁶⁴⁴ 7669 Discussion Draft § 2(c).

⁶⁴⁵ A product was “biosimilar” to a reference product if “there [were] no clinically meaningful differences” between the two “in terms of . . . safety, purity, and potency.” S. 1695, 110th Cong. § 2(b) (proposed PHSA § 351(i)(2)).

⁶⁴⁶ *Id.* § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(i)(I)).

⁶⁴⁷ *Id.* (proposed PHSA § 351(k)(2)(A)(i)(I)(cc)).

⁶⁴⁸ *Id.* (proposed PHSA § 351(k)(2)(A)(i)(I)(cc)(AA)).

cal clinical testing.”⁶⁴⁹ Similar language had first appeared in the initial Waxman bill. Moreover, FDA would have been given discretion to waive any of these three data requirements upon a finding that the data in question were “unnecessary.”⁶⁵⁰

S. 1695’s sparse legislative language on application requirements paralleled the approach in Europe.⁶⁵¹ The general requirements to provide analytical, animal, and clinical data also paralleled the approach laid out in CHMP guidance.⁶⁵² Although the S. 1695 data requirements are less specific than CHMP guidance,⁶⁵³ FDA would have had the discretion to ask for the analytical, animal, and clinical it deemed appropriate to show biosimilarity. Allowing waiver of individual data requirements on a case-by-case basis also accords with the formal legal approach in Europe.⁶⁵⁴ In guidance and in practice, however, the CHMP has called for fairly substantial data packages, and FDA would have had the authority to do the same under this language.

The S. 1695 approach to clinical data differed from that in previous discussion drafts in several regards. First, the first discussion draft called for a “clinical trial or trials” rather than a “clinical study or studies.”⁶⁵⁵ *FDA Week* suggested that the change “appear[ed] to lower the bar for determining comparability.”⁶⁵⁶ Second, early discussion drafts would not have permitted FDA to waive clinical data requirements except for the requirement to test immunogenicity, and then only upon a showing that clinically relevant immunogenicity could be excluded through other means.⁶⁵⁷ Third, several early discussion drafts would have allowed FDA to require that the application contain “additional elements”; this approach was not reflected in S. 1695.⁶⁵⁸ Fourth, the first discussion draft did not contain language directing FDA to avoid requiring duplicative and unethical testing.⁶⁵⁹ This language was added in the second draft and retained in subsequent drafts and the introduced version of the bill,⁶⁶⁰ but as noted below, it was dropped from S. 1695 when the bill was reported. Fifth, the second discussion draft included language stating that, upon approval of a biosimilar application, FDA could, “as appropriate” license the biosimilar for “one or more conditions of use for which the reference product is labeled and for which the applicant has demonstrated that [the biosimilar] utilizes the same mechanism or mechanisms of action as the reference product.”⁶⁶¹ In contrast, as noted above, the introduced bill generally would have required submission of clini-

⁶⁴⁹ *Id.* (proposed PHSA § 351(k)(2)(A)(i)(I)(cc)(BB)).

⁶⁵⁰ *Id.* (proposed PHSA § 351(k)(2)(A)(ii)).

⁶⁵¹ See Rossignol Testimony, at 44.

⁶⁵² See *supra* notes 180-183 and accompanying text.

⁶⁵³ See *supra* notes 180-183 and accompanying text.

⁶⁵⁴ See Rossignol Testimony, at 29.

⁶⁵⁵ See 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(3)(C)); *Generic Biologics May See Life After PDUFA: Senate Mark-Up Possible in May*, THE PINK SHEET, Apr. 23, 2007, at 6.

⁶⁵⁶ *Kennedy’s Latest Biogenerics Draft More Friendly to Generics*, FDA WEEK, May 4, 2007.

⁶⁵⁷ 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(3)(C)); 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(3)(C)). The 7645 Discussion Draft, which added the waiver language, also proposed language directing FDA to take into account the degree of similarity shown in analytical studies when determining the extent to which animal and clinical studies were necessary. 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(k)(2)(B)(ii)). This language did not appear in the introduced bill.

⁶⁵⁸ 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(3)(C)(iii)); 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(3)(C)(iii)).

⁶⁵⁹ 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(3)(C)(iii)).

⁶⁶⁰ See, e.g., 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(4)).

⁶⁶¹ 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(8)).

cal data sufficient to show safety, purity, and potency “in 1 or more appropriate conditions of use” of the reference product.⁶⁶²

Early discussion drafts called for the active ingredient of the biosimilar to be highly similar to that of the reference product,⁶⁶³ whereas the introduced version of the bill called for the proposed product — rather than its active ingredient — to be highly similar. While all of the drafts provided that comparability, similarity, or biosimilarity would require an absence of clinically meaningful differences between the products, a late discussion draft added the qualifier “notwithstanding minor differences in clinically inactive components”—language that is present in the final legislation.⁶⁶⁴

ii. *Other Aspects of the Pathway*

S. 1695 also would have required that a biosimilar applicant make several other showings generally not required by earlier discussion drafts. These would have included that the products had the same route of administration, dosage form, strength, and (if known) mechanism(s) of action; that the reference product was previously licensed for the conditions of use for which the biosimilar applicant sought licensure; and that the facilities for manufacture, processing, packing, and holding of the biosimilar satisfied cGMP.⁶⁶⁵ Under S. 1695 and most discussion drafts, FDA would have been required to license a proposed product if the applicant submitted sufficient information to show it was “biosimilar” (or “comparable,” depending on the draft) to, or “interchangeable with,” the reference product.⁶⁶⁶

The bill provided that FDA’s authority regarding risk evaluation and mitigation strategies (REMS) would have applied to biosimilars “in the same manner” as it applied to innovative products licensed under section 351(a) of the PHSA.⁶⁶⁷ This approach was developed relatively early in the drafting process. The first two discussion drafts would have mandated that all biological product applications (including biosimilar applications) propose a REMS with a strategy for assessing immunogenicity,⁶⁶⁸ but the third draft substituted text that was essentially the same as the introduced language.⁶⁶⁹ In Europe, guidance calls for submission of a risk management plan in biosimilar applications, as well as certain other applications (including those for new active substances).⁶⁷⁰

The introduced bill provided that the application could include, at the applicant’s option, publicly available information regarding FDA’s previous finding that the reference product was safe, pure, and potent, as well as additional information “including publicly-available information” regarding the reference product or

⁶⁶² Steve Usdin, *Politics & Policy: The Senate’s biosimilar deal*, *BIOCENTURY*, June 25, 2007 at A12 (finding the language of S. 1695 “suggests” that biosimilars “could” be approved for all indications, even those the manufacturer did not study).

⁶⁶³ 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(2)(A)); 7641 Discussion Draft § __ (d) (same); 7645 Discussion Draft § 2(a)(2) (proposed PHSA § 351(i)(2)(A)); 7655 Discussion Draft § 2(a)(3) (proposed PHSA § 351(i)(2)(A)) (language is bracketed).

⁶⁶⁴ 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(i)(I)(aa)).

⁶⁶⁵ S. 1695, 110th Cong. § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(i)(I)(cc)).

⁶⁶⁶ *Id.* (proposed PHSA § 351(k)(3)); 7669 Discussion Draft § 2(a)(2) (same); 7655 Discussion Draft § 2(b)(2) (same); 7645 Discussion Draft § 2(b)(2) (same).

⁶⁶⁷ S. 1695, § 2(a)(2) (proposed PHSA § 351(k)(5)(C)).

⁶⁶⁸ 7574 Discussion Draft § __ (b) (proposed PHSA § 351(a)(2)(D)); 7641 Discussion Draft § __ (b) (proposed PHSA § 351(a)(2)(E)).

⁶⁶⁹ 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(k)(5)(C)).

⁶⁷⁰ Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005), adopted Nov. 2005, Paragraph 4.3.

another biologic.⁶⁷¹ This language was not proposed until the 7669 Discussion Draft, just before agreement was reached.⁶⁷² One trade press report commented that this language permitted “references to FDA’s determination that a reference product is safe and effective, as well as the submission of” medical literature on the reference product.⁶⁷³

Under S. 1695, FDA could have issued general or specific guidance on the submission and licensure processes for 351(k) applications.⁶⁷⁴ Subject to one condition, these guidances would have needed to be issued in accordance with section 701(h) of the FDCA, which specifies procedures and principles that FDA must follow in issuing guidance documents. S. 1695 added that FDA would be required to solicit public comment on draft guidances, even though this is not always required under section 701(h).⁶⁷⁵ Unlike the Inslee bill, S. 1695 did not prohibit approval of 351(k) applications without class-specific guidance in place; instead, it stated the opposite, that the existence or non-existence of guidance would have no impact on FDA’s ability to review and approve applications.⁶⁷⁶ Under S. 1695, FDA could indicate in guidance that biosimilars in certain product classes could not be licensed given the current state of science. The lack of such a statement in guidance would not require the agency to approve any particular biosimilar application.⁶⁷⁷ If FDA decided to issue a product class-specific guidance, it would have been required to describe the criteria for showing that products in the class were highly similar to their reference products, and if available, for showing interchangeability.⁶⁷⁸ The key aspect of the guidance paragraph — that FDA would not be required to issue final product class-specific guidance before approving applications in that class — was developed at the beginning of the drafting process, remained in every discussion draft,⁶⁷⁹ and appears in the final legislation.

c) *Interchangeability*

The interchangeability criteria included in S. 1695 departed from every prior approach considered during the discussion process. The introduced bill provided that a single-use product would meet the standard for interchangeability if it could “be expected to produce the same clinical result as the reference product in any given patient.”⁶⁸⁰ For products intended to be used more than once, the applicant would have been required also to demonstrate that the risk to patients in terms

⁶⁷¹ S. 1695, § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(iii)).

⁶⁷² 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(iii)).

⁶⁷³ Steve Usdin, *Politics & Policy: The Senate’s biosimilar deal*, BIOCENTURY, June 25, 2007 at A12.

⁶⁷⁴ S. 1695, § 2(a)(2) (proposed PHSA § 351(k)(8)(A)).

⁶⁷⁵ S. 1695, § 2(a)(2) (proposed PHSA § 351(k)(8)(A) & (B)(i)). Under section 701(h), FDA must obtain public comment before implementing a guidance in several situations, unless the agency finds that this “is not feasible or appropriate,” in which case comment may be obtained upon implementation. FDCA § 701(h)(1)(C). These situations include where the guidance involves initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues. *Id.* Other guidance documents do not require public comment prior to implementation. FDCA § 701(h)(1)(D)). Section 701(h) also provides that guidance documents may not “create or confer any rights for or on any person” but FDA employees may not deviate from them “without appropriate justification and supervisory concurrence.” FDCA § 701(h)(1)(A) & (B).

⁶⁷⁶ *Id.* (proposed PHSA § 351(k)(8)(C)).

⁶⁷⁷ *Id.* (proposed PHSA § 351(k)(8)(E)(iii)).

⁶⁷⁸ *Id.* (proposed PHSA § 351(k)(8)(D)).

⁶⁷⁹ *See, e.g.*, 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(4)(C)).

⁶⁸⁰ S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(4)(A)(ii)). Information showing interchangeability could have been submitted in an original application or a supplement. *Id.* (proposed PHSA § 351(k)(2)(B)).

of safety or diminished efficacy from switching between the two products was no greater than the risk from exclusive use of the reference product.⁶⁸¹ Providing for determinations of interchangeability as part of the approval process for biosimilar applications contrasted with the EU approach, where interchangeability decisions are made at the Member State level.⁶⁸²

An early discussion draft would have required that the applicant show: (1) “equivalence of the identity, strength, quality, purity, and potency” of the products “as they relate to” the proposed product’s safety and effectiveness for the labeled conditions of use; and (2) that no adverse events, including immunogenic events, were expected when patients were switched between the products.⁶⁸³ This early draft would not have permitted interchangeability designations until either FDA issued a required guidance on the interchangeability standard or two years elapsed.⁶⁸⁴ The next draft modified the second condition above to provide that the applicant would need to show that substituting the proposed product could not result in a significant increase in the rate or severity of adverse events (including with respect to immunogenicity) as compared to using the reference product.⁶⁸⁵ Some trade press characterized this change as lowering the bar for interchangeability.⁶⁸⁶ The third and fourth discussion drafts deleted all of this language and inserted text requiring FDA to establish criteria for interchangeability. Allowing FDA to establish the criteria may have represented an acknowledgment that in the generic FDCA drug setting, the agency — and not Congress — had determined the showing necessary for a conclusion of therapeutic equivalence. These discussion drafts would have permitted FDA to begin licensing products as interchangeable prior to adoption of criteria for interchangeability.⁶⁸⁷ A later discussion draft provided a different standard for interchangeability: the biosimilar had to be “the same as” and “therapeutically equivalent” to the reference product, and, for products used more than once, the risk of switching between the two products could not be greater than the risk of exclusively using the reference product.⁶⁸⁸ This approach is different from the one used by FDA in the Hatch-Waxman context, where sameness and pharmaceutical equivalence allow an inference of therapeutic equivalence.⁶⁸⁹

The introduced bill also defined the term “interchangeable” to mean that the product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”⁶⁹⁰ This language did not appear in most discussion drafts and was added toward the end of the drafting process.⁶⁹¹

⁶⁸¹ *Id.* (proposed PHSA § 351(k)(4)(B)).

⁶⁸² See *supra* note 491 and accompanying text.

⁶⁸³ 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(5)(A)).

⁶⁸⁴ *Id.* (proposed PHSA § 351(k)(5)(B)).

⁶⁸⁵ 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(7)(A)(ii)).

⁶⁸⁶ *Kennedy's Latest Biogenerics Draft More Friendly to Generics*, FDA WEEK, May 4, 2007.

⁶⁸⁷ 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(k)(3)(B) & (4)); 7655 Discussion Draft § 2(b)(2) (same).

⁶⁸⁸ 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(4)).

⁶⁸⁹ See *supra* note 380 and accompanying text.

⁶⁹⁰ S. 1695 § 2(b)(3) (proposed PHSA § 351(i)(3)).

⁶⁹¹ 7669 Discussion Draft § 2(b)(3) (proposed PHSA § 351(i)(3)). Early in the drafting process it was proposed that, for approved comparable biological products not deemed interchangeable, FDA require the labeling to include a statement that the product was not interchangeable with the reference product. See, e.g., 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(5)(C)); 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(7)(D)). This language was later deleted and did not appear in the introduced bill.

2) *Exclusivity*

S. 1695 would have provided that a biosimilar application could not be submitted until four years after the date on which the reference product was “first licensed” under section 351(a), or approved until twelve years after the date of first licensure.⁶⁹² Pediatric exclusivity would not have been available.⁶⁹³ Unlike the European model, S. 1695 would not have offered supplemental exclusivity. And biosimilar applications could have been submitted much earlier in the United States (four years after licensure of the innovative product) than they may be in Europe (eight years).⁶⁹⁴

Like the Waxman bill, S. 1695 would have provided a period of exclusivity for the first biosimilar designated as interchangeable with a particular reference product. During this period, no other biosimilar product could be deemed interchangeable with that reference product.⁶⁹⁵ This exclusivity period would have ended one year after first commercial marketing of the interchangeable biosimilar or on a date dependent on the initiation, status, and outcome of patent litigation brought under the bill’s patent provisions.⁶⁹⁶

This relatively straightforward data exclusivity provision was selected after an array of options was considered. The 7574 Discussion Draft proposed a tiered approach to exclusivity. Only reference products containing no previously approved active ingredient could qualify for either tier of exclusivity.⁶⁹⁷ Tier one products — those approved based on “a clinical trial or trials conducted or sponsored by the applicant” — would receive one (unspecified) period of exclusivity; if the reference product was not “solely” approved based on such trials, the tier two period (also of unspecified length) would have applied.⁶⁹⁸ The trade press reported that, based on a leaked version of the discussion draft, the first tier data exclusivity period was intended to be five years.⁶⁹⁹ In either case, exclusivity would block submission, not approval, of section 351(k) applications.⁷⁰⁰ An extension (of unspecified length)

⁶⁹² S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(7)(A) & (B)).

⁶⁹³ Under section 505A of the FDCA, sponsors or holders of a 505(b)(1) application may receive six months of exclusivity for performing pediatric studies in accordance with the terms of the FDCA. FDCA § 505A(b) & (c). Pediatric exclusivity can extend the applicable data exclusivity period, orphan exclusivity period, and the period during which FDA cannot approve an ANDA or 505(b)(2) application based on a paragraph III certification or loss of a patent challenge. *Id.*

⁶⁹⁴ S. 1695 therefore created an eight-year window between application submission and application approval. It also, as described below, contained provisions creating a premarket patent resolution scheme, under which submission of an application constituted an act of patent infringement commencing the patent resolution procedure. Pre-launch patent litigation is not an option in Europe.

⁶⁹⁵ S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(6)).

⁶⁹⁶ *Id.* (proposed PHSA § 351(k)(6)(A)-(C)). Other potential end dates for the exclusivity were: (1) eighteen months after a final court decision as to all patents in suit in, or dismissal of, patent litigation commenced pursuant to the bill’s litigation procedure; (2) forty-two months after approval of the first interchangeable product, if this patent litigation was ongoing; or (3) eighteen months after approval of the first interchangeable product, if no such patent litigation was initiated. This provision appears to have been modeled on the similar text in the Waxman bill. *See supra* notes 383-385 and accompanying text. Other options for biosimilar exclusivity were considered during the drafting process, including a period starting on first commercial marketing of the interchangeable biosimilar and ending ninety or 180 days later, regardless of patent litigation. *See* 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(10)); 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(k)(6)). The possibility of having the exclusivity block the BLA holder for the reference product from marketing a “rebranded” interchangeable product was also considered, *see e.g.* 7641 Discussion Draft § __ (d) (proposed PHSA § 351(k)(10)), but ultimately abandoned prior to introduction of the bill.

⁶⁹⁷ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(1)(A)).

⁶⁹⁸ *Id.* (proposed PHSA § 351(l)(1)(A)(i) & (ii)).

⁶⁹⁹ *Generic Biologics May See Life After PDUFA; Senate Mark-Up Possible in May*, THE PINK SHEET, Apr. 23, 2007, at 6.

⁷⁰⁰ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(1)(A)(i) & (ii)). The application could have been submitted one year earlier than would otherwise be permitted if the applicant was challenging a patent. *Id.* (proposed PHSA § 351(l)(1)(B)).

of the applicable base exclusivity period would have been available, if within a certain (also unspecified) period of time after its initial approval, the reference product was approved for a new condition of use based on “new clinical investigations” — conducted or sponsored by the applicant and essential to approval of the application — showing that the reference product “brings a significant clinical benefit in comparison with existing therapies.”⁷⁰¹ The extension provision used the phrase “clinical investigations,” whereas the base data exclusivity provision used the phrase “clinical trial or trials.” Certain reference products licensed before enactment would receive one of two transitional exclusivity periods of unspecified length (depending on whether the approval of the product was based solely on clinical trial(s) conducted or sponsored by the applicant). Each of these periods would be reduced by the number of days that had passed since licensure.⁷⁰²

Pediatric exclusivity would have been available to extend data exclusivity and orphan exclusivity.⁷⁰³ The 7574 Discussion Draft also provided that, where the reference product had been orphan-designated, section 351(k) would have “appli[ed] to” biosimilars only after expiration of the seven-year period of orphan exclusivity.⁷⁰⁴ The 7574 Discussion Draft included a provision allowing a sponsor to elect to obtain a period of exclusivity (also of unspecified length) in substitution for patent protection.⁷⁰⁵ The BLA holder would have been required to state in a notice to FDA that it would consider the applicant to have “a license with no royalty” allowing manufacture, sale, and use the biosimilar under all patents owned by, or licensed to, the BLA holder.⁷⁰⁶ The notice also would have been required to state that, if an action were brought against the applicant for infringement of any patent claiming the reference product (including any patent that the BLA holder neither owned nor licensed) or a request for a license were made to the applicant, the BLA holder would license the reference product to the applicant at the cost of manufacture plus five percent.⁷⁰⁷

The second discussion draft retained the approach of the first, with four significant changes. First, the provisions allowing for exclusivity as an alternative to patent protection were dropped. Second, the language in the second “tier” of exclusivity (*i.e.*, the shorter period) was modified to provide that this period of exclusivity would apply to reference products licensed based on a clinical trial or trials conducted or sponsored by a person other than the applicant (rather than

⁷⁰¹ *Id.* (proposed PHSA § 351(l)(1)(C)).

⁷⁰² *Id.* § __ (b)(1). Transitional exclusivity would have blocked approval, not submission, of a 351(k) application, unlike the basic data exclusivity provisions. *Id.* § __ (b)(1)(A).

⁷⁰³ *Id.* (proposed PHSA § 351(n)). The draft also would have applied section 505A of the FDCA, the pediatric exclusivity provision, to “patents with respect to which an action for infringement is brought under” proposed section 351(l)(5)(B) of the PHSA. *Id.* (proposed PHSA § 351(n)(1)(A)(ii)). Under section 505A, however, pediatric exclusivity does not extend a patent’s expiration date; instead it delays by six month the prohibition on FDA approval that stems from a paragraph III certification or loss of a patent challenge. *See* FDCA § 505A(b)(1)(B)(i) (“the period during which an application may not be approved . . . shall be extended by a period of six months after the date the patent expires . . .”). The 7574 Discussion Draft contained no similar provision tying a prohibition on FDA approval to patent expiry, so the patent-related pediatric exclusivity provision may have been a drafting error.

⁷⁰⁴ *Id.* § __ (d) (proposed PHSA § 351(k)(1)(B)).

⁷⁰⁵ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(m)).

⁷⁰⁶ *Id.* (proposed PHSA § 351(m)(1)). For patents that the BLA holder did not own or license but that it reasonably believed might have claimed the reference product, the notice would have had to include a detailed statement of the factual and legal bases for the BLA holder’s belief that the patent was invalid or unenforceable, or would not be infringed by commercial sale of the reference product. *Id.* (proposed PHSA § 351(m)(2)(A)(iii)).

⁷⁰⁷ *Id.* (proposed PHSA § 351(m)(2)(B)).

“not” conducted or sponsored “solely” by the applicant).⁷⁰⁸ Third, in the supplemental exclusivity provision, the “significant clinical benefit” standard was changed to one of “clinical superior[ity],” and a reference product could receive no more than three extensions.⁷⁰⁹ Finally, the orphan exclusivity provision now indicated that the 351(k) pathway would not have applied to biosimilars for which licensure was sought “for [the] rare disease or condition” during the seven-year orphan exclusivity period.⁷¹⁰ The previous draft provided that subsection (k) would apply to a biosimilar “only after the expiration for such reference product of the 7-year [orphan exclusivity] period.”⁷¹¹ In other words, the first discussion draft would have precluded licensure of the biosimilar for any indication during the orphan exclusivity term, while the second draft would have precluded biosimilar licensure only for the orphan indication.

The next two discussion drafts contained no data exclusivity provisions. The 7669 Discussion Draft would have provided a base period of unspecified length running from licensure of the reference product and would have permitting an extension of unspecified length in the event of licensure for a new indication “in a new therapeutic category” that, in the opinion of FDA, was “expected to provide significant clinical benefit” in comparison with other “commercially available” therapies.⁷¹² It would not have provided pediatric exclusivity, nor would it have addressed the relationship between data exclusivity and orphan drug exclusivity.

3) *Patent Provisions*

Unlike the Inslee bill and European law, S. 1695 contained patent litigation provisions. S. 1695’s complex patent provisions contrast with those of the Hatch-Waxman amendments in several respects. First, its process for identifying patents relevant to biosimilar market entry differed substantially from the process under the Hatch-Waxman amendments. Second, it contained procedures for parties to exchange views about patent infringement and validity, prior to patent litigation; these differed from the process in the Hatch-Waxman setting. Third, S. 1695 created a two-stage premarket patent litigation process, where the Hatch-Waxman amendments created only one. Fourth, in contrast to the Hatch-Waxman amendments, S. 1695 did not provide for a stay of FDA approval of a biosimilar application pending litigation, and it had different provisions regarding the remedies available to the innovator upon a finding that the patent was valid and infringed. Fifth, S. 1695 contained provisions that would have limited remedies for patent infringement in certain circumstances—provisions not present in the Hatch-Waxman scheme. Finally, the bill has very different declaratory judgment provisions than do the Hatch-Waxman amendments.

a) *Patent Identification Procedure*

As described above, the Hatch-Waxman amendments require innovators to list, and FDA to publish, any patent claiming the innovator’s drug or a method of using

⁷⁰⁸ 7641 Discussion Draft § __ (a) (proposed PHSA § 351(l)(1)(A)(ii)). This draft and the 7574 draft would have required FDA to post, on its website, the applicable period of data exclusivity for a reference product within 60 days of approval. *Id.* (proposed PHSA § 351(l)(1)(D)); 7574 Discussion Draft § __ (a) (same).

⁷⁰⁹ 7641 Discussion Draft § __ (a) (proposed PHSA § 351(l)(1)(C)(i)(III) & (ii)).

⁷¹⁰ *Id.* § __ (d) (proposed PHSA § 351(k)(1)(B)). In addition, the 7641 Discussion Draft contained a slightly modified version of the 7574 provision purporting to apply pediatric exclusivity to extend a patent. *Id.* (proposed PHSA § 351(m)(2)); see *supra* note 703. The modifications did not address the issues identified in note 703.

⁷¹¹ 7574 Discussion Draft § __ (d) (proposed PHSA § 351(k)(1)(B)).

⁷¹² 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(7)).

it and “with respect to which a claim of patent infringement could reasonably be asserted” if an unlicensed person marketed the drug.⁷¹³ Generic applicants must address patents meeting the listing criteria when submitting their applications.⁷¹⁴ S. 1695 did not contain a process for public identification of patents relevant to market entry. Although a listing process modeled on the Hatch-Waxman process was considered early in the drafting process, this approach was rejected in favor of a private information exchange procedure.

Under the bill, upon submission of its application, the applicant would have had to provide confidential access to the biosimilar application and information describing the manufacturing process(es) for the biosimilar.⁷¹⁵ The applicant could also have, in “its sole discretion” provided additional information it deemed appropriate, including information requested by the reference product sponsor.⁷¹⁶ This language differed from the discussion drafts in two respects: (1) the discussion drafts did not require the applicant to provide information about the manufacturing process⁷¹⁷; and (2) the first two discussion drafts would have required the applicant to provide confidential access to any amendments to the biosimilar application “relevant to the issue of patent infringement”; this approach was dropped in the middle of the drafting process.⁷¹⁸

S. 1695 provided a default procedure for confidential access, but would have allowed the parties to agree to use a different procedure.⁷¹⁹ The bill’s default confidential access provisions contrasted with those under the Hatch-Waxman amendments, where the offer of confidential access may specify the “restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information.”⁷²⁰ Although language comparable to this had been considered,⁷²¹ it was rejected late in the drafting process in favor of describing the persons entitled to confidential access and the restrictions that would govern their use of the information in question.

Specifically, one in-house lawyer of the reference product sponsor and one or more designated outside counsel that were employees of “an entity” other than the reference product sponsor — none of whom engaged in patent prosecution relating to the reference product — could have had confidential access to the application and manufacturing information.⁷²² These individuals could not have disclosed any of this confidential information to “any other person or entity” without the biosimilar

⁷¹³ FDCA § 505(b)(1)(G).

⁷¹⁴ FDCA §§ 505(b)(2)(A), 505(j)(2)(A)(vii).

⁷¹⁵ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(1) & (2)).

⁷¹⁶ *Id.* (proposed PHSA § 351(l)(1)(B)(i) & (1)(2)(B)).

⁷¹⁷ *See, e.g.*, 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(l)(2)).

⁷¹⁸ *Compare* 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(2)(B)(i)) *and* 7641 Discussion Draft § __ (a) (same) *with* 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(l)(1)(A)).

⁷¹⁹ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(1)(A)).

⁷²⁰ FDCA §§ 505(c)(3)(D)(i)(III), 505(j)(5)(C)(i)(III). The confidential access provisions of the Hatch-Waxman amendments were added in 2003 and hence were not part of the original compromise. *See* Pub. L. No. 108-173, § 1101(b)(2)(C), (D) (amending FDCA § 505(c)(3)(D)(i)(III)); *id.* § 1101(a)(2)(B), (C) (amending FDCA § 505(j)(5)(C)(i)(III)).

⁷²¹ *See, e.g.*, 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(2)(B)); 7641 Discussion Draft § __ (a) (same); 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(l)(1)(A)); 7655 Discussion Draft § 2(b)(2) (same); 7669 Discussion Draft § 2(a)(2) (same). Some of the later discussion drafts also proposed allowing the reference product sponsor to either accept the terms of the confidential access offered by the applicant or “modify” the terms “in consultation with the applicant.” *See, e.g.*, 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(l)(1)(B)(ii)).

⁷²² S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(1)(B)(ii)(I) & (II)).

applicant's prior written consent, which the applicant could not "unreasonably with[o]ld."⁷²³ Other employees of the reference product sponsor, outside scientific consultants, and other outside counsel could not have accessed the application without such consent.⁷²⁴ The bill did not require biosimilar applicants to provide confidential access to third party patent owners.

b) *Process for Exchange of Patent Information*

The drafters considered a number of schemes for communication between the parties regarding patents relevant to biosimilar market entry. These included a procedure in which the reference product sponsor and the applicant had the option to notify each other regarding patents they deemed relevant⁷²⁵ and a mandatory information exchange process.⁷²⁶ The drafters ultimately selected the latter option.

Within sixty days of receiving the biosimilar application and manufacturing information, the reference product sponsor would have been required to provide an initial list of patents to the applicant.⁷²⁷ This list would need to include all patents as to which the reference product sponsor believed it "could reasonably . . . assert[]" a claim of patent infringement if an unlicensed person commercially marketed the biosimilar.⁷²⁸ This did not include patents that could be reasonably asserted by a third party patent owner. The drafters considered requiring the reference product sponsor to instead list patents that the reference product sponsor "believe[d] in good faith" claimed the reference product or biosimilar.⁷²⁹ Other drafts described the types of patents that would need to be listed, such as product, method, component, and manufacturing method/process patents claiming either the reference product or the biosimilar.⁷³⁰

The biosimilar applicant would have been required to respond to the reference product sponsor's initial list within sixty days of receipt. The applicant would have been required to include, for each listed patent, either: (1) a detailed statement describing, on a claim-by-claim basis, the factual and legal basis for the applicant's opinion that the patent was invalid, was unenforceable, or would not be infringed by the commercial marketing of the biosimilar; or (2) a statement that it would not launch the biosimilar until after patent expiry.⁷³¹ The applicant would also have been permitted to list additional patents that it believed met the listing criterion.⁷³²

Finally, within another sixty-day period, the reference product sponsor would have been required to provide to the biosimilar applicant, as to each patent that the applicant claimed was invalid, unenforceable, or not infringed, both: (1) a de-

⁷²³ *Id.* (proposed PHSA § 351(l)(1)(C)).

⁷²⁴ *Id.*

⁷²⁵ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(3) & (4)); 7641 Discussion Draft § __ (a) (same).

⁷²⁶ *E.g.* 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(l)(3)).

⁷²⁷ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(3)(A)(i)). If a patent meeting the listing criteria issued or was licensed after provision of the initial patent list, the reference product sponsor would have had to supplement its list to include this patent within thirty days of its issuance or licensure. *Id.* (proposed PHSA § 351(l)(7)).

⁷²⁸ *Id.*

⁷²⁹ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(3)(A)); 7641 Discussion Draft § __ (a) (same).

⁷³⁰ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(3)(A)); 7641 Discussion Draft § __ (a) (same).

⁷³¹ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(3)(B)(ii)). If the reference product sponsor had supplemented its initial list to include a later issued or licensed patent, the biosimilar applicant would have been required to supplement this response. *Id.* (proposed PHSA § 351(l)(7)).

⁷³² S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(3)(B)(i)).

tailed statement describing, on a claim-by-claim basis, the factual and legal basis for its opinion that the patent would be infringed by commercial marketing of the biosimilar; and (2) a response to the applicant's statements concerning validity and enforceability of the patent.⁷³³ In contrast, the Hatch-Waxman amendments do not require an innovator to respond to a generic applicant's paragraph IV certification or explain its view that the patent is valid and infringed. The first two discussion drafts also lacked this requirement.⁷³⁴

c) *Patent litigation process*

In contrast to the Hatch-Waxman amendments, S. 1695 called for a two-phase patent litigation process. From the patents identified through the process just described, the parties would identify patents for immediate litigation. Patents that had been identified but were not selected would be litigated in the second phase. This approach was crafted in the middle of the drafting process. The first two discussion drafts had provided for a conventional one-phase litigation process.⁷³⁵

Under S. 1695, for fifteen days running from the date of the applicant's receipt of the reference product sponsor's statement of the factual and legal basis for infringement, the applicant and reference product sponsor would need to participate in good faith negotiations to select patents for "immediate" (phase one) litigation.⁷³⁶ If no agreement were reached during this time, an alternative procedure would apply.⁷³⁷ The applicant first would be required to notify the reference product sponsor of the number of patents it planned to list for immediate litigation.⁷³⁸ The bill did not impose a deadline for this notification. Next, on a date agreed to by the parties but no more than five days later, the applicant and the reference product sponsor would have had to simultaneously exchange lists of patents to be litigated immediately.⁷³⁹ With one exception, the reference product sponsor could not have listed more patents than the applicant. If the biosimilar applicant indicated that it would list no patents for immediate litigation, the reference product sponsor would be permitted to list one.⁷⁴⁰

Within thirty days of agreeing on a list of patent for the first stage of litigation or completing the list exchange process, the reference product sponsor would have been required to initiate patent litigation.⁷⁴¹ If agreement had been reached, the reference product sponsor would have had to bring suit on all patents selected by the parties. If the list exchange process had been used, the reference product sponsor would have been required to sue on all patents appearing on its own list and all

⁷³³ *Id.* (proposed PHSA § 351(l)(3)(C)).

⁷³⁴ See 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(3) & (4)); 7641 Discussion Draft § __ (a) (same).

⁷³⁵ See 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(5)(A)) (patent suit could be initiated, as to any identified patent or patent believed in good faith to claim the reference product or biosimilar, after receiving the applicant's notice or when the applicant's time period for providing that notice expired); 7641 Discussion Draft § __ (a) (same) (patent suit could be initiated, as to any identified patent, after receiving the applicant's notice or when the applicant's time period for providing that notice expired).

⁷³⁶ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(4)(A) & (6)).

⁷³⁷ *Id.* (proposed PHSA § 351(l)(4)(B)).

⁷³⁸ *Id.* (proposed PHSA § 351(l)(5)(A)).

⁷³⁹ *Id.* (proposed PHSA § 351(l)(5)(B)(i)).

⁷⁴⁰ *Id.* (proposed PHSA § 351(l)(5)(B)(ii)). Prior drafts would have allowed the reference product sponsor to list three patents when the applicant listed zero. See, e.g., 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(l)(5)(B)(ii)(II)).

⁷⁴¹ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(6)).

patents appearing on the applicant's list. The drafters considered a process in which the reference product sponsor would have been required to sue only as to patents that appeared on both lists,⁷⁴² but they ultimately abandoned this approach. After the reference product sponsor initiated the suit, the applicant would have been required to provide notice and a copy of the complaint to FDA for publication in the *Federal Register*.⁷⁴³

The second phase of litigation would have begun with notice of commercial marketing. The applicant would have been required to provide this notice at least 180 days before launching the biosimilar.⁷⁴⁴ After the reference product sponsor received notice, it could have sought a preliminary injunction prohibiting the applicant from launching the biosimilar until the court decided the issues of patent validity, enforceability, and infringement, regarding any patent that: (1) was identified as a potentially relevant patent in the reference product sponsor's initial list, a supplement to it, or the applicant's optional list; and (2) was not selected for the first phase of litigation.⁷⁴⁵ This provision was added just prior to introduction of the bill.⁷⁴⁶

d) *Stay of FDA Approval and Remedies*

As noted above, under the Hatch-Waxman amendments, FDA approval of a generic drug is stayed for thirty months if the NDA holder or patent owner brings a patent infringement suit within forty-five days of receipt of notice of a paragraph IV challenge.⁷⁴⁷ A similar connection between FDA approval and patent litigation was briefly considered in the drafting process for S. 1695. Under the 7574 Discussion Draft, if the BLA holder or patent owner initiated suit on all challenged patents within forty-five days of the date on which it received notice of the patent challenge, the court would have informed FDA by order that the data exclusivity period would be deemed to be an additional (unspecified) number of years.⁷⁴⁸ The 7641 Discussion Draft contained the same provision, but added that the court could not stay approval of the biosimilar application or extend the data exclusivity period if suit had not been brought with respect to every challenged patent.⁷⁴⁹ Both discussion drafts provided that a court could not otherwise extend the data exclusivity period

⁷⁴² See, e.g., 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(l)(5)(C)). These bills provided a special procedure for patents that appeared in the reference product sponsor's list of patents for immediate litigation but not the applicant's list. E.g. *id.* (proposed PHSA § 351(l)(5)(D)). With respect to these patents, the applicant would have been required to provide notice in advance of marketing the biosimilar. E.g. *id.* The deadline for providing this notice was left blank. E.g. *id.* The reference product sponsor then would have been able to seek a preliminary injunction. E.g. *id.* These drafts would have precluded the reference product sponsor from bringing a patent infringement action prior to the (unspecified) deadline. E.g. *id.* A drafting note in these discussion drafts indicated that the provisions creating this special procedure would have been omitted if another proposed provision (the one stating that a reference product sponsor could designate three patents for immediate litigation even if the applicant selected zero) was retained. E.g. *id.* Notwithstanding this drafting note, the introduced bill both: (1) allowed the reference product sponsor to list one patent if the applicant listed zero; and (2) included a provision requiring notice of planned biosimilar launch and allowing for a preliminary injunction action. See S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(5)(B)(ii)(II) & (l)(8)).

⁷⁴³ *Id.* (proposed PHSA § 351(l)(6)(C)).

⁷⁴⁴ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(8)(A)).

⁷⁴⁵ *Id.* (proposed PHSA § 351(l)(8)(B)). Newly issued or licensed patents would have been required to be subject to the second phase of litigation. See *id.* (proposed PHSA § 351(l)(7)).

⁷⁴⁶ Compare *id.* (proposed PHSA § 351(l)(8)) with 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(l)).

⁷⁴⁷ *Id.*

⁷⁴⁸ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(5)(B)).

⁷⁴⁹ 7641 Discussion Draft § __ (a) (proposed PHSA § 351(l)(5)(B)(i) & (ii)).

or stay approval of the biosimilar application.⁷⁵⁰ This stay provision was dropped after the second discussion draft and was not present in S. 1695 when introduced.

These early proposals also included remedy provisions not seen in the final bill. Under the first two discussion drafts, if the BLA holder identified a patent as relevant within sixty days of receiving notice of confidential access to the biosimilar application, an injunction would have been required upon a “final decision” of validity and infringement.⁷⁵¹ In contrast, S. 1695 provided that a court would be required to permanently enjoin infringement of the patent until its expiry, if: (1) the patent was the subject of a final court decision of infringement in the first phase of litigation, and (2) the biosimilar had not yet been licensed because the data exclusivity period had not yet expired.⁷⁵²

e) *Provisions Limiting Remedies for Patent Infringement*

S. 1695 contained two provisions that would have limited the remedies available for infringement of innovator patents. First, if a patent should have been identified in the reference sponsor’s initial patent list (or a supplement to it) but was not timely included, the patent owner could not have brought an action for infringement of the patent with respect to the biosimilar, whether before or after marketing of the biosimilar.⁷⁵³ This article refers to this as a “list it or lose it” provision. Second, if the reference product sponsor did not initiate patent litigation within the applicable thirty-day period, or timely suit was brought but dismissed without prejudice or not prosecuted to judgment in good faith, only a reasonable royalty could be recovered upon a finding of infringement.⁷⁵⁴ This article refers to this as a “reasonable royalty” provision. Both provisions limiting available remedies would have applied to patent owners, whether or not they were the same entity as the reference product sponsor.⁷⁵⁵ These two provisions were similar to those proposed in the first and second Waxman bills.⁷⁵⁶

The drafters considered the reasonable royalty provision early in the drafting process⁷⁵⁷ and then considered other approaches before reverting to this and the list it or lose it provision. One option considered was shortening of the data exclusivity period by an unspecified amount of time based on the BLA holder’s or patent owner’s failure to reasonably cooperate in expediting the action or failure

⁷⁵⁰ *Id.* (proposed PHSA § 351(l)(7)); 7574 Discussion Draft § __ (a) (same).

⁷⁵¹ 7574 Discussion Draft § __ (a), (c)(1)(B)(iii) (proposed PHSA § 351(l)(3)(B) & proposed 35 U.S.C. § 271(e)(4)(D)); 7641 Discussion Draft § __ (a), (c)(1)(B)(iii) (proposed PHSA § 351(l)(3)(C) & proposed 35 U.S.C. § 271(e)(4)(D)). “Final decision” was defined in these discussion drafts to mean a decision from which no appeal had been or could be taken other than a petition for a writ of certiorari to the Supreme Court. 7574 Discussion Draft § __ (a), (c)(1)(B)(iii) (proposed PHSA § 351(l)(3)(B) (iii)); 7641 Discussion Draft § __ (a), (c)(1)(B)(iii) ((proposed PHSA § 351(l)(3)(C)(iii)). This approach contrasts with that of 35 U.S.C. § 271(e)(4), under which a district court finding serves as the basis for an injunction barring infringement until patent expiry.

⁷⁵² S. 1695 § 2(c)(1)(B)(iii) (proposed 35 U.S.C. § 271(e)(4)(D)). “Final court decision” meant a decision from which no appeal has been or could be taken other than a writ of certiorari to the United States Supreme Court. *Id.* §§ 2(a)(2) & 2(c)(1)(B)(iii) (proposed PHSA § 351(l)(6) & 35 U.S.C. § 271(e)(4)(D)).

⁷⁵³ *Id.* § 2(c)(1)(C) (proposed 35 U.S.C. § 271(e)(6)(C)).

⁷⁵⁴ *Id.* (proposed 35 U.S.C. § 271(e)(6)(A) & (B)).

⁷⁵⁵ The 7645 discussion draft also provided that nothing in the bill should be “construed to restrict or invalidate the enforceability of any patent right held by a third party in effect on the date of enactment.” 7645 Discussion Draft § 2(e). This language was not included in the introduced bill.

⁷⁵⁶ See *supra* notes 398-400 and accompanying text.

⁷⁵⁷ 7641 Discussion Draft § __ (c)(1)(C) (proposed 35 U.S.C. § 271(e)(6)).

to sue on or defend a patent (unless it consented to an order that the patent was invalid or not infringed by the biosimilar).⁷⁵⁸ In lieu of the list it or lose it provision, the drafters also considered requiring FDA to appoint a special master to review the reference product sponsor's initial list "to ensure that the [patents] listed were included in good faith."⁷⁵⁹

f) *Declaratory Judgment Provisions*

The declaratory judgment provisions of the bill were developed just prior to introduction. If the applicant provided the reference product sponsor a copy of its application and manufacturing information, neither party could have brought a declaratory judgment action concerning a patent included in either party's initial list but not selected for the first phase of litigation prior to the date on which the applicant provided notice of commercial marketing.⁷⁶⁰ If the biosimilar applicant failed to respond to the reference product sponsor's initial list or any supplements to that list, participate in the list exchange process, provide notice and a copy of the complaint to FDA, or provide notice of commercial marketing of its product, only the reference product sponsor could bring a declaratory judgment action regarding patents on its initial list or supplements to that list.⁷⁶¹ Finally, if the biosimilar applicant failed to provide its application and manufacturing information, only the reference product sponsor could bring a declaratory judgment as to a patent that claimed the biological product or a use of the biological product.⁷⁶²

The first two discussion drafts included a declaratory judgment provision similar to that in the FDCA; an applicant could have brought a declaratory judgment action as to any challenged patent in the defendant's principal place of business (or a regular and established place of business) if the reference product sponsor or patent owner did not initiate patent litigation within the prescribed forty-five-day period.⁷⁶³

b. *Subsequent Draft of the Bill, Markup, and Beyond*

The Gang of Four reached agreement on the language of S. 1695 on June 22, 2007,⁷⁶⁴ and a markup was scheduled for June 27. In the meantime, stakeholders debated a number of the provisions, including the data exclusivity provisions. For example, BIO continued to argue in favor of a fourteen-year period and also contended that the legislation should not provide for interchangeability.⁷⁶⁵ GPhA argued in favor of a shorter period applicable only to innovative products licensed after enactment.⁷⁶⁶

In addition, then Secretary of HHS Michael Leavitt sent a letter to Senator Kennedy, dated June 26, 2007, describing the Administration's views on biosimilars legislation generally and its objections to certain aspects of S. 1695.⁷⁶⁷ First, the

⁷⁵⁸ 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(5)(C)); 7641 Discussion Draft § __ (a) (same).

⁷⁵⁹ 7645 Discussion Draft § 2(b)(2) (proposed PHSA § 351(l)(3)(D)); 7655 Discussion Draft § 2(b)(2) (same).

⁷⁶⁰ S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(9)(A)).

⁷⁶¹ *Id.* (proposed PHSA § 351(l)(9)(B)).

⁷⁶² *Id.* (proposed PHSA § 351(l)(9)(C)).

⁷⁶³ *See, e.g.*, 7574 Discussion Draft § __ (a) (proposed PHSA § 351(l)(6)); 7641 Discussion Draft § __ (a) (same). *See also* FDCA §§ 505(c)(3)(D), 505(j)(5)(C).

⁷⁶⁴ Press Release, Senators Kennedy, Hatch, Clinton, Enzi Announce FDA Biologics Agreement (June 22, 2007), available at <http://help.senate.gov/newsroom/press/release/?id=bddb3b98-6c0b-4479-8bfd-f57bc2328da5&groups=Chair>.

⁷⁶⁵ Steve Usdin, *The Senate's Biosimilars Deal*, BIOCENTURY, June 25, 2007, at A12.

⁷⁶⁶ *Id.*

⁷⁶⁷ Letter of Michael O. Leavitt, Sec'y of HHS, to Sen. Kennedy (June 26, 2007).

Administration took issue with the scope of S. 1695. While agreeing that science had advanced to the point that FDA could “approve relatively simple proteins and peptides under some abbreviated pathway,” the letter stressed that the existing state of science did not support licensure of biosimilar versions of vaccines and blood products, which should be subject to a moratorium or excluded entirely from the legislation.⁷⁶⁸ In addition, the letter stated that FDCA proteins should not be included in the new pathway without “very careful consideration” of the legal and policy implications.⁷⁶⁹ Second, while supporting a twelve-year data exclusivity period that was independent of patent protection, the letter stated that the legislation should provide supplemental exclusivity for new indications requiring clinical trials other than bioavailability studies.⁷⁷⁰ Third, the Administration favored a public process for developing product class guidance, which should describe, among other things, the clinical data required to obtain licensure in the product class in question.⁷⁷¹ The letter also stated the Administration’s “belief[] that the legislation should be amended to require a predictable and public product-class guidance process prior to acting on any follow-on applications.”⁷⁷² Fourth, the letter stated that preapproval immunogenicity data should not be waivable because these data are “critical.”⁷⁷³ Fifth, according to the letter, S. 1695 should require applicants to show biosimilarity for each reference product condition of use.⁷⁷⁴ Sixth, the letter stated that each biosimilar should be required to have the same mechanism of action as its reference product if that mechanism of action was “known” or could “reasonably be determined.”⁷⁷⁵

Seventh, according to the letter, the legislation should not allow for determinations of interchangeability. The Administration stated that a biosimilar should be considered interchangeable only if it had been “proven to produce the same clinical result in patients so that it can be used in the same manner as therapeutically equivalent, generic drugs approved under section 505(j) of the FDCA” and noted that “[t]echnology is not yet sufficiently advanced to allow this type of comparison for more complex protein products.”⁷⁷⁶ In addition, to the extent the legislation nonetheless permitted interchangeability, the Administration stated that an applicant should be required to show interchangeability — for all indications — to the reference product and all previously licensed biosimilars based on that reference product.⁷⁷⁷ The Administration also objected to S. 1695’s definition of “interchangeable” as intruding on state regulation of medicine and pharmacy. Although the letter did not explain this statement, the Administration was likely concerned that this definition could be viewed as preempting state substitution law, as was Senator Coburn (R-OK) (discussed below).⁷⁷⁸ Finally, the Administration contended that the legislation should require unique nonproprietary names for biosimilars as well as labeling on every biologic, *i.e.*, biosimilars and reference products, indicating whether FDA had determined that the product was interchangeable with any other product.⁷⁷⁹

⁷⁶⁸ *Id.* at 2, 3.

⁷⁶⁹ *Id.* at 3.

⁷⁷⁰ *Id.* at 2.

⁷⁷¹ *Id.* at 3-4.

⁷⁷² *Id.* at 3.

⁷⁷³ *Id.* at 4.

⁷⁷⁴ *Id.*

⁷⁷⁵ *Id.*

⁷⁷⁶ *Id.* at 5.

⁷⁷⁷ *Id.* at 5-6.

⁷⁷⁸ *Id.* at 6.

⁷⁷⁹ *Id.*

1) *The 7721 Draft*

A Manager's Amendment, known as the 7721 draft based on its file path, was circulated in advance of the HELP markup on June 27, 2007. The 7721 draft included a new subparagraph in the data exclusivity provision. As noted, the data exclusivity provision of S. 1695 as introduced had provided that a biosimilar application could not be approved until twelve years after the reference product was "first licensed" under section 351(a) of the PHSA.⁷⁸⁰ The new subparagraph provided that the date of first licensure "[did] not include the date of approval of a supplement or of a subsequent application for a new indication, route of administration, dosage form, or strength for the previously licensed reference product."⁷⁸¹ Senator Kennedy stated that "[t]he 12 years of exclusivity applies only to products that are analogous to a 'new chemical entity'" under the Hatch-Waxman amendments,⁷⁸² pursuant to which the maximum exclusivity period is granted only to drugs having no previously approved active ingredients. A new subsection provided that, where a reference product had been orphan-designated, a biosimilar could be licensed for that orphan indication only after both the orphan exclusivity period and the data exclusivity period expired.⁷⁸³

The new draft also included changes to the regulatory provisions. First, the definition of "biosimilar" was amended to include a requirement that the proposed product be "highly similar to the reference product notwithstanding minor difference in clinically inactive components," in addition to the requirement that the products have no clinically meaningful differences.⁷⁸⁴ Second, the new draft omitted the language stating that any required clinical studies should be designed to avoid duplicative and unethical testing, and it clarified that the required animal testing generally must include an assessment of toxicity.⁷⁸⁵ Third, the bill was revised to provide that an applicant was required to consent to an inspection of its facility as a condition of approval.⁷⁸⁶

The patent provisions had also changed. Specifically, the confidential access provisions were revised to provide that a third party patent owner who had exclusively licensed a patent to the reference product sponsor and who had retained a right to assert the patent or participate in litigation could be provided confidential information, if the patent owner notified the biosimilar applicant of its agreement to be subject to the confidentiality provisions of section 351(l).⁷⁸⁷ Also, the reference product sponsor's initial list of relevant patents was to include patents that reasonably could be asserted by either the reference product sponsor or a third party patent owner that had granted it an exclusive license,⁷⁸⁸ whereas the introduced version of the bill had required listing of only those patents that reasonably could be asserted by the reference product sponsor.⁷⁸⁹

2) *Markup*

On June 27, 2007, the HELP Committee passed the 7721 Draft by voice vote, but indicated it would continue to work on several aspects of the draft.⁷⁹⁰ According to the trade press, Senator Kennedy said that the HELP Committee planned

⁷⁸⁰ S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(7)(A)).

⁷⁸¹ 7721 draft § 2(a)(2) (proposed PHSA § 351(k)(7)(C)).

⁷⁸² See *Senate Committee Passes Follow-On Biologics Bill*, WASHINGTON DRUG LETTER, July 2, 2007, at 4.

⁷⁸³ 7721 draft § 2(i).

⁷⁸⁴ *Id.* § 2(b)(3) (proposed PHSA § 351(i)(2)).

⁷⁸⁵ *Id.* § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(i)(I)(bb) & (cc)).

⁷⁸⁶ *Id.* (proposed PHSA § 351(k)(3)(B)).

⁷⁸⁷ *Id.* § 2(a)(2) (proposed PHSA § 351(l)(1)(B)(iii)).

⁷⁸⁸ *Id.* (proposed PHSA § 351(l)(3)(A)(i)).

⁷⁸⁹ See *supra* note 728 and accompanying text.

⁷⁹⁰ *Senate Panel Passes Biogenics Bill; Still Working on Changes*, FDA WEEK, June 29, 2007.

to attach the bill to the PDUFA legislation when the latter was conferenced with the House.⁷⁹¹ As noted, the Senate had passed the PDUFA legislation in May 2007 with a placeholder for insertion of text on biosimilars.⁷⁹²

During the markup, Senator Coburn proposed an amendment that would have modified the bill's definition of "interchangeability" to provide it did not affect state laws allowing prescribers to preclude substitution of a biosimilar for the reference product.⁷⁹³ According to the trade press, Senator Clinton responded that the bill would not require substitution so the amendment was not needed.⁷⁹⁴ After Senator Kennedy agreed to work with Senator Coburn on the issue, the amendment was withdrawn.⁷⁹⁵ Senator Alexander (R-TN) proposed an amendment to provide pediatric exclusivity for biologics, but this amendment did not pass.⁷⁹⁶ Senator Sherrod Brown (D-OH) offered and then withdrew an amendment that would have reduced the data exclusivity period to seven years.⁷⁹⁷

3) *Evergreening Debate and Concern Regarding Addition of the Bill to PDUFA*

Because there was continued disagreement about the data exclusivity language and in light of objections that the bill had undergone insufficient consideration in the House,⁷⁹⁸ the HELP Committee-passed language was not attached to PDUFA in conference, and the bill was not formally reported out of Committee until November 2008.

Shortly after the bill passed the Committee GPhA issued a press release objecting to two provisions of the Manager's Amendment. First, GPhA stated that the twelve-year period was "arbitrary and excessive."⁷⁹⁹ Second, GPhA contended that the bill "could allow brand companies to make multiple minor changes to their products and receive 12 years [of exclusivity] for each change, in effect maintaining their monopolies in perpetuity."⁸⁰⁰ The press release stated that "[t]his practice, commonly known as 'evergreening,' would essentially prevent safe and affordable lifesaving biogenerics from ever reaching patients."⁸⁰¹ According to its press release, GPhA was informed by the Senate staff that "this is not the true intent of the compromise."⁸⁰² GPhA pledged to "work with the negotiators to craft language that addresses this issue."⁸⁰³

BIO also expressed its intent to continue working with Congress to improve the legislation, but identified different aspects of the legislation for improvement.⁸⁰⁴

⁷⁹¹ *Senate Committee Passes Follow-On Biologics Bill*, WASHINGTON DRUG LETTER, July 2, 2007, at 1.

⁷⁹² 153 Cong. Rec. S5759, S5803 (daily ed. May 7, 2007).

⁷⁹³ *Id.*

⁷⁹⁴ *Id.*

⁷⁹⁵ *Id.*

⁷⁹⁶ *Id.*

⁷⁹⁷ *Senate Committee Passes Follow-On Biologics Bill*, WASHINGTON DRUG LETTER, July 2, 2007, at 4.

⁷⁹⁸ Steve Usdin, *Biosimilars Dropped from FDARA*, BIOCENTURY, Sept. 10, 2007, at A15.

⁷⁹⁹ Press Release, GPhA, GPhA Statement on Sens. Kennedy-Enzi-Clinton-Hatch Biogenerics Legislation (June 27, 2007), available at <http://www.gphaonline.org/media/press-releases/2009/02/12/gpha-statement-sens-kennedy-enzi-clinton-hatch-biogenerics-legislati>.

⁸⁰⁰ *Id.*

⁸⁰¹ *Id.*

⁸⁰² *Id.*

⁸⁰³ *Id.*

⁸⁰⁴ Press Release, BIO, *Leading Biotechnology Organizations Praise Effort and Express Concerns with New Follow-on Biologics Proposal* (June 27, 2007), available at http://www.bio.org/news/pressreleases/newsitem.asp?id=2007_0627_02.

While BIO was “pleased that the bill ma[de] a strong statement” about data exclusivity, it continued to “believe, however, that a strong case has been made that 14 years of data exclusivity is the needed period.”⁸⁰⁵ BIO also opposed the interchangeability provision, stating that “[t]o protect patient safety, Congress should ensure that patients are not given follow-on biologics unless expressly prescribed by a physician.”⁸⁰⁶ BIO stated that the bill’s patent provisions would “restrict the ability of innovators and third parties . . . to enforce their patents against follow-on manufacturers, while enabling follow-on products to enter the market in advance of the expiration of the innovator’s patent and prior to the conclusion of patent enforcement activity.”⁸⁰⁷ BIO also pointed out that the bill would allow applicants to “limit the number of patents resolved prior to market entry to a single patent.”⁸⁰⁸

In the months that followed, a variety of proposals for “anti-evergreening” language were floated on the Hill. Stakeholders discussed whether a new twelve-year exclusivity period could be obtained for a new product that represented a modification to a previously licensed reference product. (This issue thus was distinct from the issue of whether an extension of the base exclusivity period could be obtained for changes to a reference product, as proposed in the Inslee and Gregg bills.) The initial discussions focused on whether an innovator (or related entity) could receive a new twelve-year period for products reflecting the following types of changes to a previously licensed reference product: (1) changes that could be approved via a supplement to a reference product BLA; (2) changes in the reference product’s conditions of use, delivery system, or delivery device, proposed in a subsequent application; (3) modifications to the structure of the reference product through post-translational events, proposed in a subsequent application; and (4) changes to the reference product’s amino acid sequence that had no impact on the product’s safety, purity, or potency, proposed in a subsequent application. Disputes ensued over whether exclusivity determinations should be left to case-by-case determination by FDA. For example, the legislation might have provided exclusivity only for full BLAs, not for supplements, and allowed FDA to decide whether a full application was required. Another approach would have been to preclude twelve-year exclusivity for a new application proposing: (1) any of certain nonstructural changes to a previously licensed product, including changes in conditions of use and changes in delivery device; or (2) a structural change to a previously licensed product’s active ingredient that had no effect on the safety, purity, potency of the product and that did not require submission of new clinical data.

Representative Eshoo and ten other House lawmakers wrote to Senators Kennedy and Enzi as well as then Chairman of the House Energy and Commerce Committee John Dingell (D-MI) and then Ranking Member of that Committee, Joe Barton (R-TX), requesting that the bill not be added to the PDUFA legislation in conference.⁸⁰⁹ The signatories emphasized that the biosimilars legislation “ha[d] not passed the full Senate” and that the House Committee on Energy and Commerce “ha[d] not had the opportunity to deliberate and consider the compli-

⁸⁰⁵ *Id.*

⁸⁰⁶ *Id.*

⁸⁰⁷ *Id.*

⁸⁰⁸ *Id.*

⁸⁰⁹ Letter from Rep. Eshoo et al. to Rep. Dingell, Rep. Barton, Sen. Kennedy, and Sen. Enzi (July 18, 2007), at 1. Signatories of the letter besides Representative Eshoo were Representatives Blackburn (R-TN), Myrick (R-NC), Rogers (R-MI), Ferguson (R-NJ), Gonzales (D-TX), Buyer (R-IN), Boucher (D-VA), Gordon (D-TN), Burgess (R-TX), and Cubin (R-WY). *Id.* at 2.

cated scientific, legal, and economic issues” implicated by the legislation.⁸¹⁰ These legislators stated their belief that Congress should consider biosimilars legislation after “full deliberation, hearings, and markup by appropriate committees.”⁸¹¹ The trade press reported that Representative Dingell, then Chair of the House Energy and Commerce Committee, “made it clear that he wanted the House to have the opportunity to debate and shape any biosimilars legislation.”⁸¹² The trade press subsequently reported that Senators Clinton, Kennedy, Enzi, and Hatch made a ““member-level”” decision to leave the bill out of the PDUFA legislation.⁸¹³ Although it was briefly considered possible that the legislation would be included in the Patent Reform Act under consideration in September 2007,⁸¹⁴ this did not happen, and in late October, House lawmakers agreed to wait until 2008 to pursue biosimilars legislation.⁸¹⁵

In November, Keith Webber, Deputy Director of the Office of Pharmaceutical Science at FDA, stated that FDA would “wait to publish [the biosimilar guidances under development] until [agency personnel] know what the law is going to be” to ensure that the guideline was not “inappropriate in light of laws that get passed.”⁸¹⁶

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The Senate waited for the House to act. Thus in early 2008, the major negotiations on biosimilars took place in the House of Representatives.⁸¹⁷ Representatives Eshoo and Barton introduced a bill in March (H.R. 5629 or “the first Eshoo bill”).⁸¹⁸ The first Eshoo bill combined elements of the Inslee bill and S. 1695, and it was generally supported by the innovative industry and opposed by the generic industry.⁸¹⁹ Shortly thereafter, Representatives Pallone (D-NJ) and Deal (R-GA) sought input from key stakeholders by asking them for responses to a list of questions.⁸²⁰

Through the year, the Administration sent mixed signals regarding the roles it planned to take and the views it held. In its budget request in early 2008, for example, the White House announced that it was planning a legislative proposal on biosimilars, and then FDA Chief Operating Officer John Dyer commented during a press teleconference that FDA indeed was drafting its own proposal.⁸²¹ Later, FDA spokesperson Christopher Kelly told the trade press that FDA would not be proposing specific legislative language but instead was “looking to Congress to act on legislation consistent with HHS views about [biosimilars].”⁸²² Ultimately,

⁸¹⁰ *Id.*

⁸¹¹ *Id.*

⁸¹² Steve Usdin, *Biosimilars Dropped from FDARA*, BIOCENTURY, Sept. 10, 2007, at A15.

⁸¹³ *Flubbing the FOBs Opportunity: Follow-On Biologics Winners & Losers*, RPM REPORT, Oct. 2007, at 24.

⁸¹⁴ *BIO Worries That Biogenerics May Be Attached to Patent Bill*, FDA WEEK, Sept. 7, 2007.

⁸¹⁵ *House Lawmakers Hold Off On Biogenerics Until Next Year*, FDA WEEK, Nov. 2, 2007.

⁸¹⁶ *FDA Gets Practical on Follow-On Biologics as Pathway Remains Theoretical*, THE PINK SHEET, Nov. 5, 2007.

⁸¹⁷ *Bush Proposes Biosimilars in Budget; CBO Working to Score Savings*, FDA WEEK, Feb. 8, 2008; *Biogenerics Bill From Reps. Eshoo and Barton “Expects” Limits on Substitution*, THE PINK SHEET, Feb. 25, 2008.

⁸¹⁸ H.R. 5629, 110th Cong. (2008).

⁸¹⁹ *Reps. Eshoo, Barton Introduce Bill on FDA Approval of Biogeneric Drugs*, PHARM. L. & IND. R., Mar. 21, 2008, at 330.

⁸²⁰ Letter of Frank J. Pallone, Chairman of the Subcommittee of Health, H. Comm. On Energy & Commerce & Nathan Deal, Ranking Member, Comm. On Energy & Commerce (Apr. 3, 2008).

⁸²¹ *FDA Does About-Face on Biosimilar Bill, Will Not Write Legislation*, FDA WEEK, Feb. 8, 2008, at 7.

⁸²² *Id.*

in a submission to Representative Pallone, FDA expressed its view on appropriate legislation in a way that aligned with the Leavitt letter of June 26, 2007.⁸²³

The November 2008 elections had a profound effect on the momentum of biosimilars legislation in 2008. The trade press reported that the brand industry pushed for adoption of a bill during 2008 because it expected 2009 might “offer a less sympathetic Congress and administration,”⁸²⁴ whereas the generic industry was “in no hurry to get a bill passed [that] year, banking on getting a better deal” after the November elections.⁸²⁵ Thus, although Representative Eshoo introduced a bill, and although the Energy and Commerce Committee sought stakeholder input, progress toward passage of a compromise bill was not made prior to the elections.⁸²⁶ After the 2008 elections, the HELP Committee finally reported the 7721 version of S. 1695 that had been passed in the summer of 2007. According to the trade press, some industry sources speculated that this signaled an intent to pass biosimilars legislation before the end of the 110th Congress.⁸²⁷

1. *First Eshoo Bill*

Representative Eshoo had been considering legislative language since mid-2007. She refined her proposal in late 2007 and early 2008, before introducing the Pathway for Biosimilars Act on March 13, 2008.⁸²⁸ The regulatory pathway provisions were similar to those in S. 1695, although there were also some similarities to the Inslee bill. Although the first Eshoo bill provided twelve years of core data exclusivity — like S. 1695 and the 7721 Draft, referred to in this section as the HELP bills — it also provided data exclusivity for supplemental indications and pediatric exclusivity. And the patent litigation provisions were nothing like the provisions in the HELP bills.⁸²⁹

a. *Regulatory Pathway*

1) *Scope*

H.R. 5629 would have created a pathway for licensure of products “biosimilar” to a “reference product.”⁸³⁰ Unlike every other bill introduced in the 109th and 110th Congress, however, the Eshoo bill did not define “reference product.”⁸³¹ The bill’s data exclusivity provisions referred to reference products licensed under subsection (a) of PHSA section 351, however, which suggested that only biologics licensed on the basis of full BLAs could serve as reference products.⁸³² The Eshoo bill contained the same transition provisions as the HELP bills with respect to products approved under the FDCA. Under these provisions, certain biological product applications could be filed

⁸²³ *FDA Follow-On Biologics Letter Creates Hurdle for Obama Administration*, THE PINK SHEET, Jan. 19, 2009, at 7.

⁸²⁴ *Biogenerics In Holding Pattern As Legislation and Election Campaigns Simmer*, THE PINK SHEET, Feb. 18, 2008, at 7.

⁸²⁵ *BIO “Ferociously Lobbying” for a Biosimilar Bill This Year*, FDA WEEK, Feb. 1, 2008, at 3.

⁸²⁶ *See Senate Biosimilars Bill Reported 112 Years After Committee Passed It*, FDA WEEK, Nov. 28, 2008.

⁸²⁷ *Id.*

⁸²⁸ H.R. 5629, § 1.

⁸²⁹ *See Barton’s Decision to Back Eshoo on Biogenerics May Hurt House Negotiations*, FDA WEEK, Feb. 15, 2008.

⁸³⁰ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)).

⁸³¹ The Inslee and Gregg bills also used the term “qualified biological product.” *See* H.R. 1956, 110th Cong. § 2(a)(2) (proposed PHSA § 351(k)(1)(B)); S. 1505, 110th Cong. § 2(a)(2) (same).

⁸³² H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(7)(A)).

under section 505 until the expiry of a ten-year transition period.⁸³³ As noted, the HELP bills would have amended the definition of “biological product” to expressly include proteins and therefore clarify that all proteins would be subject to the new pathway except as provided in the transition provisions. Although the first Eshoo bill contained the same transition provisions generally as S. 1695, it would not have amended the definition of “biological product” to explicitly include proteins.

Like the HELP bills, H.R. 5629 would have noted that FDA could issue a guidance indicating that it could not license biosimilars in a product or product class — other than a recombinant protein — because the state of science and experience did not permit it.⁸³⁴ Unlike the HELP bills, however, the first Eshoo bill would have mandated that FDA publish final product class guidance within two years of a petition to commence the guidance development process for that product class.⁸³⁵ The trade press noted that the interplay of these two provisions could have had the effect of requiring FDA to issue guidance on a recombinant protein even if FDA believed the science did not support it.⁸³⁶ Unlike the other bills introduced in the 109th and 110th Congress, the first Eshoo bill would have barred licensure of a biosimilar containing a “select agent or toxin” listed in certain HHS and USDA regulations, which included, for example, ebola virus, botulinum neurotoxins, avian influenza virus, and bovine spongiform encephalopathy agents.⁸³⁷

2) *Application Content Requirements*

Like the HELP bills, H.R. 5629 generally would have required biosimilar applications to contain information showing the proposed product to be “biosimilar” to the reference product based on data from: (1) analytical studies showing that the biosimilar was “highly similar to the reference product notwithstanding minor differences in clinically inactive components”; (2) data from animal studies; and (3) data from “a clinical study or studies.”⁸³⁸ The clinical data would have needed to include immunogenicity data and an assessment of either pharmacokinetics or pharmacodynamics.⁸³⁹ Unlike the HELP bills, however, the first Eshoo bill would have required — subject to the waiver described in the next paragraph — that clinical data be submitted to show the safety, purity, and potency of the biosimilar “for each condition of use for which the reference product [was] approved.”⁸⁴⁰ The bill did not define “biosimilar.”

As in the HELP bills, FDA would have had discretion to waive any of these data requirements upon a finding that the data in question were “unnecessary.” FDA could not grant a waiver from the requirement for an immunogenicity assessment unless it first published a final guidance noting that immunogenicity determinations for the product class were feasible and describing the data to support those determinations.⁸⁴¹ Also as under the HELP bills, a biosimilar application would have been required to show that the proposed product had the same route of administration, dosage form, strength, and

⁸³³ *Id.* § 101(b).

⁸³⁴ *Id.* § 101(a)(2) (proposed PHSA § 351(k)(9)(C)(i)).

⁸³⁵ *Id.* proposed PHSA § 351(k)(9)(D)).

⁸³⁶ *Eshoo Bill Could Force FDA's Hand on Some Generic Biologics*, FDA WEEK, Mar. 21, 2008, at 1, 9.

⁸³⁷ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(5)(D)); 42 C.F.R. §§ 73.3 & 73.4; 9 C.F.R. §§ 121.3 & 121.4; 7 C.F.R. § 331.3.

⁸³⁸ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(2)(A)(i)(I)).

⁸³⁹ *Id.* (proposed PHSA § 351(k)(2)(A)(i)(I)-(III)).

⁸⁴⁰ *Id.* (proposed PHSA § 351(k)(2)(A)(i)(III)); *see also id.* (proposed PHSA § 351(k)(3)(A)) (providing that FDA must license a proposed product under section 351(k) if the application shows that the product is biosimilar to the reference product for each condition of use for which the reference product is approved).

⁸⁴¹ *Id.* (proposed PHSA § 351(k)(2)(B)(i) & (ii)).

(if known) mechanism(s) of action as the reference product; that the reference product had been licensed for the conditions of use proposed for the biosimilar; and that the facilities for manufacture, processing, packing, and holding of the biosimilar met cGMP.⁸⁴² FDA's authority regarding REMS (under section 505-1 of the FDCA) would have applied to biosimilars "in the same manner" as it applied to innovative products.⁸⁴³ And the application would have been required to contain publicly available information about FDA's finding of safety, purity, and potency for the reference product, and, at the applicant's option, "additional information, including publicly-available information" regarding the reference product or another biologic.⁸⁴⁴ Under the first Eshoo bill, FDA would have been required to approve a biosimilar application if: (1) the agency determined that the proposed product was biosimilar to the reference product for each condition of use for which the reference product was licensed, and (2) the applicant consented to an inspection of the relevant facility.⁸⁴⁵

Under the first Eshoo bill, FDA would have been required to issue guidance "with respect to the licensure under [subsection (k)] of a biological product or product class,"⁸⁴⁶ whereas the issuance of guidance on biosimilars was optional under the HELP bill.⁸⁴⁷ In contrast to the HELP bill, the first Eshoo bill would not have permitted FDA to license biosimilars in a particular product class until the agency had issued final guidance specific to the product class.⁸⁴⁸ Moreover, FDA also could not have accepted a biosimilar application until the guidance development process for that product class had been initiated.⁸⁴⁹ The first Eshoo bill also contained a provision allowing any person to file a petition asking for guidance regarding biosimilar versions of reference products licensed more than seven years prior to enactment. FDA would have been required to respond with product class-specific guidance within two years of the filing of this petition.⁸⁵⁰

3) *Interchangeability and Naming*

The first Eshoo bill's interchangeability provisions largely tracked the language of the HELP bills. There were, however, several important differences. First, to be interchangeable with a reference product under the Eshoo bill, a product would have had to be biosimilar not only to the reference product, but also to any other licensed product that already had been deemed interchangeable with that reference product.⁸⁵¹ Second, as in the HELP bills, the biosimilar applicant would have been required to demonstrate that the biosimilar product could be expected to produce the same clinical result as the reference product in any given patient, but under the first Eshoo bill that showing would have had to be made for each condition of use in the reference product labeling.⁸⁵² Finally, FDA could not have made any interchangeability designations until it had published final guidance indicating that interchangeability determinations for the product class were scientifically possible and describing the data necessary to support these determinations.⁸⁵³

⁸⁴² *Id.* (proposed PHSA § 351(k)(2)(A)(ii)-(v)).

⁸⁴³ *Id.* (proposed PHSA § 351(k)(5)(C)).

⁸⁴⁴ *Id.* (proposed PHSA § 351(k)(2)(C)).

⁸⁴⁵ *Id.* (proposed PHSA § 351(k)(3)).

⁸⁴⁶ *Id.* (proposed PHSA § 351(k)(9)(A)).

⁸⁴⁷ See *supra* note 674 and accompanying text.

⁸⁴⁸ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(9)(E)).

⁸⁴⁹ *Id.*

⁸⁵⁰ *Id.* (proposed PHSA § 351(k)(9)(D)).

⁸⁵¹ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(4)(A)(i)(I)).

⁸⁵² *Id.* (proposed PHSA § 351(k)(4)(A)(i)(II)).

⁸⁵³ *Id.* (proposed PHSA § 351(k)(4)(B)).

Unlike the HELP bills, the first Eshoo bill contained a provision on naming of biosimilars. It required FDA to “ensure” that a biosimilar’s labeling bore a name that “uniquely identif[ie]d” it and that distinguished it from both the reference product and other products licensed as biosimilar to that reference product.⁸⁵⁴

b. *Exclusivity*

The exclusivity provisions of the first Eshoo bill combined elements of the Inslee, Gregg, and HELP bills. Like the HELP bills, it would have provided a twelve-year period of data exclusivity running from the “first licensure” of the reference product.⁸⁵⁵ And as in the 7721 draft, the date of first licensure would not have included the dates on which the innovator obtained approval of a supplement or a subsequent application for a new indication, route of administration, dosage form, or strength of a previously licensed reference product.⁸⁵⁶ Like the Inslee and Gregg bills, the first Eshoo bill contained supplemental exclusivity provisions. If, within the first eight years after licensure of the reference product, FDA approved a supplement for a new indication constituting “a significant improvement, compared to marketed products, in the treatment, diagnosis, or prevention of disease,” the data exclusivity period would have been extended by two years.⁸⁵⁷ This provision parallels the European provision on supplemental exclusivity, where an additional year is available based on approval of a supplement for a new indication found “to bring a significant clinical benefit in comparison with existing therapies.”⁸⁵⁸

Unlike any prior biosimilars bill, the first Eshoo bill contained pediatric exclusivity provisions. Under these provisions, a reference product sponsor could have obtained a six-month extension of the otherwise applicable data exclusivity period based on submission and FDA acceptance of a pediatric study report.⁸⁵⁹ As under the pediatric exclusivity provisions for FDCA products,⁸⁶⁰ this exclusivity would have been available only if FDA had accepted the written study report at least nine months prior to the expiry of the period to be extended (*i.e.*, the twelve-year data exclusivity term or fourteen-year data exclusivity term if supplemental exclusivity had been obtained).⁸⁶¹ The first Eshoo bill also stated that certain FDCA provisions related to pediatric studies would apply to reference products, including the provision in section 505A stating that any pediatric study required by another provision of law could satisfy the requirements for pediatric exclusivity and the provisions governing FDA review and acceptance of pediatric study reports.⁸⁶²

Finally, the first Eshoo bill provided a 24-month exclusivity period for the first biosimilar deemed interchangeable with a particular reference product. During this time, no other product could be deemed interchangeable with that reference product. This period of exclusivity would have begun on the later of: (1) the date of first commercial marketing of the first interchangeable biosimilar, or (2) if the biosimilar product was first marketed prior to the interchangeability determination, the date of FDA’s interchangeability finding.⁸⁶³

⁸⁵⁴ *Id.* proposed PHSA § 351(k)(10)).

⁸⁵⁵ *Id.* (proposed PHSA § 351(k)(7)(A)).

⁸⁵⁶ *Id.* (proposed PHSA § 351(k)(7)(C)).

⁸⁵⁷ *Id.* (proposed PHSA § 351(k)(7)(D)).

⁸⁵⁸ See *supra* note 169 and accompanying text.

⁸⁵⁹ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(8)(A)).

⁸⁶⁰ FDCA § 505A(b)(2) & (c)(2).

⁸⁶¹ H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(8)(B)).

⁸⁶² *Id.* (proposed PHSA § 351(k)(8)(C)) (referencing the following subsections of FDCA section 505A: (a), (d), (e), (f), (h), (j), (k), and (l)).

⁸⁶³ *Id.* (proposed PHSA § 351(k)(6)).

c. Patent Provisions

The first Eshoo bill contained patent provisions unlike those in S. 1695 and the first two Waxman bills. It took the same general approach as these bills: the biosimilar applicant and the reference product sponsor would exchange information about relevant patents and could resolve infringement and validity disputes through premarket litigation.⁸⁶⁴ Nevertheless, H.R. 5629 included provisions designed to ensure that an “interested third party” — defined as a person other than the reference product sponsor who owned a relevant patent or had the right to commence or participate in infringement actions concerning the relevant patent — could participate in the process of identifying patents for litigation.⁸⁶⁵ It called for one phase of patent litigation and contained no provisions limiting the remedies available for patent infringement. It would have enabled the reference product sponsor to bring suit on all challenged patents and provided for a stay of FDA approval until patent expiry based on a district court decision of infringement. For these reasons and others, the Eshoo patent provisions were very different from those in the first two Waxman bills and S. 1695.

The bill’s procedure would have begun thirty days after FDA accepted a biosimilar application. By that date: (1) FDA would have had to publish a notice identifying the reference product cited in the application and a contact person for the biosimilar applicant to receive patent notices; and (2) the applicant would have had to provide the reference product sponsor a copy of the application and “information” concerning the biosimilar product and its production, including a “detailed” description of the biosimilar and the methods and materials used in manufacturing it.⁸⁶⁶ The reference product sponsor was required to identify one or more persons to receive this confidential information from the applicant, and those individuals would have been required to execute confidentiality agreements in accordance with FDA regulations that were to require recipients of the information to take “reasonable steps” to maintain its confidentiality and “use the information solely for the purposes authorized under” proposed section 351(l) of the PHSA.⁸⁶⁷

Within sixty days of receiving this information, the reference product sponsor would have been required to provide the applicant a list of “relevant patents” in which it had an interest.⁸⁶⁸ At an unspecified time, the reference product sponsor would have had to explain in writing why it believed the patents in question would be infringed by commercial marketing or use of the biosimilar.⁸⁶⁹ “Relevant patent” was defined to mean any patent expiring after the data exclusivity period for the reference product that could reasonably be asserted against the applicant based on commercial use or sale of the biosimilar product or materials used in its manufacture.⁸⁷⁰ An interested third party could have provided the applicant notice that it owned or had rights to potentially relevant patent(s) “[a]t any time” after FDA published notice of the application’s filing.⁸⁷¹ The individual to receive the information for the interested third party would be required to execute a confidentiality agreement in accordance with the FDA regulations described

⁸⁶⁴ *Id.* (proposed PHSA § 351(l)(1)).

⁸⁶⁵ *Id.* (proposed PHSA § 351(l)(1)(D)).

⁸⁶⁶ *Id.* (proposed PHSA § 351(l)(3) & (4)(A)(i)).

⁸⁶⁷ *Id.* (proposed PHSA § 351(l)(2)).

⁸⁶⁸ *Id.* (proposed PHSA § 351(l)(4)(A)(ii) & (4)(C)). This list would have had to be updated within thirty days if a new patent issued to, or interest in a patent was newly acquired by, the reference product sponsor. *Id.* (proposed PHSA § 351(l)(4)(A)(iii)). The same rule would have applied to interested third parties. *Id.* (proposed PHSA § 351(l)(4)(B)(iv)).

⁸⁶⁹ *Id.* (proposed PHSA § 351(l)(4)(C)).

⁸⁷⁰ *Id.* (proposed PHSA § 351(l)(1)(B)).

⁸⁷¹ *Id.* (proposed PHSA § 351(l)(4)(B)(i)).

in the previous paragraph.⁸⁷² The applicant would have been required to provide the application and information to the third party's designated recipient within thirty days of receiving the notice, and the interested third party would have had ninety additional days to provide the applicant a list of relevant patents that it owned or with respect to which it had the right to commence or participate in infringement litigation.⁸⁷³ At some time not specified in the bill, the reference product sponsor also would have had to explain to the applicant why it believed the identified patents would be infringed by commercial marketing or use of the biosimilar.⁸⁷⁴

Within forty-five days of the date on which the sponsor or third party identified the relevant patents, the applicant would have been required to reply with a certification about each identified patent, either: (1) stating that it did not intend to launch the biosimilar until expiry of the patent and had requested FDA not approve the biosimilar application until that date, or (2) explaining the basis for its belief that the patent was invalid, unenforceable, or not infringed.⁸⁷⁵ Submission of the latter certification (a paragraph (4)(D)(ii) certification) would have constituted an act of patent infringement,⁸⁷⁶ giving rise to federal court jurisdiction for litigation of the patent issues.

The bill did not require premarket patent litigation. If, however, the reference product sponsor or interested third party initiated litigation within sixty days of receiving a paragraph (4)(D)(ii) certification and the district court found a patent infringed prior to expiry of the data exclusivity period (including any applicable extension for a new indication or pediatric research), FDA could not have approved the application until the relevant patent had expired.⁸⁷⁷ The applicant could not have brought a declaratory judgment action regarding a patent subject to a paragraph (4)(D)(ii) certification until the later of the date: (1) three years before expiry of the data exclusivity period; or (2) 120 days after the paragraph (4)(D)(ii) certification was provided.⁸⁷⁸

After introduction of the first Eshoo bill, GPhA issued a press release calling the bill "a pathway to the wrong destination."⁸⁷⁹ In particular, GPhA opposed the data exclusivity provisions of H.R. 5629, which it called "unjustifiable."⁸⁸⁰ GPhA called for a compromise like that resulting in the Hatch-Waxman amendments, which provided, in GPhA's view, "a reasonable five-year period of market exclusivity for novel medicines . . ."⁸⁸¹ GPhA reiterated its support for the second Waxman bill in the press release.⁸⁸²

In contrast, BIO wrote to Representatives Eshoo and Barton to "offer [its] support" for the bill.⁸⁸³ BIO noted that H.R. 5629 reflected "the need for clinical trial evidence and data, including immunogenicity testing" and would have "protect[ed] patients by only allowing a [biosimilar] to be approved as interchangeable with its reference product if [FDA], through final guidance, expressly permit[ted] interchangeability for a specific class of products."⁸⁸⁴ BIO also supported the bill's approach to naming, because it would have "ensure[d] that a [biosimilar] will have a non-proprietary name readily distinguish-

⁸⁷² *Id.*

⁸⁷³ *Id.* (proposed PHSA § 351(l)(4)(B)(iii)).

⁸⁷⁴ *Id.* (proposed PHSA § 351(l)(4)(C)).

⁸⁷⁵ *Id.* (proposed PHSA § 351(l)(4)(D)).

⁸⁷⁶ *Id.* § 201(3) (proposed 35 U.S.C. § 271(e)(2)(C)).

⁸⁷⁷ *Id.* § 101(a)(2) (proposed PHSA § 351(l)(5)).

⁸⁷⁸ *Id.* (proposed PHSA § 351(l)(6)).

⁸⁷⁹ Press Release, GPhA, GPhA Statement on Reps. Eshoo-Barton Biologics Bill (Mar. 14, 2008), available at <http://www.gphaonline.org/media/press-releases/2009/02/12/gpha-statement-reps-eshoo-barton-biologics-bill>.

⁸⁸⁰ *Id.*

⁸⁸¹ *Id.*

⁸⁸² *Id.*

⁸⁸³ Letter from James C. Greenwood, President & Chief Executive Officer, BIO, to Reps. Eshoo & Barton, at 1 (May 9, 2008).

⁸⁸⁴ *Id.* at 2.

able from that of the innovative product, to avoid confusion and inadvertent substitution without patient and physician knowledge.”⁸⁸⁵ BIO reiterated its “belie[ff] that a 14-year period of exclusivity is necessary” and noted that H.R. 5629 provided for up to fourteen-and-a-half years of exclusivity.⁸⁸⁶ Finally, BIO praised the bill’s “balanced procedure for the resolution of patent-related disputes . . . [that made] it likely that such disputes [could] fairly be resolved prior to [biosimilar] market-entry”⁸⁸⁷ According to BIO, these “mechanisms will serve to protect the intellectual property rights of innovators and other third parties such as academic institutions.”⁸⁸⁸

2. Energy and Commerce Questions and FDA Letter

On April 3, 2008, Representatives Pallone and Deal sent a letter to thirty-five stakeholders requesting input on specific topics regarding biosimilars legislation, including safety, regulatory process, interchangeability, patents, and exclusivity.⁸⁸⁹ Responses came from thirty stakeholders, including trade associations BIO, PhRMA, and GPhA, as well as federal agencies the FTC and FDA.⁸⁹⁰ On the whole, stakeholders took positions generally consistent with their previously articulated points of view. The most significant response was filed by then FDA Principal Deputy Commissioner and Chief Scientist Frank Torti in September 2008 but apparently not made public by Representative Pallone until the week of January 12, 2009.⁸⁹¹ This response was consistent with, and in some places used the same language as, the June 2007 Leavitt letter.

Specifically, the Torti letter and the Leavitt letter took similar positions on the need for clinical and immunogenicity data⁸⁹²; naming⁸⁹³; applying the new pathway to FDCA proteins⁸⁹⁴; requiring guidance development prior to FDA action on biosimilar applications⁸⁹⁵; and data exclusivity.⁸⁹⁶ Both concluded, for example, that legislation should not at this time allow for interchangeability determinations and that a patient should

⁸⁸⁵ *Id.*

⁸⁸⁶ *Id.*

⁸⁸⁷ *Id.* at 3.

⁸⁸⁸ *Id.*

⁸⁸⁹ Letter of Frank J. Pallone, Chairman of the Subcommittee of Health, H. Comm. on Energy & Commerce & Nathan Deal, Ranking Member, Comm. on Energy & Commerce (Apr. 3, 2008), available at http://energycommerce.house.gov/Press_110/110-ltr.040308.list.Biologic%20ltr.pdf; see also Pallone, Deal Circulate Far-Reaching Biogenics Questionnaire, FDA WEEK, Apr. 11, 2008.

⁸⁹⁰ H. Comm. on Energy & Commerce, *Responses to April 3, 2008 letter to 35 groups in regard to generic versions of biologic products*, http://energycommerce.house.gov/Press_110/040308.FOB.Responses.shtml (last visited Aug. 27, 2010).

⁸⁹¹ *FDA Follow-On Biologics Letter Creates Hurdle for Obama Administration*, THE PINK SHEET, Jan. 19, 2009, at 7.

⁸⁹² Letter of Frank M. Torti, M.D., M.P.H., to Rep. Pallone, Chairman, Subcomm. On Health, H. Comm. On Energy & Commerce, (Sept. 18, 2008) (Torti Letter), at 2, 5 (stating that the legislation should require clinical and immunogenicity data but provide FDA the discretion to specify the type and content in specific cases, using a public process).

⁸⁹³ *Id.* at 3 (stating that unique names should be required). Unlike the Leavitt letter, the Torti letter did not state that a biological product’s labeling should indicate whether the product had been deemed interchangeable with any other product. See *supra* note 779.

⁸⁹⁴ Torti Letter, at 7 (noting that there could be “significant regulatory implications” associated with applying the new pathway to FDCA proteins and that FDA was still considering these implications).

⁸⁹⁵ *Id.* at 8 (noting that requiring a public product class guidance process prior to action on biosimilar applications “would be beneficial”).

⁸⁹⁶ *Id.* at 11 (stating that innovators should be eligible for a significant period of data exclusivity “independent from any patent protections” and should receive an additional exclusivity period based on a supplement for a new indication requiring new clinical studies (other than bioavailability studies)). FDA did not take a position on the design of legislative provisions regarding the exchange of patent information; the agency did note, however, that FDA’s ministerial role in the patent listing process under the Hatch-Waxman amendments sometimes “embroil[ed] the [a]gency in litigation.” *Id.* at 12.

not be switched to a biosimilar unless the switch was directed by the prescriber.⁸⁹⁷ The Torti letter also stated that, in the future, an interchangeability designation “would be based on, among other things, a showing of similar relevant structural characteristics between the two products, an understanding of the structure-function relationships, and clinical data evaluating the impact of switching patients from one product to the other,” and possibly a requirement for standards to ensure interchangeability over the products’ lifetimes.⁸⁹⁸

FDA’s position in the Torti letter seemed to differ in one key respect from the position taken in the Leavitt letter of June 2007. With respect to the question whether a demonstration of biosimilarity regarding one reference product indication should suffice for licensure for all reference product indications (the extrapolation question), the Torti letter stated that the amount of indication-specific clinical data “will depend on a number of factors,” including, for example, the level of understanding of the biosimilar’s mechanism of action.⁸⁹⁹ The Leavitt letter had stated that biosimilarity should be shown for each condition of use.⁹⁰⁰

The Torti letter was considered by some trade press to “take[] several positions favored by biotech manufacturers.”⁹⁰¹ This trade press characterized the Torti letter as presenting a “hurdle” for the incoming Obama Administration given “the heft of having [been signed by] FDA’s chief scientist” and the need for new leadership of the agency to devote time and resources “to develop a formal response to the letter in an effort to refute its findings.”⁹⁰²

Both innovative and generic stakeholders filed comments generally reflecting the positions they had previously taken with respect to both regulatory and intellectual property issues. Innovators, for example, continued to favor a statutory requirement for clinical work and, in particular, an immunogenicity assessment. For example, BIO stated “[c]linical trial data are fundamental for evaluating the safety and effectiveness of a [biosimilar] and must be required as part of the approval process for such products.”⁹⁰³ Johnson & Johnson took the position that “an immunogenicity assessment should be required in any premarket approval package” for a biosimilar,⁹⁰⁴ a viewpoint consistent with the testimony of Dr. Siegel at the 2007 hearing.⁹⁰⁵ In accord with its previous positions, GPhA stated that “[t]he need for testing of a [biosimilar], including immunogenicity studies, should be decided by FDA on a case-by-case basis based on the latest scientific knowledge.”⁹⁰⁶ Other generic stakeholders, such as Barr, agreed.⁹⁰⁷

⁸⁹⁷ *Id.* at 9.

⁸⁹⁸ *Id.* at 9-10. The Torti letter did not state that a biosimilar applicant should be required to show interchangeability with both the reference product and any other product licensed as biosimilar to that reference product, as the Leavitt letter had. *See supra* note 777.

⁸⁹⁹ Torti Letter, at 2.

⁹⁰⁰ *See supra* note 774.

⁹⁰¹ *FDA Follow-On Biologics Letter Creates Hurdle for Obama Administration*, THE PINK SHEET, Jan. 19, 2009, at 7.

⁹⁰² *Id.*

⁹⁰³ BIO Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 6 (May 2, 2008).

⁹⁰⁴ Johnson & Johnson, Responses to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 3-4 (Apr. 28, 2008).

⁹⁰⁵ Siegel Testimony, at 18 (“[C]linical studies to address questions such as immunogenicity, pharmacokinetics, and common adverse events under controlled conditions will always be important before a product is marketed.”).

⁹⁰⁶ GPhA Response to House Energy & Commerce Committee Questionnaire on Biogenics 1 (May 6, 2008).

⁹⁰⁷ Written Responses From Barr Pharmaceuticals, Inc. 1 (May 2, 2008) (“FDA must be given the authority to determine on a case-by-case basis whether immunogenicity studies are needed for generic biologics and, if studies are needed, the discretion to decide what types of studies should be conducted. Indeed, FDA should have the authority to determine what types of studies in general are necessary and appropriate when evaluating generic biologic applications”); *see id.* at 4.

Consistent with its support of H.R. 5629, BIO called for the agency to adopt “guidance [that is] specific to a particular product or product group” and asked that “the guidance-development process be conducted prior to [biosimilar] approvals.”⁹⁰⁸ PhRMA and individual innovative companies agreed.⁹⁰⁹ As before, many generic companies opposed any requirement that guidance or regulations be completed before agency action on biosimilar applications.⁹¹⁰ Also as before, innovators generally stated that existing science did not permit interchangeability determinations for biologics and favored distinctive nonproprietary names for biosimilars.⁹¹¹ GPhA restated its positions that: (1) “interchangeability decisions are a reality for some biopharmaceuticals and the numbers will increase over the next five to ten years,” and (2) “[t]here should be no statutory requirement for separate and distinct names for biogenerics.”⁹¹²

With respect to intellectual property issues, stakeholders on the whole expressed views consistent with their previous positions. For example, BIO again stated its “belie[f] that a 14-year period of data exclusivity should be granted for biologics in any [biosimilars] regime,”⁹¹³ and many individual innovators agreed.⁹¹⁴ BIO’s comments on patent provisions were consistent with its support of H.R. 1548.⁹¹⁵ Novartis again stated that “[t]here is no need to couple [the regulatory review and approval processes

⁹⁰⁸ BIO Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 9 (May 2, 2008).

⁹⁰⁹ See, e.g., PhRMA, Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 10-11 (May 2, 2008) (“As the Secretary of [HHS] has stated, a requirement that FDA issue product-specific guidance before acting on [biosimilar] applications will help ‘ensure the agency has optimum information regarding safety and effectiveness considerations for [biosimilars]; enhance transparency of decision making; establish a level-playing field for all [biosimilar] applicants; and encourage [biosimilar] applications by describing [a]gency expectations for application content.’”) (citing Leavitt letter, *supra* note 767, at 3); Johnson & Johnson, Responses to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 12 (Apr. 28, 2008) (“It is critical for public confidence and to ensure patient safety that regulations and guidance be in place prior to FDA approving applications to ensure a consistent and transparent standard is applied and we do not end up with two tiers of products with respect to public confidence and risk.”).

⁹¹⁰ See, e.g., Written Responses From Barr Pharmaceuticals, Inc. 6 (May 2, 2008) (“FDA . . . should not be required to issue guidances or promulgate regulations before accepting, reviewing, or acting on generic applications. As is the case for brand products, the use of guidances or regulations for generic products should be left entirely to FDA’s discretion.”).

⁹¹¹ See, e.g., BIO Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 11 (May 2, 2008) (“[T]he current state of science does not support substitutability for biologics.”); *id.* (“BIO believes that, consistent with the policies of EMEA and many European countries, patients should not be dispensed follow-on biologics unless expressly prescribed by a physician.”); *id.* at 4 (“[Biosimilars] should be required by statute to have non-proprietary names that are readily distinguishable from those of the innovator products, and to be prescribed using those distinct names.”).

⁹¹² GPhA Response to House Energy & Commerce Committee Questionnaire on Biogenerics 3, 9 (May 6, 2008) (emphasis in original).

⁹¹³ BIO Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 15 (May 2, 2008).

⁹¹⁴ See, e.g., Johnson & Johnson Responses to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 25 (Apr. 28, 2008) (“Ideally, therefore, the period of data protection for biotechnology innovators should equal the period of market exclusivity contemplated by Congress under the patent term restoration provisions of the Hatch-Waxman amendments, *i.e.*, 14 years.”).

⁹¹⁵ See BIO Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 15-16 (May 2, 2008). In November 2008, Eli Lilly announced that it was proposing a framework in which innovators could choose between a data exclusivity period and patent protection within the first four years that a product is on the market. See *Lilly Proposes Forfeiting Biologics Patents If Exclusivity Sufficient*, FDA WEEK, NOV. 28, 2008.

for biosimilars] to any of the Title 35 patent rights” and indicated its preference for a system in which, “immediately subsequent to the FDA issuing the license for a [biosimilar], the reference product holder is given notice of . . . 45 or 90 days in which to initiate suit,” if it believes it has patents infringed, during which the applicant “will not launch [the biosimilar].”⁹¹⁶ With respect to data exclusivity, Novartis stated “a minimum of 12 years of exclusivity is essential and there may be sound arguments for more.”⁹¹⁷ GPhA supported a data exclusivity period of, at most, five years,⁹¹⁸ while Barr reiterated that it had not “seen [any] actual evidence demonstrating that branded biologic companies need any additional incentives, let alone greater incentives than traditional drug companies receive under Hatch-Waxman.”⁹¹⁹ GPhA’s statements on the patent provisions were generally consistent with its previous support for the second Waxman bill,⁹²⁰ and Barr’s patent comments generally were consistent with Mr. Downey’s prior testimony on these issues.⁹²¹

The FTC also submitted comments to Representatives Pallone and Deal regarding intellectual property provisions for biosimilars legislation. It did not comment on an appropriate length for the data exclusivity period but did state that the legislation “should ensure that a branded biologics company may not obtain multiple lengthy exclusivity periods for minor, non-clinically significant changes to its products.”⁹²² It added that “[a] pre-marketing patent litigation process can create consumer benefits by enabling [biosimilar] applicants to enter the market sooner than they otherwise would by allowing early resolution of patent litigation.”⁹²³ According to the Commission, “the more complicated the pre-marketing patent litigation system, the greater the chance that the system may be gamed or may result in competitive consequences unforeseen at the time the legislation is enacted.”⁹²⁴ It added that “[a] system of premarketing patent litigation that is simple and transparent is less likely to result in competitive harm. Such a system could involve private exchange of patent information . . . [or] publication of relevant patents at the FDA or otherwise in a public forum.”⁹²⁵ A little over a year later, the FTC would release a report concluding that “[s]pecial procedures, providing an early start to resolving patent disputes between pioneer and [biosimilar] manufacturers prior to FDA [biosimilar] approval, are not necessary” and are “likely to lead to consumer harm, including the facilitation of anticompetitive conduct that defeats the purpose of starting the patent litigation early.”⁹²⁶

3. Reporting of S. 1695 by HELP Committee in November 2008

On November 19, 2008, the Senate HELP Committee reported S. 1695, amended as reflected in the 7721 Draft.⁹²⁷ No committee report accompanied the reported

⁹¹⁶ Novartis Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 26-27 (May 1, 2008).

⁹¹⁷ *Id.* at 30.

⁹¹⁸ GPhA Response to House Energy & Commerce Committee Questionnaire on Biogenics 14, 18 (May 6, 2008).

⁹¹⁹ See Written Responses From Barr Pharmaceuticals, Inc. 13 (May 2, 2008).

⁹²⁰ See GPhA Response to House Energy & Commerce Committee Questionnaire on Biogenics 16 (May 6, 2008).

⁹²¹ See Written Responses From Barr Pharmaceuticals, Inc. 10-11 (May 2, 2008).

⁹²² Letter from C. Landis Plummer, Acting Sec’y, FTC, to Rep. Pallone 9 (May 2, 2008).

⁹²³ *Id.* at 6.

⁹²⁴ *Id.* at 9.

⁹²⁵ *Id.*

⁹²⁶ FEDERAL TRADE COMMISSION, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (June 2009) (FTC Report), at viii, 48.

⁹²⁷ S. 1695, 110th Cong. (as reported by the S. Comm. on Health, Education, Labor, and Pensions, Nov. 19, 2008). The reported language is identical to the language circulated with a file stamp of O:\KER\KER08523.xml.

bill, which was considered unusual.⁹²⁸ In addition, some considered the timing of this action to be “curious.”⁹²⁹ The trade press speculated that there might be some interest in attaching the bill to the automotive bailout package in December 2008, or that it might be attached to the health care reform in the following Congress, which ultimately proved to be correct.⁹³⁰

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In 2009, the length and applicability of the data exclusivity period — including with respect to second generation products — were the primary focus of negotiations in both the House and Senate. In February, the Administration released its Fiscal Year 2010 budget proposal. As part of the President’s message section of that budget proposal, President Obama stated that “the Administration will accelerate access to make affordable generic biologic drugs available through the establishment of a workable regulatory, scientific, and legal pathway for generic versions of biologic drugs.”⁹³¹ According to President Obama, this pathway would have an exclusivity period “generally consistent with the principles in the Hatch-Waxman law” but that “prohibit[ed] . . . ‘ever-greening.’”⁹³² In March, Representatives Waxman and Eshoo again introduced competing bills in the House. Although Representative Eshoo’s second bill (initially co-sponsored by forty-three others) was largely the same as her first, Representative Waxman’s bill, co-sponsored by Representatives Pallone, Deal, and Emerson (R-MO) was substantially different from his second bill.

The Senate HELP Committee circulated revised draft language on data exclusivity in March and June, but no bill was introduced during those months. In July, Senator Kennedy inserted his new proposal, with a tiered data exclusivity structure offering up to nine years of exclusivity, as a placeholder into the HELP Committee’s health care reform legislation. The Committee voted to pass an amendment offered by Senators Hatch, Enzi, and Kay Hagan (D-NC), which was nearly identical to S. 1695 as reported but with new “first licensure” language. Pediatric exclusivity was added when the HELP-passed bill was consolidated with the bill that the Senate Finance Committee passed.⁹³³ The consolidated health care reform package, known as the Patient Protection and Affordable Care Act (PPACA), was drafted as an amendment (Amendment 2786) in the nature of a substitute to H.R. 3590. The PPACA passed in the Senate on December 24, 2009 following amendments not affecting the biosimilars language.⁹³⁴

Representative Eshoo then modified her bill to largely copy the regulatory provisions of the Hatch/Enzi/Hagan amendment while retaining her patent litigation provisions, and she offered this version as an amendment to health care reform legislation during the Energy and Commerce markup. Representative Waxman

⁹²⁸ See *Senate Biosimilars Bill Reported 1 1/2 Years After Committee Passed It*, FDA WEEK, Nov. 28, 2008.

⁹²⁹ *Id.*

⁹³⁰ *Id.*

⁹³¹ OFFICE OF MANAGEMENT AND BUDGET, A NEW ERA OF RESPONSIBILITY: RENEWING AMERICA’S PROMISE 28 (Feb. 26, 2009).

⁹³² *Id.*

⁹³³ Amendment No. 2786 in the Nature of a Substitute to H.R. 3590 intended to be proposed by Mr. Reid, Title VII, Subtitle A, 155 Cong. Rec. S11607, S11794-S11799 (daily ed. Nov. 19, 2009); Senate Unveils Consolidated Health Care Reform Bill, Health Care Lawyer Blog (Nov. 19, 2009), http://www.healthcarelawyerblog.com/2009/11/senate_unveils_consolidated_he.html (last visited Aug. 25, 2010).

⁹³⁴ H.R. 3590, 111th Cong., Title VII, Subtitle A (as passed by Senate Dec. 24, 2009).

was then Chairman of the Energy and Commerce Committee, and his bill was also under consideration by the Committee. The Eshoo amendment passed the Committee, and it was included in the House health care reform bill that passed the House on November 7, 2009.

1. *Second Eshoo Bill*

Representative Eshoo made three substantive changes to her bill before re-introducing it as H.R. 1548 (or “the second Eshoo bill”).⁹³⁵ First, she modified the requirements for demonstrating interchangeability for products administered more than once to an individual. The second Eshoo bill required the applicant to show that risk of switching a patient between the biosimilar and reference product — in terms of safety, diminished efficacy, and reduced or enhanced potency — was no greater than the risk of exclusively using the reference product.⁹³⁶ The first Eshoo bill had not included the “reduced or enhanced potency” language.⁹³⁷ Second, H.R. 1548 contained a new provision stating that “[n]othing in [section 351(k) of the PHSA] shall be construed as preempting or otherwise affecting the authority of a State to require or regulate prescriptions.”⁹³⁸ Third, the select agent and toxins provision from the first Eshoo bill had been modified. The first bill had prohibited licensure of biosimilar versions of products containing select agents or toxins. The second bill precluded FDA from licensing such a product prior to consultation with appropriate national security and drug enforcement agencies and a determination that there would be no increased risk to the health or security of the public from licensing the biosimilar.⁹³⁹

2. *Third Waxman Bill*

Although the patent provisions in the third Waxman bill were similar to the patent provisions in the first two Waxman bills, its regulatory and exclusivity provisions were quite different.⁹⁴⁰ The third bill used, for the first time, the term “biosimilar” rather than the term “comparable.”⁹⁴¹ A proposed product would be biosimilar to its reference product if “no clinically meaningful differences” between the products “would be expected in terms of the safety, purity, and potency if treatment were to be initiated with” the proposed product instead of the reference product.⁹⁴² The previous Waxman bills had stated that a biosimilar would be comparable to its reference product in the “absence of clinically meaningful differences . . . in terms of the safety, purity, and potency.”⁹⁴³ The new language was criticized on the ground

⁹³⁵ H.R. 1548, 111th Cong. (2009).

⁹³⁶ *Id.* § 101(a)(2) (proposed PHSA § 351(k)(4)(A)(ii)).

⁹³⁷ See H.R. 5629 § 101(a)(2) (proposed PHSA § 351(k)(4)(A)(ii)) (“for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”).

⁹³⁸ H.R. 1548 § 101(a)(2) (proposed PHSA § 351(k)(4)(C)).

⁹³⁹ *Id.* (proposed PHSA § 351(k)(5)(D)). According to one trade press account, this change was made to reverse unintended protections for Botox. See *Eshoo-Barton Biosimilars Bill Drops Unintended Botox Protection*, FDA WEEK, Mar. 13, 2009.

⁹⁴⁰ H.R. 1427, 111th Cong. (2009). Senator Schumer introduced identical legislation in the Senate on March 26, 2009. S. 726, 111th Cong. (2009).

⁹⁴¹ See generally H.R. 1427.

⁹⁴² *Id.* § 3(a)(2) (proposed PHSA § 351(k)(1)).

⁹⁴³ H.R. 6257 § 2(2) (proposed PHSA § 351(i)(4)).

that it would preclude clinical trials in patients who had already received the reference product. For clinical trials in orphan populations, recruitment of sufficient numbers of subjects is already challenging, and a bar on enrolling patients who had received the reference product would increase this challenge.⁹⁴⁴

Like the first two Waxman bills, H.R. 1427 proposed two licensure pathways. The first pathway — proposed section 351(k)(3) of the PHSA — was for biosimilar products meeting certain requirements, such as the requirement that its molecular structural features be highly similar to those of the reference product. The second pathway — proposed section 351(k)(4) of the PHSA⁹⁴⁵ — again seemed to have been modeled on FDA’s interpretation of section 505(b)(2) of the FDCA and was for biologics that “differ[ed] from, or incorporate[d] a change to, the reference product,” provided the application contained enough information to show the product’s safety, purity, and potency.⁹⁴⁶ The first and second Waxman bills had required that this showing be made “relative to the reference product,” but the third Waxman bill omitted this requirement.⁹⁴⁷

a. *Changes to Regulatory Provisions*

There were six key differences between the regulatory provisions of the third Waxman bill and the regulatory provisions of the previous Waxman bills. First, the third Waxman bill would have permitted biosimilar versions of products approved under the FDCA,⁹⁴⁸ whereas the previous bills had permitted biosimilar versions of only biologics licensed under the PHSA.⁹⁴⁹ Second, the new bill omitted the provision, seemingly modeled on the orphan drug regulations, that would have deemed certain proposed products comparable as a matter of law — for example, products that had differences in amino acid sequence.⁹⁵⁰ This language was placed in the data exclusivity provision of the third Waxman bill and served a different purpose. Third, the bill was changed to mandate that a biosimilar have the same mechanism of action as its reference product to the extent that mechanism of action: (1) was known; or (2) reasonably could be determined.⁹⁵¹ The first two bills had not addressed the situation where the mechanism of action could reasonably be determined.⁹⁵²

Fourth, the provisions related to extrapolation of indications were changed. These provisions applied when an applicant wished to show interchangeability for one reference product indication and rely on that showing to obtain an interchangeability determination for other reference product indications having the same mechanism of action. Under the third Waxman bill, this applicant would have

⁹⁴⁴ See *NORD Seeks Minor Fix to Ease Trial Costs in Waxman Biosimilars Bill*, FDA WEEK, Mar. 20, 2009.

⁹⁴⁵ H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(3) & (4)). While the first two bills required the biosimilar to have “highly similar principal molecular structural features,” the word “principal” was dropped in the third bill version. Compare *id.* (proposed PHSA § 351(k)(3)(A)) with *supra* note 363 and accompanying text. The qualifier to this language— “notwithstanding minor differences in heterogeneity profile, impurities, or degradation patterns”—was retained in the third Waxman bill. H.R. 1427, § 3(a)(2) (proposed PHSA § 351(k)(3)(A)).

⁹⁴⁶ *Id.* (proposed PHSA § 351(k)(4)).

⁹⁴⁷ See *supra* note 355 and accompanying text.

⁹⁴⁸ H.R. 1427 § 2(a)(2) (proposed PHSA § 351(i)(2)).

⁹⁴⁹ See *supra* note 358 and accompanying text.

⁹⁵⁰ See H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(3)); see *supra* notes 365–368 and accompanying text.

⁹⁵¹ H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(3)(C) & (5)(A)(iii)).

⁹⁵² See *supra* note 373 and accompanying text.

been required to submit information showing the extrapolation was “scientifically appropriate.”⁹⁵³ FDA would have been required to license the biosimilar for any additional indications with the same mechanism of action, unless the information available was “insufficient” to show that the biosimilar was safe, pure, and potent for the additional condition(s) of use.⁹⁵⁴ The previous bills did not contain this submission requirement or exception from extrapolation.⁹⁵⁵ Fifth, the third Waxman bill included new language providing that FDA could consult “information in the application for the reference product” in approving section 351(k)(3) and 351(k)(4) applications.⁹⁵⁶ The first two Waxman bills had instead provided that the applicant could submit any information, “including publicly-available information,” in the application.⁹⁵⁷ Finally, unlike the first two Waxman bills, the third Waxman bill did not prohibit FDA from requiring a postmarketing study of a biosimilar as a condition of approval.⁹⁵⁸

b. *Changes to Interchangeability Provisions*

The third Waxman bill took a new approach to interchangeability. In this bill, “interchangeability” for a single use product was defined to mean that the proposed product was biosimilar to the reference product.⁹⁵⁹ In other words, no additional showing beyond biosimilarity would have been required. For a product administered more than once to a given patient to be deemed interchangeable, the applicant would have needed to show that a patient could be switched between the products one or more times “without an expected increase in the risk of adverse events, including a clinically significant change in immunogenicity, or diminished effectiveness.”⁹⁶⁰

c. *Data Exclusivity*

The third Waxman bill proposed tiered data exclusivity; the period could be five or three years, depending on the circumstances.⁹⁶¹ Specifically, a reference product generally would have received the five-year period if four conditions were met: (1) the reference product had been licensed pursuant to a BLA submitted under section 351(a) of the PHSA; (2) no “major substance” of the innovative product, and no highly similar major substance, had been licensed pursuant to another section 351(a) application; (3) the reference product BLA had been approved after enactment of section 351(k); and (4) the reference product BLA “could not and did not rely on” a clinical safety, purity, or potency study described in any other application approved under section 351 of the PHSA or any clinical safety or effectiveness study described in an approved NDA.⁹⁶²

The bill did not define the term “major substance.” Certain products — *e.g.*, one with a “minor difference[] in amino acid sequence” from a previously licensed product — were excluded as a matter of law from receiving the five-year exclusivity

⁹⁵³ H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(3)(C)).

⁹⁵⁴ *Id.* (proposed PHSA § 351(k)(5)(A)(iv)).

⁹⁵⁵ *See supra* notes 369-370 and accompanying text.

⁹⁵⁶ H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(5)(A) & (7)).

⁹⁵⁷ *See supra* note 375 and accompanying text.

⁹⁵⁸ *See generally* H.R. 1427 § 3(a)(2); *see supra* note 362 and accompanying text.

⁹⁵⁹ H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(2)(A)).

⁹⁶⁰ *Id.* (proposed PHSA § 351(k)(2)(B)).

⁹⁶¹ *Id.* (proposed PHSA § 351(k)(10)).

⁹⁶² *Id.* (proposed PHSA § 351(k)(10)(B)).

period.⁹⁶³ The list of exclusions again seemed to have been drawn from the similar list in FDA's regulations implementing the Orphan Drug Act.⁹⁶⁴ As noted, the previous Waxman bills used the same list to describe products that were deemed comparable as a matter of law.⁹⁶⁵ Like the first and second Waxman bills, the third Waxman bill used the Orphan Drug regulation list for a new purpose unrelated to the purpose for which they were originally drafted. As noted earlier, the orphan drug regulations provide that a biological product's orphan exclusivity blocks for seven years licensure of any subsequent biological product that satisfies a criterion in the list.⁹⁶⁶ The third Waxman bill provided that any reference product that satisfied a criterion (e.g., differed from a previously licensed reference product due to minor differences in amino acid sequence) would be excluded from five-year exclusivity.⁹⁶⁷ FDA also could have designated, by regulation, additional products not eligible for five-year exclusivity.⁹⁶⁸

Three-year exclusivity was the alternative to five-year exclusivity, although some reference products would get neither. A reference product would have been entitled to three years of exclusivity if: (1) it was licensed pursuant to a BLA submitted under section 351(a) of the PHSA; (2) the product contained a "major substance" that had been previously licensed on the basis of a 351(a) application, or a major substance highly similar to that of a previously licensed product; (3) it was licensed after enactment of section 351(k); (4) the BLA contained reports of new clinical investigations, other than pharmacokinetic or pharmacodynamic studies, essential to its approval and conducted or sponsored by the applicant; and (5) the product represented a "significant therapeutic advance."⁹⁶⁹ The third Waxman bill contained no transitional provisions for products licensed prior to enactment. The Hatch-Waxman amendments had included special transition provisions that applied to products approved between 1982 and 1984.⁹⁷⁰

The requirement of a "significant therapeutic advance" and the exclusion of products supported only by pharmacodynamic and pharmacokinetic data meant that this three-year exclusivity provision was narrower than the corresponding provision in the FDCA.⁹⁷¹ In another respect, however, the provision was like three-year exclusivity in the Hatch-Waxman amendments; it offered the exclusivity only

⁹⁶³ *Id.* (proposed PHSA § 351(k)(10)(B)(ii)). The list was: (1) "[p]rotein biological products that differ in structure solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence"; (2) "[p]olysaccharide biological products with similar saccharide repeating units, even if the number of units differ and even if there are differences in post-polymerization modifications"; (3) glycosylated protein products that differ in structure solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence, and if they had similar saccharide repeating units, even if the number of units differed and even if there were differences in post-polymerization modifications; (4) polynucleotide biological products with identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars); and (5) "[c]losely related, complex partly definable biological products with similar therapeutic intent, such as live viral products for the same indication." *Id.*

⁹⁶⁴ See 21 C.F.R. § 316.3(b)(13)(ii); see also Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).

⁹⁶⁵ See *supra* notes 365-368 and accompanying text.

⁹⁶⁶ See 21 C.F.R. §§ 316.3(b)(13)(ii); 316.31(a).

⁹⁶⁷ H.R. 1427 § 3(a)(2) (proposed PHSA § 351(k)(10)(B)(ii)).

⁹⁶⁸ *Id.* (proposed PHSA § 351(k)(10)(B)).

⁹⁶⁹ *Id.* (proposed PHSA § 351(k)(10)(C)). Approval for a "significant new indication or subpopulation," other than a pediatric subpopulation, was deemed to be a "significant therapeutic advance."

⁹⁷⁰ See *supra* notes 91-92 and accompanying text.

⁹⁷¹ See *supra* note 89 and accompanying text.

for the product's newly licensed conditions of use.⁹⁷² In other words, three-year exclusivity would not have precluded licensure of a biosimilar altogether. It would have prevented licensure of a biosimilar for the conditions of use for which the (second) reference product was licensed.

Under the Third Waxman bill, the five-year and three-year exclusivity periods would be extended by six months if: (1) a supplemental BLA for the reference product was approved more than one year prior to expiry of the period in question; (2) the supplement contained reports of new clinical investigations, other than pharmacokinetic or pharmacodynamic studies, essential to its approval and conducted or sponsored by the applicant; and (3) the change described in the supplement provided a "significant therapeutic advance."⁹⁷³ The supplemental exclusivity period would have been reduced by three months if the combined annual gross sales in the United States for all biological products containing the major substance and owned or marketed by the applicant (or its affiliates) exceeded \$1 billion in the year preceding approval of the supplement.⁹⁷⁴ Only one extension would have been permitted for a reference product.⁹⁷⁵

Six months of pediatric exclusivity also would have been available under H.R. 1427 to extend both the applicable period of data exclusivity (including any extensions) and any applicable period of orphan exclusivity.⁹⁷⁶ This pediatric exclusivity would have been available under essentially the same conditions as under section 505A of the FDCA, *i.e.*, FDA would have had to make a written request for pediatric studies from the reference product sponsor; that company would have needed to complete the studies using appropriate formulations for each age group for which the studies were requested; and FDA would have had to accept the reports of the studies no later than nine months prior to expiry of the period to be extended.⁹⁷⁷ In addition, the third Waxman bill provided that section 505A of the FDCA would have applied to biologics — including biosimilars — "to the same extent and in the same manner" as it applied to drugs approved under the FDCA, "except as inconsistent with [section 351 of the PHSA]."⁹⁷⁸

d. Patent Provisions

The third Waxman bill's patent provisions were similar in basic structure to those in the first and second Waxman bills. Representative Waxman inserted a requirement that the biosimilar applicant notify third party patent owners; required that the BLA holder identify additional types of patents to the biosimilar applicant; and added new venue and declaratory judgment provisions.

Within thirty days of receiving an applicant's request for patent information, the BLA holder would have had to provide notification of the request to the owner of any patent that: (1) the BLA holder identified as "relate[d] to" the reference product; and (2) was licensed to the BLA holder or otherwise under its control.⁹⁷⁹ As in the previous Waxman bills, the BLA holder (not the patent owner, if a different entity) was required to identify to the applicant all patents meeting the "relate[d]

⁹⁷² See *supra* note 89 and accompanying text.

⁹⁷³ H.R. 1427, § 3(a)(2) (proposed PHSA § 351(k)(10)(D)(i)).

⁹⁷⁴ *Id.* (proposed PHSA § 351(k)(10)(D)(ii)).

⁹⁷⁵ *Id.* (proposed PHSA § 351(k)(10)(D)(iii)).

⁹⁷⁶ H.R. 1427 § 4 (proposed PHSA § 351(l)(2) & (3)).

⁹⁷⁷ *Id.* (proposed PHSA § 351(l)(2)-(4)).

⁹⁷⁸ *Id.* (proposed PHSA § 351(l)(1)).

⁹⁷⁹ H.R. 1427, § 3(a)(2) (proposed PHSA § 351(k)(18)(A)(iv)).

to” criterion in response to a request.⁹⁸⁰ The new bill provided that patents meeting this criterion included patents claiming “any method or process that can be used to manufacture such product or component, regardless of whether that method or process [was] used to manufacture the reference product.”⁹⁸¹

The first two Waxman bills had stated that the applicant could have given notice that it intended to challenge any identified patent.⁹⁸² (If the applicant elected to provide such notice, it would have had to provide the notice to the patent holder and the BLA holder.⁹⁸³) The third bill also permitted the applicant to provide a notice, at any time after submitting its application, challenging any other patent owned by, licensed to, or under the control of the BLA holder but not included in the BLA holder’s list.⁹⁸⁴ The list it or lose it provision was modified to apply to all licensees of patents (not just exclusive licensees); previously it had applied only to patent owners.⁹⁸⁵

As noted, the previous Waxman bills would have allowed a BLA holder or patent owner to initiate a patent infringement suit only in a judicial district identified by the applicant.⁹⁸⁶ This provision was struck in the third Waxman bill, and a new venue provision was substituted. Under the new provision, the BLA holder or patent owner could initiate a patent infringement suit in the forum of its choice, but the defendant could move for a transfer on an accelerated basis.⁹⁸⁷ The court could not stay the action pending resolution of the transfer motion, and when ruling on the transfer motion it was required to assign the “greatest weight” to: (1) the court in which the case would be “adjudicated expeditiously,” and (2) the “strong public interest” in prompt resolution of the case so that the biosimilar could “be brought to market as expeditiously as possible, consistent with fair and prompt resolution of patent disputes.”⁹⁸⁸

Finally, under the third Waxman bill’s new declaratory judgment provision, the biosimilar applicant could have brought a declaratory judgment action with respect to any identified patent, if the BLA holder or patent owner: (1) did not bring suit within forty-five days of receiving the applicant’s notice that it planned to challenge the patent; or (2) brought suit but that suit was dismissed without prejudice or was not prosecuted to judgment in good faith.⁹⁸⁹ Like the first two Waxman bills, H.R. 1427 contained a provision stating that neither the BLA holder nor the patent owner could bring a declaratory judgment action with respect to a patent that was not challenged by the applicant in its notice, until the biosimilar applicant began to market its product.⁹⁹⁰

After introduction of the third Waxman and second Eshoo bills, Representative Eshoo began to collect co-sponsors for her bill. In late April, leaders of the New Democrat Coalition⁹⁹¹ voted to endorse the second Eshoo bill.⁹⁹² The trade press

⁹⁸⁰ *Id.* (proposed PHSA § 351(k)(18)(A)(i)).

⁹⁸¹ *Id.* (proposed PHSA § 351(k)(18)(A)(i)).

⁹⁸² *See supra* note 391 and accompanying text.

⁹⁸³ *See supra* note 391.

⁹⁸⁴ H.R. 1427, § 3(a)(2) (proposed PHSA § 351(k)(18)(B)).

⁹⁸⁵ *See id.* § 3(b)(2) (proposed 35 U.S.C. § 271(e)(6)(C)); *see supra* note 400 and accompanying text.

⁹⁸⁶ *See supra* note 396 and accompanying text.

⁹⁸⁷ H.R. 1427, § 3(b)(1) (proposed 28 U.S.C. § 1404(e)).

⁹⁸⁸ *Id.* (proposed 28 U.S.C. § 1404(e)(3)(A) & (B)).

⁹⁸⁹ *Id.* § 3(a)(2) (proposed PHSA § 351(k)(18)(E)).

⁹⁹⁰ *Id.* § 3(a)(2) (proposed PHSA § 351(k)(18)(D)).

⁹⁹¹ The New Democrat Coalition is a Congressional Member Organization comprising Democrats with objectives described as “moderate” and “pro-growth.” New Democrat Coalition, *About the New Democrat Coalition*, http://ndc.crowley.house.gov/index.php?option=com_content&view=article&id=53&Itemid=53 (last visited Aug. 23, 2010).

⁹⁹² Press Release, New Dems Backs [Sic] Eshoo/Inlee Proposal to Create Pathway for Approval of “Follow-On” Biologics (Apr. 23, 2009), available at http://www.house.gov/list/press/pa13_schwartz/Biologics.html.

reported that a Waxman aide said that Representative Waxman was “disappointed” at this development.⁹⁹³ By May 1, the second Eshoo bill had fifty-six co-sponsors, and twelve more were added in June.⁹⁹⁴ On June 8, Representative Waxman sent a letter to President Obama indicating he was “pleased” that the Fiscal Year 2010 Budget included a proposal for a biosimilars pathway.⁹⁹⁵ He also “urge[d] the Administration to consider what steps may be taken under existing authority to prepare and even begin to use a pathway for generic biologics.”⁹⁹⁶

3. *Discussions in the Senate during Spring 2009*

In March 2009, the HELP Committee considered amendments to the bill it had reported in November 2008, including amendments to the first licensure language and the addition of pediatric exclusivity. In late March, the trade press reported that the bill was expected to remain essentially similar to the reported version, because Senators Kennedy and Enzi were “sticking to their original deal”—including the twelve-year exclusivity period, with the first licensure language as the only provision still subject to negotiations.⁹⁹⁷ First licensure language was circulated in late March and in early June.

a. *9127 Draft*

In late March, Senator Kennedy’s staff circulated the first proposal, in the form of a discussion draft containing a new data exclusivity provision to be substituted into the bill. This draft was stamped with the file path “O:\KER\KER09127.xml” and is referred to in this article as the “9127 draft.” This draft would have established two exclusivity rules: one rule for products as to which there was “no original biological product” and a second rule for supplements and for new products as to which there was “an original biological product.”⁹⁹⁸ Products in the first group would have received twelve years of exclusivity.⁹⁹⁹ Data exclusivity for products in the second group would have expired when data exclusivity for the previously licensed product expired.¹⁰⁰⁰ The draft provided that products in the second group would have included those proposed in: (1) any BLA supplement; and (2) any application submitted by the sponsor or manufacturer of a previously licensed product or a “licensor, licensee, predecessor in interest, or other affiliated or related entity,” if the new application proposed “1 or more changes” to the previously licensed product.¹⁰⁰¹ The draft did not define “change,” but provided that the term would have included changes that altered the amino acid sequence, changes that did not alter the amino acid sequence (such as a change resulting in a new indication), and changes to the structure of the previously licensed reference product (including pegylation and glycosylation).¹⁰⁰²

⁹⁹³ *Coalition of Moderate Dems Backs Eshoo Biosimilars Bill*, FDA WEEK, May 1, 2009.

⁹⁹⁴ See Thomas — The Library of Congress Bill Summary & Status, 111th Congress (2009 - 2010), H.R. 1548, Cosponsors, <http://thomas.loc.gov/cgi-bin/bdquery/z?d111:HR01548:@@:@P> (last visited Aug. 16, 2010).

⁹⁹⁵ Letter from Rep. Waxman to President Obama (June 8, 2009), at 1.

⁹⁹⁶ *Id.*

⁹⁹⁷ *Kennedy-Enzi Biosimilars Bill to Retain 12-Year Exclusivity*, FDA WEEK, Mar. 27, 2009.

⁹⁹⁸ See generally Discussion Draft stamped O:\KER\KER09127.xml (2009).

⁹⁹⁹ *Id.* (A)(ii).

¹⁰⁰⁰ *Id.* (B)(i)(II).

¹⁰⁰¹ *Id.* (B)(ii)(I) & (II).

¹⁰⁰² *Id.* (B)(ii)(II)(aa)-(cc).

Pediatric exclusivity language, stamped O:\KER\KER09151.xml, was circulated at the same time. The trade press speculated that “this measure was likely drafted to gain Sen. Christopher Dodd’s [(D-CT)] support” for the bill.¹⁰⁰³ The proposed pediatric exclusivity language — to be codified in section 351(m) — was substantially similar to the pediatric exclusivity language in the third Waxman bill, with two exceptions. First, the HELP proposal would have provided for a six-month extension of the four-year bar on submitting a biosimilar application.¹⁰⁰⁴ The third Waxman bill did not bar submission of applications for a fixed period of time in the first instance, so there was nothing to extend by six months. Second, the draft contained different language regarding the applicability of section 505A of the FDCA to biologics. It provided that certain subsections of section 505A would “apply with respect to the extension of a period under [new section 351(m)] to the same extent and in the same manner as such provisions apply with respect to” a pediatric exclusivity extension under section 505A.¹⁰⁰⁵ Finally, the HELP Committee was “weighing a series of technical corrections” to the bill.¹⁰⁰⁶

b. 9374 Discussion Draft

On June 9, the HELP Committee released its draft health care reform bill with a placeholder for biosimilars language.¹⁰⁰⁷ At about the same time, the HELP Committee staff circulated a full discussion draft of biosimilars provisions, stamped O:\KER\KER09374.xml and referred to in this article as the “9374 Discussion Draft.” The new language was intended to comprise Subtitle A of Title VI of proposed health care reform legislation, so the sections of the bill were re-numbered. The draft was modeled on S. 1695 as reported in November 2008, but there were some significant differences, including three bracketed options for data exclusivity language and the addition of pediatric exclusivity language.

The first bracketed option for data exclusivity, Option A, was identical to the exclusivity language in the 9127 Discussion Draft.¹⁰⁰⁸ Option B was identical to the exclusivity language of S. 1695, as reported.¹⁰⁰⁹ Option C would have provided the same four-year bar on submission of a biosimilar application and twelve-year bar

¹⁰⁰³ *Senators Eye Extra 6 Months Exclusivity for Biologics Tested in Kids*, FDA WEEK, Apr. 17, 2009. Senator Dodd was the original sponsor of the Best Pharmaceuticals for Children Act. See S. 1789, 107th Cong. (2001) (enacted as Pub. L. No: 107-109, 115 Stat. 1408 (2002)); see also S. 838, 107th Cong. (2001).

¹⁰⁰⁴ Draft stamped O:\KER\KER09151.xml __ (a) (proposed PHSA § 351(m)(2)(A) & (3)(A)).

¹⁰⁰⁵ *Id.* (proposed PHSA § 351(m)(1)) (cross-referencing subsections (a), (d), (e), (f), (i), (j), (k), (l), (p), and (q) of section 505A).

¹⁰⁰⁶ *Senate Health Panel Eyes New ‘Evergreening’ Piece of Biosimilars Bill*, FDA WEEK, Apr. 17, 2009.

¹⁰⁰⁷ HELP Committee Draft of the Affordable Health Choices Act, stamped O:\BAI\BAI09A84.xml, Title VI (released June 9, 2009), available at <http://www.amcp.org/content/legislative/pdf/HELP%20Cmte%20Draft%20HCR%20Bill%20Text%206%209%2009.pdf>.

¹⁰⁰⁸ 9374 Discussion Draft § 602(a)(2) (proposed PHSA § 351(k)(7) [OPTION A]). Under this option, only products for which there was no original biological product would receive twelve years of exclusivity. Products as to which there was an original product would be protected by the exclusivity term of that original product. Products in the second group would have been those proposed in: (1) any BLA supplement; and (2) any application submitted by the manufacturer of a previously licensed product or a related entity, if the new application proposed a “change” to the previously licensed product, including a change in amino acid sequence or structure and a change that did not alter the amino acid sequence. *Id.*

¹⁰⁰⁹ 9374 Discussion Draft § 602(a)(2) (proposed PHSA § 351(k)(7) [OPTION B]). Under this option, the date of first licensure would not have included the date of approval of a supplement or a subsequent application for a new indication, route of administration, dosage form, or strength for the previously licensed reference product. *Id.*

on approval as S. 1695, as reported, but it contained a different first licensure provision.¹⁰¹⁰ Specifically, neither the four-year bar on submission nor the twelve-year bar on approval would have applied to: (1) any supplement to a reference product BLA; (2) any “subsequent application filed by the same sponsor or manufacturer of the biological product (or a licensor, licensee, predecessor in interest or other affiliated or related entity)” for either: (a) “a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength”; or (b) “a modification to the structure of the biological product that [did] not result in a change in safety, purity, or potency.”¹⁰¹¹ The discussion draft included pediatric exclusivity language nearly identical to the draft stamped O:\KER\KER09151.xml, as described in the previous section.¹⁰¹²

The 9374 Discussion Draft contained five additional substantive changes and a number of editorial and technical changes. First, the discussion draft included a new provision regarding the implications for substitution under state law of an interchangeability designation. This text would have provided that “nothing in” proposed section 351(k) or 351(i)(3) (the definition of “interchangeable” and “interchangeability”) could have been “construed to limit the extent to which substitution of 1 biological product for another biological product [was] otherwise permitted or restricted under State and local law.”¹⁰¹³

Second, the 9374 Discussion Draft would have amended the definition of “reference product.” This phrase had been previously defined to mean the single biological product licensed under section 351(a) of the PHSA against which the biosimilar would be evaluated. The 9374 Discussion Draft provided that a biological product could be a reference product even if it had been withdrawn from sale unless FDA had: (1) withdrawn or suspended its license for reasons of safety, purity, or potency; (2) published a notice of opportunity for a hearing to withdraw the license for one of these reasons; or (3) determined that the product had been withdrawn from sale for one of these reasons.¹⁰¹⁴

Third, the discussion draft would have modified the list it or lose it provision, which had previously provided that the owner of a patent that was not timely included in the initial listing procedure could not enforce the patent with respect to the biosimilar applicant,¹⁰¹⁵ to provide that an “exclusive licensee” (not just the patent owner) would be subject to this prohibition.¹⁰¹⁶ Fourth, the exclusivity provision for interchangeable biosimilars was amended to state that this exclusivity would not prevent FDA from licensing other products as biosimilar to the reference product.¹⁰¹⁷ In other words, the exclusivity would prohibit FDA only from deeming a subsequent biosimilar as interchangeable. Finally, the language in the patent provisions relating to newly issued or licensed patents would have been modified. Under the reported version of S. 1695, these patents would have been automatically been subject to the second phase of litigation.¹⁰¹⁸ The 9374 Discussion Draft instead provided that a newly issued or licensed patent would

¹⁰¹⁰9374 Discussion Draft § 602(a)(2) (proposed PHSA § 351(k)(7) [OPTION C]).

¹⁰¹¹*Id.*

¹⁰¹²*Id.* § 603(a) (proposed PHSA § 351(m)).

¹⁰¹³*Id.* § 602(a)(2) (proposed PHSA § 351(k)(9)).

¹⁰¹⁴*Id.* § 602(b)(3) (proposed PHSA § 351(i)(4)).

¹⁰¹⁵See *supra* note 753 and accompanying text.

¹⁰¹⁶9374 Discussion Draft § 602(c)(1)(C) (proposed 35 U.S.C. § 271(e)(6)(C)).

¹⁰¹⁷*Id.* § 602(a)(2) (proposed PHSA § 351(k)(6)(B)).

¹⁰¹⁸S. 1695, 110th Cong. (as reported by the S. Comm. on Health, Education, Labor, and Pensions, Nov. 19, 2008) § 2(a)(2) (proposed PHSA § 351(l)(7)).

not be subject to the first phase of litigation unless the applicant and reference product sponsor agreed to include it.¹⁰¹⁹

4. *The FTC Report, Related Hearing, and Reactions to the Report*

The day after the HELP Committee released its draft health care reform bill, the FTC released a report discussing its predictions as to how competition in the biosimilars market would evolve and its views on the appropriate approach to data exclusivity and patent litigation.¹⁰²⁰ Prior to preparing the report, the FTC had held a public workshop and invited stakeholder comments on these issues.¹⁰²¹ The second day after the HELP Committee released its draft health care reform bill, the Subcommittee on Health of the House Energy and Commerce Committee held a hearing on the report, with then FTC Commissioner Pamela Jones Harbour as the sole witness.¹⁰²² Michael S. Wroblewski, author of the FTC report and Deputy Director of the FTC Office of Policy and Planning was available for and answered questions but did not testify.¹⁰²³

a. *The FTC Report*

The FTC report reached three main conclusions. First, the FTC found that a twelve-to-fourteen-year data exclusivity period was “[u]nnecessary” to foster biotechnology innovation.¹⁰²⁴ Second, the FTC determined that biosimilars legislation need not establish special procedures to resolve patent issues prior to FDA approval of biosimilar applications.¹⁰²⁵ Third, according to the FTC, there was no need for exclusivity as an incentive for development of interchangeable biosimilars.¹⁰²⁶

The Commission’s conclusions rested on its prediction that competition between innovators and biosimilar manufacturers is more likely to resemble brand-to-brand competition than brand-to-generic competition under the Hatch-Waxman amendments.¹⁰²⁷ According to the FTC, biosimilar entrants likely will be “large companies with substantial resources,” entry will occur only in markets with sales over \$250 million per year, and only two or three companies will seek licensure of biosimilars of any particular reference product.¹⁰²⁸ The Commission concluded that biosimilars likely will be priced at 10-30 percent lower than their reference product prices and that “pioneer[s] . . . will likely continue to reap substantial profits years after entry by [biosimilars].”¹⁰²⁹

In turn, these expectations rested on five assumptions that the FTC made about the biosimilars market. First, the costs of developing a biosimilar are likely to be much higher than the costs of developing a generic drug due to the “substantial

¹⁰¹⁹ 9374 Discussion Draft § 602(a)(2) (proposed PHSA § 351(l)(7)).

¹⁰²⁰ FTC Report; *see also* Press Release, FTC, FTC Releases Report on “Follow-on Biologic Drug Competition,” (June 10, 2009).

¹⁰²¹ 73 Fed. Reg. 51479 (Sept. 3, 2008).

¹⁰²² Preliminary Transcript of *Emerging Health Care Issues: Follow-on Biologic Drug Competition: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce* (2009), available at http://energycommerce.house.gov/Press_111/20090611/transcript_20090611_he.pdf.

¹⁰²³ *Id.* at 6 (statement of Rep. Pallone).

¹⁰²⁴ FTC Report, at vi.

¹⁰²⁵ *Id.* at vii.

¹⁰²⁶ *Id.* at ix.

¹⁰²⁷ *Id.* at iii.

¹⁰²⁸ *Id.* at iii-iv.

¹⁰²⁹ *Id.* at v.

costs to obtain FDA approval” and the significant fixed costs of the necessary manufacturing capacity.¹⁰³⁰ **Second**, most biosimilars will not be automatically substituted for their reference products; biosimilars manufacturers will have to market their products and negotiate contracts with purchasers, further adding to their costs.¹⁰³¹ **Third**, physicians may be reluctant to switch patients to biosimilars based on concerns that patients may react differently.¹⁰³² **Fourth**, there may be a need for re-training of healthcare providers upon a switch to a biosimilar, because biologics “are combined with ancillary medical services and products that require specialty training for proper handling and administration.”¹⁰³³ **Fifth**, biologics are often reimbursed as medical benefits rather than pharmacy benefits. This will mean that traditional incentives for using lower priced drugs — such as co-pays and tiered formularies — are unlikely to apply.¹⁰³⁴

Based on these assumptions, in the FTC’s view, then-existing incentives for development of innovative products — patent protection and market-based pricing — probably would be adequate to promote innovation, and the Commission did not “recommend[] a specific length for an exclusivity period.”¹⁰³⁵ The FTC found little evidence that “biologic drugs under development [were] likely to be unpatentable” or that patents claiming biologics were “designed around more frequently than those claiming small-molecule products.”¹⁰³⁶ Instead, the FTC asserted, innovative biologics are “covered” by more patents and more “varied” patents . . . than “small-molecule branded products.”¹⁰³⁷ In addition, the FTC stated, a twelve-to-fourteen-year data exclusivity period would cause companies to direct their resources “toward developing low-risk clinical and safety data for drug products with proven mechanisms of action rather than toward new inventions to address unmet medical needs.”¹⁰³⁸

The FTC also stated that “a special pre-approval patent resolution process is unlikely to succeed in raising and resolving all pertinent patent issues prior to FDA approval,” due to the size and complexity of biologics patent estates and the possibility that the biosimilar “manufacturer’s application and product . . . may change during the [FDA] approval process,” after the pre-approval patent proceedings had already begun.¹⁰³⁹ Moreover, according to FTC, the special patent procedures in the Hatch-Waxman amendments were created “to address the issue of ‘judgment proof’ generic defendants”; because biosimilars manufacturers were likely to be large companies with “expertise and resources necessary to assess whether to launch their product before any patent infringement litigation is resolved,” the primary rationale for special patent provisions in the Hatch-Waxman setting would not apply in the biosimilars context.¹⁰⁴⁰

Finally, the Commission concluded that the rationales justifying 180-day exclusivity for generic drugs were inapplicable to biosimilars. In the FTC’s view, 180-day exclusivity under the Hatch-Waxman amendments provides an incentive for generic

¹⁰³⁰ *Id.* at iii.

¹⁰³¹ *Id.* at iv.

¹⁰³² *Id.*

¹⁰³³ *Id.*

¹⁰³⁴ *Id.*

¹⁰³⁵ *Id.* at v & vii.

¹⁰³⁶ *Id.* at vii.

¹⁰³⁷ *Id.* at vi.

¹⁰³⁸ *Id.* at vii.

¹⁰³⁹ *Id.* at viii.

¹⁰⁴⁰ *Id.*

applicants to expend resources on litigation challenging patents.¹⁰⁴¹ It allows the first generic company to recoup its patent litigation costs prior to entry of subsequent generic products, after which the price of its generic product may drop to twenty percent of the original price of the reference product.¹⁰⁴² Because the FTC did not expect the entry of subsequent interchangeable biosimilars to result in a significant price drop, it deemed exclusivity for these biosimilars unnecessary.¹⁰⁴³

b. *Subcommittee on Health Hearing*

The primary focus of the hearing in the Subcommittee on Health was the FTC's finding that a twelve-to-14-year data exclusivity period was unnecessary. Representative Baldwin (D-WI) pointed out that, at the time, innovative biologics "enjoy[ed] infinite data exclusivity."¹⁰⁴⁴ Representative Inslee agreed, stressing that companies "[r]ight now . . . have an incentive to investment [in biotechnology] in part because of data exclusivity."¹⁰⁴⁵ When Commissioner Harbour was asked whether she agreed that the existing data exclusivity was considered by investors when deciding whether to invest in biotechnology, she responded "No, only if there is truly a perceived failure with the patent system."¹⁰⁴⁶ When Representative Inslee asked if the FTC study examined how the lack of data exclusivity would affect investment in new products, Mr. Wroblewski responded "We did not evaluate that in particular . . . because patent protection has been very, very strong."¹⁰⁴⁷

Mr. Wroblewski indicated that the FTC had looked at "existing brand competition" in assessing the strength of biologics patents because "there is plenty of opportunity for another branded competitor to . . . duplicate all the clinical and safety efficacy data . . . and then compete."¹⁰⁴⁸ According to Mr. Wroblewski, patents have been sufficiently strong that they have "even kept out a branded competitor from doing just that."¹⁰⁴⁹ "[I]f the patents have been strong [enough] to keep out the branded competitors," he continued, "they are going to be equally as strong to keep out the follow-on competitors who have to be similar."¹⁰⁵⁰

Representative Christensen (D-Virgin Islands) expressed skepticism that any evidence existing at the time could provide a basis for firm conclusions about the strength of patent protection against biosimilar entry. "If there are no [biosimilar] pathways that exist," she asked, "how could there be any evidence as to how patents could [be] worked around?"¹⁰⁵¹ Representative Eshoo agreed, asking "how can you be sure that a new and untested standard [of similarity] would not facilitate a path for patent workarounds . . . ?"¹⁰⁵² She added that biosimilar-to-brand competition would differ from brand-to-brand competition because biosimilar manufacturers would face "about a tenth of the [development] cost[s]" that would be faced by an innovative manufacturer.¹⁰⁵³

¹⁰⁴¹ *Id.* at ix.

¹⁰⁴² *Id.*

¹⁰⁴³ *Id.*

¹⁰⁴⁴ Preliminary Transcript, *supra* note 1022, at 53 (statement of Rep. Baldwin).

¹⁰⁴⁵ *Id.* at 132 (statement of Rep. Inslee).

¹⁰⁴⁶ *Id.* at 133-134 (statement of Commissioner Harbour).

¹⁰⁴⁷ *Id.* at 134 (statement of Mr. Wroblewski).

¹⁰⁴⁸ *Id.* at 103.

¹⁰⁴⁹ *Id.*

¹⁰⁵⁰ *Id.* at 104.

¹⁰⁵¹ *Id.* at 102 (statement of Rep. Christensen).

¹⁰⁵² *Id.* at 117 (statement of Rep. Eshoo).

¹⁰⁵³ *Id.* at 116.

c. *Reactions to the Report*

Numerous Representatives expressed “disappoint[ment]” that they had received the report fewer than twenty-four hours earlier and that only one witness had been called.¹⁰⁵⁴ Subcommittee Chair Pallone indicated that additional hearings would be held, but that a date had not yet been determined.¹⁰⁵⁵ In fact, no subsequent Energy and Commerce hearing specific to biosimilars was held prior to enactment of the BPCIA.

Representative Waxman praised the FTC report. In a statement, he said that the FTC’s “unbiased, expert analysis” had “completely dispose[d] of the drug industry’s argument that they need 12 to 14 years of exclusive marketing, indeed that they need any additional exclusivity, to sustain innovation.”¹⁰⁵⁶ GPhA issued a press release supporting the report, calling it “yet another endorsement of the need to move forward on passage of [biosimilars] legislation.”¹⁰⁵⁷ The press release also noted with approval that “[t]he FTC makes the point that the exclusivity period being pushed by the brands is ‘too long to promote innovation.’”¹⁰⁵⁸

In contrast, BIO called the report “fundamentally flawed” for five reasons.¹⁰⁵⁹ First, according to BIO, brand-to-brand competition was an imperfect model for biosimilar-to-brand competition because brand competitors “have to engage in the same lengthy and costly R&D process,” whereas biosimilar manufacturers will be given a “scientific and regulatory short-cut.”¹⁰⁶⁰ Second, BIO cited six cases for the proposition that “successful biotech design-arounds have occurred” in the brand-to-brand market “even without the major incentives of an abbreviated pathway.”¹⁰⁶¹ Third, BIO emphasized that a peer-reviewed study by Professor Grabowski “found that, even with expected smaller market erosion based on Congressional Budget Office estimates, innovators will not be able to recoup their investment in a reasonable period of time without 12 - 14 years of data exclusivity.”¹⁰⁶² Fourth, according to BIO, the FTC’s conclusion that a twelve-to-14-year exclusivity period would not promote innovation was contrary to experience under the existing regime of unlimited data exclusivity, pursuant to which “there ha[d] been tremendous innovation.”¹⁰⁶³ Finally, according to BIO, a pre-approval patent resolution procedure for biosimilars was necessary, because, without it, biosimilars “would systematically have to enter the market under a cloud of patent uncertainty,” resulting in confusion “about the long-term availability” of particular biosimilars.¹⁰⁶⁴

¹⁰⁵⁴ *E.g. id.* at 17-18 (statement of Rep. Eshoo); *id.* at 22 (statement of Rep. Burgess).

¹⁰⁵⁵ *Id.* at 21 (statement of Rep. Pallone).

¹⁰⁵⁶ *FTC Says Generic Biologics Pathway Would Reduce Costs of Biologic Drugs*, PHARM. L. & IND. REPORT, June 12, 2009.

¹⁰⁵⁷ Press Release, GPhA, GPhA Statement on FTC Report on “Follow-on Biologic Drug Competition,” (June 10, 2009).

¹⁰⁵⁸ *Id.*

¹⁰⁵⁹ Press Release, BIO, FTC Report on Biosimilars Is Fundamentally Flawed (June 10, 2009).

¹⁰⁶⁰ BIO, FTC Biosimilars Report Rebuttal (2009), at 1.

¹⁰⁶¹ *Id.* at 2 (citing *Hormone Res. Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558 (Fed. Cir. 1990); *Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364 (Fed. Cir. 1996); *Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555 (Fed. Cir. 1994); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003); *Biogen, Inc. v. Berlex Labs., Inc.*, 318 F.3d 1132 (Fed. Cir. 2003); *Genzyme Corp. v. TKT, Inc.*, 346 F.3d 1094 (Fed. Cir. 2003)).

¹⁰⁶² *Id.*

¹⁰⁶³ *Id.* at 3.

¹⁰⁶⁴ *Id.* See also Letter from Henry Grabowski, Professor of Economics and Director of the Program in Pharms. & Health Economics, Duke Univ. (July 6, 2009). It was also argued that the FTC’s conclusion that patent protection would be a sufficient incentive for innovation was flawed because it assumed no changes to existing patent law, whereas both H.R. 1427 and S. 1695 as reported would have diminished the value of patent protection through limitations on remedies and other aspects of their patent provisions.

A few days after the Subcommittee on Health hearing, Representative Eshoo and eight other lawmakers sent a letter to Representative Waxman, then Chair of the House Energy and Commerce Committee. The letter requested that Chairman Waxman and Subcommittee on Health Chair Pallone incorporate the second Eshoo bill into the health care reform legislation that they were then drafting.¹⁰⁶⁵ The letter stated that the signatories wished to “work collaboratively . . . to ensure that there is a pathway for biosimilars” in the legislation, but if agreement could not be reached, they “intend[ed] to pursue an amendment at markup to incorporate H.R. 1548 into the Committee draft.”¹⁰⁶⁶ At that time, the second Eshoo bill had 100 co-sponsors.¹⁰⁶⁷

About a week later, the Executive Office of the President responded to Representative Waxman’s June 8 letter to the President urging the Administration “to consider what steps may be taken under existing authority to prepare and even begin to use a pathway for generic biologics.”¹⁰⁶⁸ The letter, signed by White House Office of Health Reform¹⁰⁶⁹ Director Nancy-Ann DeParle and OMB Director Peter Orszag, stated that “the policy in the FY 2010 Budget strikes the appropriate balance between innovation and competition by providing for seven years of exclusivity.”¹⁰⁷⁰ Citing the FTC’s conclusion that a twelve-to-fourteen-year data exclusivity period was unnecessary, the letter stated that the seven-year policy of the Budget “is a generous compromise between what the FTC research has concluded and what the pharmaceutical industry has advocated.”¹⁰⁷¹ In addition, the letter noted that “[t]he Administration is working closely with the FDA to ensure” that the agency could implement a biosimilars pathway, and “[a]s part of this effort, a serious review of FDA’s existing authorities is underway to ensure that we are effectuating this critical policy as quickly as possible.”¹⁰⁷² According to *FDA Week*, the White House Office of Health Reform did not respond to the question whether this statement meant FDA would begin to approve biosimilar applications without legislation.¹⁰⁷³

5. *Competing Proposals in the Senate*

Meanwhile, discussions on potential evergreening language continued in the Senate. In early July, the Senate HELP Committee held a meeting at which com-

¹⁰⁶⁵ Letter from Rep. Eshoo et al. to Chairman Waxman and Chairman Pallone, at 1 (June 16, 2009). The signatories were Reps. Eshoo, Inslee, Green, Baldwin, Hill (D-IN), Barrow (D-GA), Melancon (D-LA), Gonzalez (D-TX), and Matheson (D-UT).

¹⁰⁶⁶ *Id.*

¹⁰⁶⁷ *Id.*

¹⁰⁶⁸ See *supra* note 995-996 and accompanying text.

¹⁰⁶⁹ President Obama established the White House Office of Health Reform by Executive Order in April 2009, to “provide leadership to the executive branch in establishing policies, priorities, and objectives for the Federal Government’s comprehensive effort to improve access to health care, the quality of such care, and the sustainability of the health care system.” Exec. Order 13,507, § 2(a), 74 Fed. Reg. 17071, 17071 (Apr. 13, 2009). The Executive Order also required (to the extent permitted by law) the Secretary of HHS to establish an Office of Health Reform within HHS to “coordinate closely with the White House Office of Health Reform.” *Id.* § 2(b).

¹⁰⁷⁰ Letter from Nancy-Ann DeParle, Director, Office of Health Reform & Peter Orszag, Director, Office of Management & Budget (June 24, 2009), at 1.

¹⁰⁷¹ *Id.*

¹⁰⁷² *Id.*

¹⁰⁷³ *White House Stands Firm on 7-Year Biologics Exclusivity Period*, FDA WEEK, June 26, 2009. In late October, however, FDA Office of Pharmaceutical Science Director Helen Winkle was asked whether FDA would consider licensing biosimilars without legislation, and she responded with “a flat ‘no.’” *Drug Office Not Weighing Administrative Options for Biosimilars*, FDA WEEK, Oct. 30, 2009.

promise language providing for nine-year and three-year exclusivity periods was circulated.¹⁰⁷⁴ Compromise was not reached, however, because Committee members interpreted the language differently. According to the trade press, Senator Mikulski (D-MD) read it as allowing the reference product to receive both periods for a total of twelve years, while Senator Brown interpreted the language to mean that the reference product could receive nine years at most.¹⁰⁷⁵

Senator Kennedy introduced the language as a “placeholder” that could be modified or discarded after other Senators had an opportunity to introduce their own amendments.¹⁰⁷⁶ Senators Mikulski and McCain (R-AZ) each filed one amendment, Senators Hatch, Enzi, and Hagan together filed one amendment, and Senator Brown proposed two different amendments. Each amendment took a different approach to exclusivity. At markup on July 13, the HELP Committee rejected the first Brown amendment by a vote of 5-17 and adopted the Hatch/Enzi/Hagan amendment, which offered twelve years of exclusivity, by a vote of 16-7.¹⁰⁷⁷

After the vote, Senator Brown said he planned to introduce an amendment when the bill was on the Senate floor to shorten the exclusivity period.¹⁰⁷⁸ Senator Dodd, who had chaired the markup in Senator Kennedy’s absence, implied that the final bill would provide fewer than twelve years of exclusivity, by stating “[m]y guess is we’re looking at the outside number.”¹⁰⁷⁹ When the HELP Committee reported its health care reform bill on September 9, 2009, however, the biosimilars language was identical (with the exception of minor editorial changes and a provision indicating it was the “sense of the Senate that a biosimilars pathway . . . should be established”) to that in the Hatch/Enzi/Hagan amendment.¹⁰⁸⁰

a. *The 9653 Kennedy Proposal*

The language filed by Senator Kennedy as a placeholder — stamped O:\KER\KER09653.xml (the “9653 Kennedy proposal”) — reflected one major change from the 9374 Discussion Draft: a re-write of the exclusivity provision. Other changes were editorial in nature. The new exclusivity language appeared to have been modeled on the tiered exclusivity provision of the third Waxman bill. Under the Kennedy version of the language, exclusivity could have been nine, two, or no years, depending on the situation.¹⁰⁸¹

As in S. 1695, a biosimilar application could not have been submitted until four years after licensure of the reference product.¹⁰⁸² The criteria for receiving nine-year exclusivity were similar to the criteria for receiving five-year exclusivity under the third Waxman bill: (1) the reference product had been licensed pursuant to a BLA submitted under section 351(a) of the PHSA; (2) no “major substance” of the innovative product, and no highly similar major substance, had been licensed

¹⁰⁷⁴ *Senate Democrats’ Biosimilars Deal Falls Apart in Meeting*, FDA WEEK, July 10, 2009.

¹⁰⁷⁵ *Id.*

¹⁰⁷⁶ *Biotech Drug Copies Could Be Held Up 13 Years Under Senate Plan*, BLOOMBERG, July 8, 2009; see also *New Bill Limits Exclusivity to Biologics Approved After Enactment*, FDA WEEK, July 10, 2009.

¹⁰⁷⁷ *Panel Considers Abortion-Related Amendments to Health Care Overhaul Bill*, CQ COMMITTEE COVERAGE, July 13, 2009, at 2.

¹⁰⁷⁸ *Brown to Seek Exclusivity Cuts When Senate Health Bill Hits the Floor*, FDA WEEK, July 17, 2009.

¹⁰⁷⁹ *HELP Approves Biosimilars Provision With 12 Years of Exclusivity*, FDA WEEK, July 17, 2009.

¹⁰⁸⁰ S. ___, stamped O:\BAI\BAI09150.xml Title VI, Subtitle A (original bill as reported by Senate Committee on Health, Education, Labor, and Pensions Sept. 9, 2009).

¹⁰⁸¹ Kennedy Amendment to Senate Health Care Reform Legislation, stamped O:\KER\KER09653.xml, § 602(a)(2) (proposed PHSA § 351(k)(7)(A)).

¹⁰⁸² *Id.* (proposed PHSA § 351(k)(7)(G)).

pursuant to another section 351(a) application; (3) the reference product BLA had been approved after enactment of section 351(k); and (4) the reference product BLA “could not and did not rely on” a clinical safety, purity, or potency study described in any other application approved under section 351 of the PHSa or any clinical safety or effectiveness study described in an approved NDA.¹⁰⁸³ Like the third Waxman bill, the 9653 Kennedy proposal did not define the term “major substance” and excluded certain products — e.g., ones with a “minor change[] in amino acid sequence” from a previously licensed product — as a matter of law from receiving the nine-year exclusivity period.¹⁰⁸⁴

Two-year exclusivity was the alternative to nine-year exclusivity, although some reference products would not be entitled to either. As under the third Waxman bill, FDA could not have approved an application citing the reference product “for the conditions of approval of such product” for the specified time frame if: (1) the reference product was licensed pursuant to a BLA submitted under section 351(a) of the PHSa; (2) it contained a “major substance” that had been licensed already on the basis of a 351(a) application, or a major substance highly similar to that of a previously licensed product; (3) the reference product BLA was approved after enactment of section 351(k); (4) the BLA contained reports of new clinical investigations, other than pharmacokinetic or pharmacodynamic studies, essential to its approval and conducted or sponsored by the applicant; and (5) the product represented a “significant therapeutic advance.”¹⁰⁸⁵

Like the third Waxman bill, the 9653 Kennedy proposal provided for supplemental exclusivity under certain conditions.¹⁰⁸⁶ As in the Waxman bill, those conditions were: (1) a supplemental BLA for the reference product had been approved more than one year prior to expiry of the core exclusivity period in question (five or three years in the third Waxman bill, and nine or two years in the 9653 Kennedy proposal); (2) the supplement contained reports of new clinical investigations, other than pharmacokinetic or pharmacodynamic studies, essential to its approval and conducted or sponsored by the applicant; and (3) the change described in the supplement constituted a “significant therapeutic advance.”¹⁰⁸⁷ In addition, the 9653 Kennedy proposal would have permitted a second period of supplemental exclusivity if a second showing based on these criteria was made more than one year prior to the expiration of the extended period (i.e., within ten years of the product’s initial licensure).¹⁰⁸⁸ Only two supplemental periods were permitted.¹⁰⁸⁹ The 9653 Kennedy proposal omitted the Waxman language calling for a reduction

¹⁰⁸³ *Id.* (proposed PHSa § 351(k)(7)(B)(i)).

¹⁰⁸⁴ *Id.* (proposed PHSa § 351(k)(7)(B)(ii)). The list was modified in the Kennedy proposal to read as follows: (1) “[p]rotein biological products that differ in structure solely due to minor post-translational changes or minor changes in amino acid sequence”; (2) “[p]olysaccharide biological products with similar saccharide repeating units, even if the number of units differ and even if there are differences in post-polymerization modifications”; (3) “[g]lycosylated protein products that differ in structure solely due to minor changes in the structure or number of saccharide moieties”; and (4) “[p]olynucleotide biological products with identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars).” *Id.*

¹⁰⁸⁵ *Id.* (proposed PHSa § 351(k)(7)(C)). As in the third Waxman bill, approval for a “significant new indication or subpopulation” other than a pediatric subpopulation would have constituted a significant therapeutic advance. *Id.* (proposed PHSa § 351(k)(7)(C)(v)).

¹⁰⁸⁶ *Id.* (proposed PHSa § 351(k)(7)(D)).

¹⁰⁸⁷ *Id.* As in the third Waxman bill, approval for a “significant new indication or subpopulation” other than a pediatric subpopulation would have constituted a significant therapeutic advance. *Id.* (proposed PHSa § 351(k)(7)(D)(ii)).

¹⁰⁸⁸ *Id.* (proposed PHSa § 351(k)(7)(E)).

¹⁰⁸⁹ *Id.* (proposed PHSa § 351(k)(7)(F)).

in the supplemental period in the event that gross annual sales exceeded \$1 billion. Pediatric exclusivity would have been available under generally the same conditions as in the 9374 Discussion Draft.¹⁰⁹⁰

b. *Hatch/Enzi/Hagan Amendment*

The Hatch-Enzi-Hagan amendment was nearly identical to S. 1695 as reported — in other words, it included a four-year bar on submission and a twelve-year bar on approval of a biosimilar application — except that it substituted new “first licensure” language.¹⁰⁹¹ This new first licensure language was almost identical to that in the 9374 Discussion Draft. Under the new language, neither the four-year nor the twelve-year period would apply to a license for approval of: (1) a supplement to the reference product BLA; (2) any “subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest or other related entity)” for either (a) “a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength”; or (b) “a modification to the structure of the biological product that [did] not result in a change in safety, purity, or potency.”¹⁰⁹²

c. *Mikulski Amendment*

The Mikulski amendment was almost identical to S. 1695 as reported, except that it proposed a substantially different approach to data exclusivity. It provided for an initial exclusivity period of ten years running from the date on which the reference product was “first licensed.”¹⁰⁹³ A one-year extension of this exclusivity would be available if, within the first eight years, FDA approved a supplement “for one or more new therapeutic indications and bring[ing] a significant clinical benefit, in comparison with existing therapies.”¹⁰⁹⁴ That benefit could have been improved safety or improved efficacy, but it was required to constitute a major contribution to patient care.¹⁰⁹⁵ Only one extension would be allowed.¹⁰⁹⁶ The Mikulski amendment provided that the ten-year period was available only for “a new biological product that meaningfully differ[ed] from a previously-licensed biological product in molecular structure, starting materials, or manufacturing process.”¹⁰⁹⁷ This approach to the evergreening issue appeared to have been modeled on the approach in Europe, where ten-year exclusivity is available to a biological product that differs from a previously licensed biological product in molecular structure, starting materials, or manufacturing process.¹⁰⁹⁸ In Europe, the difference is not expressly required to be “meaningful.”

¹⁰⁹⁰ *Id.* § 603 (proposed PHSA § 351(m)). The provision had been modified slightly; pediatric exclusivity would no longer extend the bar on submission, but only the two-year or nine-year period of exclusivity.

¹⁰⁹¹ Hatch/Enzi/Hagan Amendment to Senate Health Care Reform Legislation, stamped O:\KER\KER09601.xml, § 602(a)(2) (proposed PHSA § 351(k)(7)(A) & (B)).

¹⁰⁹² *Id.* (proposed PHSA § 351(k)(7)(C)).

¹⁰⁹³ Mikulski Amendment to Senate Health Care Reform Legislation, stamped O:\KER\KER09642.xml, § 602(a)(2) (proposed PHSA § 351(k)(7)(A)).

¹⁰⁹⁴ *Id.* (proposed PHSA § 351(k)(7)(B)).

¹⁰⁹⁵ *Id.*

¹⁰⁹⁶ *Id.* (proposed PHSA § 351(k)(7)(C)).

¹⁰⁹⁷ *Id.* (proposed PHSA § 351(k)(7)(D)).

¹⁰⁹⁸ See *supra* note 166 and accompanying text.

The Mikulski amendment contained a pediatric exclusivity provision almost identical to that in the 9653 Kennedy proposal, except with respect to the extension of orphan exclusivity. As under the 9653 Kennedy proposal, the base exclusivity period could be extended by six months (here, to ten-and-a-half years) if the innovator satisfied the criteria for pediatric exclusivity. Under the Mikulski amendment, however, orphan exclusivity would have been extended from seven to nine years if the pediatric exclusivity criteria were met.

d. *McCain Amendment*

The McCain amendment contained the same language as S. 1695 as reported, with three major changes. First, the McCain amendment contained a different data exclusivity provision. Like S. 1695 as reported, the McCain amendment provided for a four-year bar on submission of an application. But under the McCain amendment, an application could be approved ten years after the first licensure of the reference product.¹⁰⁹⁹ The ten-year period could be extended by two years if there were “significant therapeutic advancements with respect to the reference product.”¹¹⁰⁰ The first licensure language in the McCain amendment was identical to that in S. 1695 as reported, *i.e.*, the date of first licensure would not have included the date of approval of “a supplement or of a subsequent application for a new indication, route of administration, dosage form, or strength for the previously licensed reference product.”¹¹⁰¹

Second, the McCain amendment would have required that, as a condition of approval, a biosimilar product have “undergone 1 or more clinical studies to establish that [it was] safe, pure, and potent.”¹¹⁰² This approach differed from that in the other amendments, where the conditions of approval were limited to a showing of biosimilarity (through clinical data and other means) and consent to inspection. Third, the McCain amendment would have added a new subparagraph stating that “[n]otwithstanding any other provision of law, no biological product may be interchanged with a reference product with respect to an individual unless such interchange is prescribed by a physician for such individual.”¹¹⁰³

e. *Brown Amendments*

Senator Brown proposed two amendments. His first amendment, stamped KER09607, was almost identical to the 9653 Kennedy proposal, with the exception of the exclusivity provisions. Senator Brown’s amendment would have substituted exclusivity language almost identical to that in the third Waxman bill, with the major difference being that the initial exclusivity period would have been seven years rather than five years.¹¹⁰⁴ In other words, it would have provided two tiers of exclusivity (seven years and three years), with the possibility of a six month extension of either period that would have been cut in half for major substances with annual gross sales exceeding \$ 1 billion.¹¹⁰⁵ This amendment also included pediatric

¹⁰⁹⁹ McCain Amendment to Senate Health Care Reform Legislation, stamped O:\AEG\AEG09288.xml, § 602(a)(2) (proposed PHSA § 351(k)(7)(A)(i) & (B)).

¹¹⁰⁰ *Id.* (proposed PHSA § 351(k)(7)(A)(ii)).

¹¹⁰¹ *Id.* (proposed PHSA § 351(k)(7)(C)).

¹¹⁰² *Id.* (proposed PHSA § 351(k)(3)(C)).

¹¹⁰³ *Id.* (proposed PHSA § 351(k)(4)(B)).

¹¹⁰⁴ First Brown Amendment to Senate Health Care Reform Legislation, stamped O:\KER\KER09607.xml, § 602(a)(2) (proposed PHSA § 351(k)(7)).

¹¹⁰⁵ *Id.*

exclusivity provisions virtually identical to those in the 9653 Kennedy proposal. AARP supported this amendment.¹¹⁰⁶

The second Brown amendment, stamped O:\WHI\WHI09723.xml, was different in two major respects from the first Brown amendment. First, the longer exclusivity period was changed from seven to nine years.¹¹⁰⁷ Second, the exclusivity adjustment (*i.e.*, loss of ninety days for major substances with annual gross sales over \$ 1 billion) was omitted.¹¹⁰⁸

6. *Hearing of the House Committee on the Judiciary*

The day after the Senate HELP Committee voted to pass the Hatch/Enzi/Hagan amendment, the Subcommittee on Courts and Competition Policy of the House Committee on the Judiciary held a hearing on incentives for innovation related to biosimilars legislation.¹¹⁰⁹ The discussion focused on the length and structure of data exclusivity provisions and the patent resolution process.

a. *Data Exclusivity*

The witnesses expressed a range of opinions as to the appropriate length of the data exclusivity period. They supported periods ranging from five to fourteen years. Representative Eshoo testified as a witness before the Committee in support of the twelve-year period in her bill, which she said was “equivalent to patent protections for small molecules.”¹¹¹⁰ She noted the Congressional Budget Office (CBO) had determined that eleven and a half years was the average length of time that drugs are marketed under patent and stated that her legislation “maintains this level of protection for biologics.”¹¹¹¹ Representative Eshoo noted that her legislation would end the status quo under which “innovators [at the time had] infinite data protection,”¹¹¹² but would “maintain[] an 12-year period . . . of concurrent data protection as a backstop to existing patent protections.”¹¹¹³

Citing the FTC’s conclusions that biotechnology patents are strong, Larry McNeely, Healthcare Reform Advocate, U.S. Public Interest Research Groups, supported the approach to exclusivity in the third Waxman bill.¹¹¹⁴ Bruce A. Leicher, Senior Vice President and General Counsel of Momenta, supported the third Waxman bill’s five-year exclusivity period.¹¹¹⁵ Mr. Leicher stated that a longer exclusivity period would “attract capital but the wrong kind. It will promote low-risk, non-innovative development and make biotech in the long run far less competitive.”¹¹¹⁶ According to Mr. Leicher, this was because “financial investors are agnostic to the degree of medical need and will certainly drive us toward the lower risk, higher

¹¹⁰⁶ Press Release, Senator Brown’s Office, Brown Calls Committee Vote a Missed Opportunity to Lower Costs and Improve Medical Care (July 14, 2009).

¹¹⁰⁷ Second Brown Amendment to Senate Health Care Reform Legislation, stamped O:\WHI\WHI09723.xml, (proposed PHSA § 351(k)(7)(A)(i)(I)).

¹¹⁰⁸ See *id.* (proposed PHSA § 351(k)(7)(D)).

¹¹⁰⁹ *Biologics and Biosimilars: Balancing Incentives for Innovation, Hearing Before the Subcomm. on Courts and Competition Policy of the H. Comm. on the Judiciary*, 111th Cong. (2009).

¹¹¹⁰ *Id.* at 8 (statement of Rep. Eshoo).

¹¹¹¹ *Id.*

¹¹¹² *Id.* at 9.

¹¹¹³ *Id.* at 9.

¹¹¹⁴ *Id.* at 190, 194 (statement of Larry McNeely, Healthcare Reform Advocate, U.S. Public Interest Research Groups).

¹¹¹⁵ *Id.* at 14 (statement of Bruce Leicher, Senior Vice President and General Counsel of Momenta).

¹¹¹⁶ *Id.* at -15.

reward [products] that have extended data exclusivity.”¹¹¹⁷ Mr. Leicher also stated that experience from the Hatch-Waxman setting has shown that generic market entry provides innovators incentives “to invest in innovative, patentable programs to fill their pipelines.”¹¹¹⁸ In Mr. Leicher’s view, delays in biosimilar market entry caused by data exclusivity would similarly delay this innovation.¹¹¹⁹ Mr. Leicher suggested that data exclusivity not be used as an insurance policy against weak patents because this would prevent the patent system from serving its function: “Strong patents . . . reward extraordinary risk, narrow or weak patents reward non-innovative, incremental research and development.”¹¹²⁰

Alex M. Brill, Research Fellow, American Enterprise Institute, supported a seven-year exclusivity period.¹¹²¹ He stated that seven years “is sufficient to ensure that innovator drug companies continue to earn the necessary economic rents,” but that “a long period” would “lead to unreasonably large rent[s] . . . and provide no additional benefit to consumers.”¹¹²² Mr. Brill agreed with the FTC report that the more modest price discounts for biosimilars as compared to generic drugs “means that the need for additional market protection” for biotech products “is weaker” because innovators “will continue to be able to profit from their innovations” after biosimilar entry.¹¹²³ Mr. Brill also stated that post-launch development of biotech products “should be encouraged,” but that the total exclusivity period—including any supplemental period—should not exceed seven years.¹¹²⁴ According to Mr. Brill, “[a]n improvement that enlarges market share would increase profits further, thereby mitigating the amount of needed exclusivity.”¹¹²⁵

Jeffrey P. Kushan, an attorney at Sidley Austin, LLP, testifying on behalf of BIO, supported Representative Eshoo’s proposed twelve-year exclusivity period.¹¹²⁶ He stated that a twelve-year period was necessary because patents would not provide the same certainty of a return on investment in the biosimilar setting as they do in the Hatch-Waxman context for two reasons.¹¹²⁷ First, patents on biotechnology-derived drugs are narrower than patents on chemically synthesized drugs.¹¹²⁸ Second, biosimilars will not be required to be the same as innovator products, which means that biosimilar manufacturers may be able to satisfy the regulatory approval standard without violating these innovator patents.¹¹²⁹ Mr. Kushan also testified that a twelve-year exclusivity period was consistent with Congress’ previous “determination that an effective patent term of 14 years following approval is an appropriate period of . . . exclusivity.”¹¹³⁰ He was referring specifically to the

¹¹¹⁷ *Id.* at 20.

¹¹¹⁸ *Id.* at 21.

¹¹¹⁹ *See id.*

¹¹²⁰ *Id.* at 247.

¹¹²¹ *Id.* at 174 (statement of Alex M. Brill, Research Fellow, American Enterprise Institute).

¹¹²² *Id.*

¹¹²³ *Id.* at 173

¹¹²⁴ *Id.* at 174.

¹¹²⁵ *Id.*

¹¹²⁶ *Id.* at 39 (statement of Jeffrey P. Kushan, an attorney at Sidley Austin LLP testifying on behalf of BIO).

¹¹²⁷ *See id.*

¹¹²⁸ *Id.* at 63 (“The unpredictability inherent in the biological products, in particular, leads to stringent applications of the patent law standards of utility, written description and enablement. In sum, this prevents issuance of broad ‘genus’ claims that cover a wide range of structural variations to the particular protein sequence discovered and tested by the innovator. By contrast, a group of structurally related bioactive molecules (a so-called genus) that are the basis of most NDA drugs can often be covered by a single patent claim.”) (footnotes omitted).

¹¹²⁹ *Id.* at 62.

¹¹³⁰ *Id.* at 60.

rule under Title II of the Hatch-Waxman amendments that new drugs are entitled to patent term restoration that, depending on the length of the regulatory delay during testing and FDA review of the application, may last until fourteen years after approval.¹¹³¹ According to Mr. Kushan, “[t]he parameters of the patent term restoration provisions of the Hatch-Waxman Act . . . reflect Congress’ determination that an effective patent term of 14 years following approval of the product is an appropriate period of patent exclusivity,” so biosimilars legislation “should at least guarantee that same degree of effective market protection” for biologics, and “that protection can be accomplished most predictably through data exclusivity.”¹¹³² Mr. Kushan noted that innovators often screen drugs during the research and development process and abandon candidates with poor patent protection, adding that “a substantial data exclusivity period for biologics will ensure that the best biologics will continue to be developed – not just the biologics with the best patents.”¹¹³³ He disagreed with Mr. Leicher’s point that a substantial period of data exclusivity would hinder innovation: “[a]ctual experience shows that innovators also do not stop clinically developing their products . . . despite being given essentially an unlimited period of data protection. Instead, it shows that innovators continue to invest heavily in new clinical development and research.”¹¹³⁴

Jack W. Lasersohn, General Partner, Ventricle Group, testifying on behalf of the National Venture Capital Association (NVCA), similarly supported Representative Eshoo’s twelve-year exclusivity period.¹¹³⁵ Mr. Lasersohn noted that different stakeholders had very different views on the strength of biotechnology patents.¹¹³⁶ He noted that, to venture capitalists, “what matters . . . most is that [this disagreement] creates uncertainty, which is what actually affects our investment decisions.”¹¹³⁷ Mr. Lasersohn emphasized that the 12-year period would be “insurance against the possibility the FTC . . . [is] wrong in [its] speculations about how strong patents will be. If [the FTC is] correct, patents will give us 12 years anyway and the data exclusivity will be completely irrelevant.”¹¹³⁸

b. *Patent Provisions*

The witnesses also articulated a range of views regarding the appropriate patent provisions for biosimilars legislation. Representative Eshoo advocated the patent provisions of her bill on the basis that they would “protect the rights of all parties” including by “preserv[ing] the ability of third-party patent holders, such as

¹¹³¹ See *supra* note 433.

¹¹³² *Biologics and Biosimilars: Balancing Incentives for Innovation*, *supra* note 1109, at 60 (statement of Mr. Kushan).

¹¹³³ *Id.* at 85.

¹¹³⁴ *Id.* at 38.

¹¹³⁵ *Id.* at 183 (statement of Jack W. Lasersohn, General Partner, Ventricle Group, testifying on behalf of the National Venture Capital Association).

¹¹³⁶ *Id.* Mr. Lasersohn also questioned the FTC’s use of brand-to-brand patent litigation as a reasonable proxy for biosimilar-to-brand patent litigation: “With no abbreviated approval pathway today, biologics developers have little incentive to incur staggering development costs only to create me-too biologics . . . with no opportunity for product differentiation . . . [I]t is by no means assured that [the existing] patent system . . . will continue to [promote innovation] under a biosimilars system that incentivizes biologics competitors to invade rather than avoid each others’ patent space.” *Id.* at 187.

¹¹³⁷ *Id.* at 183.

¹¹³⁸ *Id.* Mr. Kushan also made this point. *Id.* at 55 (statement of Mr. Kushan) (“Importantly, data exclusivity periods will run concurrently (not in addition to) any patent exclusivity that may exist for the innovator’s product, which may last up to or beyond 14 years after approval of that product. In one sense, a 14-year data exclusivity period will serve as an insurance policy that provides the innovator with certainty of protection for this period. In the case of patents that cannot be designed around and that have significant amounts of patent term remaining, long data exclusivity will have no impact.”).

universities and medical centers, to defend their patents.”¹¹³⁹ According to Representative Eshoo, the patent framework of H.R. 1548 also would “ensure that all patent disputes involving a biosimilar are resolved before . . . the expiration of the data-exclusivity period,” thus “providing certainty to the applicant, the reference product manufacturer, and the public at large.”¹¹⁴⁰

Mr. Kushan and Teresa Stanek Rea, President of the American Intellectual Property Law Association (AIPLA), supported the patent provisions of the second Eshoo bill. Mr. Kushan praised H.R. 1548 for permitting third party patent holders to “participate in pre-marketing patent identification procedures, and [not requiring] these entities to have their interests represented exclusively by the BLA holder.”¹¹⁴¹ He also favored the connection between patent litigation and FDA approval in the second Eshoo bill. Under H.R. 1548, if timely patent infringement litigation was commenced on a challenged patent and the patent was found infringed prior to expiry of the data exclusivity period, FDA could not approve the biosimilar application until the relevant patent expired.¹¹⁴² According to Mr. Kushan, this would “ensure that valid patent rights are respected” and provide “a powerful incentive for patent owners to conclude the litigation as rapidly as possible.”¹¹⁴³ Ms. Stanek Rea also stated a preference for the patent provisions of H.R. 1548 over those of H.R. 1427, noting that the former “would be less subject to gamesmanship and abuse.”¹¹⁴⁴

Mr. Leicher again supported Representative Waxman’s approach.¹¹⁴⁵ He defended the provisions in the third Waxman bill limiting innovator remedies where filing or listing deadlines are missed, noting that “[f]iling deadlines are a customary part of most judicial proceedings,” giving the example of statutes of limitations.¹¹⁴⁶ He also noted that “numerous countries like Germany . . . permit the filing of nullity actions in court seeking to invalidate patents that are improvidently granted.”¹¹⁴⁷ He offered three criticisms of the patent provisions in the second Eshoo bill. First, he stated, the Eshoo bill “includes the entire complex web of biologic patent rights in the clearance process even if they are not controlled by the brand company.”¹¹⁴⁸ According to Mr. Leicher, this “could double the time and expense for the litigation.” By way of contrast, he stated, the Waxman bill “properly limits the litigation to patents controlled by the brand company.”¹¹⁴⁹ Second, Mr. Leicher stated, the second Eshoo bill compels “disclosure of critical confidential information” about the biosimilar “that is not related to” demonstrating infringement.¹¹⁵⁰ Third, in

¹¹³⁹ *Id.* at 9 (statement of Rep. Eshoo).

¹¹⁴⁰ *Id.*

¹¹⁴¹ *Id.* at 66 (statement of Mr. Kushan).

¹¹⁴² *See supra* note 877 and accompanying text.

¹¹⁴³ *Biologics and Biosimilars: Balancing Incentives for Innovation, supra* note 1109, at 48, 67 (statement of Mr. Kushan).

¹¹⁴⁴ *Id.* at 197 (statement of Teresa Stanek Rea, President of the American Intellectual Property Law Association (AIPLA)).

¹¹⁴⁵ *Id.* at 19 (statement of Mr. Leicher).

¹¹⁴⁶ *Id.* at 249.

¹¹⁴⁷ *Id.*

¹¹⁴⁸ *Id.* at 21.

¹¹⁴⁹ *Id.*

¹¹⁵⁰ *Id.* Mr. Kushan and Ms. Stanek Rea disagreed with Mr. Leicher on this point. *See id.* at 82 (statement of Mr. Kushan) (“misplaced concerns over confidentiality and inappropriate use of information provided by a biosimilar manufacturer also are simply and routinely addressed today using standard confidentiality provisions that restrict access to and use of the information to prevent the very type of harm [envisioned].”); *id.* at 204 (statement of Ms. Stanek Rea) (noting H.R. 1548 “would require that all such information [accessed to determine potential infringement] be treated as confidential by the recipients”).

Mr. Leicher's view, the declaratory judgment provision of the second Eshoo bill was problematic. This provision stated that an applicant could not have brought a declaratory judgment action about a patent it was challenging until the later of the date: (1) three years before expiry of the data exclusivity period; or (2) 120 days after the applicant provided notice that it was challenging a patent.¹¹⁵¹ Mr. Leicher asserted that the three-year period "would not provide sufficient time to complete litigation" prior to FDA approval of the biosimilar application and hence would result in a de facto extension of the exclusivity period.¹¹⁵² Ms. Stanek Rea agreed that the three-year period might not allow for resolution of patent litigation.¹¹⁵³

Both Mr. Kushan and Ms. Stanek Rea expressed concerns about the patent provisions in the third Waxman bill. Mr. Kushan stated that this bill "would operate to arbitrarily limit the number of relevant patents that could be litigated prior to biosimilar approval."¹¹⁵⁴ Moreover, according to Mr. Kushan, "forcing patent disputes to commence only after a biosimilar has been placed on the market will undermine the value of patent exclusivity," by "rais[ing] the prospect that a court will not . . . issu[e] an injunction preventing the continued marketing of the biosimilar, even if the patent is found valid and infringed."¹¹⁵⁵ Mr. Kushan also criticized the bill's provisions limiting remedies for infringement saying they would "statutorily limit the exclusive rights conferred by the patent in unprecedented ways in American patent law."¹¹⁵⁶ Because these provisions "would single out biotechnology patents" for these limitations on remedies, in Mr. Kushan's view, they would "run afoul of U.S. commitments under [Article 27.1 of] the WTO Agreement on Trade Related Aspects of Intellectual Property (TRIPS)," which "prohibits discrimination in the availability and enjoyment of patents rights based on the field of technology of the invention."¹¹⁵⁷

Ms. Stanek Rea expressed concern that H.R. 1427 would permit pre-launch litigation related only to patents selected by the applicant.¹¹⁵⁸ This was problematic, she explained, because without a reliable mechanism for resolving all patent disputes prior to launch, patent disputes "would strain the federal judiciary by requiring — in preliminary injunction proceedings — resolution of the complex legal and scientific questions involved with each biosimilar product launch."¹¹⁵⁹ Ms. Stanek Rea further criticized H.R. 1427's requirement that reference product sponsors list all patents that might "relate to" the reference product. According to Ms. Stanek Rea, this provision "would seem to require the reference product holder to review its entire patent portfolio, as well as all patents it has in-licensed for any purpose," which in her view constituted an "onerous" burden.¹¹⁶⁰

Ms. Stanek Rea stated that the declaratory judgment provisions of H.R. 1427 would permit a biosimilar applicant to challenge a patent "for any reason, regardless of whether there is a colorable argument that the follow-on product would

¹¹⁵¹ See *supra* note 878 and accompanying text.

¹¹⁵² *Biologics and Biosimilars: Balancing Incentives for Innovation*, *supra* note 1109, at 21 (statement of Mr. Leicher).

¹¹⁵³ *Id.* at 205 (statement of Ms. Stanek Rea).

¹¹⁵⁴ *Id.* at 47 (statement of Mr. Kushan).

¹¹⁵⁵ *Id.* at 80.

¹¹⁵⁶ *Id.* at 68.

¹¹⁵⁷ *Id.* at 69.

¹¹⁵⁸ *Id.* at 197, 209 (statement of Ms. Stanek Rea).

¹¹⁵⁹ *Id.* at 201.

¹¹⁶⁰ *Id.* at 207.

infringe the patent.”¹¹⁶¹ This would allow the applicant to challenge patents not related to the biosimilar “in the hope of obtaining freedom to practice the patent with respect to other products or operations.”¹¹⁶² In Ms. Stanek Rea’s view, “[t]his provision is counter to declaratory judgment standards, which require an actual case or controversy, may violate Article III of the U.S. Constitution, and could burden the federal judiciary with needless patent cases.”¹¹⁶³

Ms. Stanek Rea also stated that H.R. 1427 “lack[ed] sufficient mechanisms for referenced product holders or third-party patent owners . . . to obtain access to . . . information necessary to determine whether there is a good-faith basis for asserting an infringement claim.”¹¹⁶⁴ She also expressed concern that innovators would have insufficient information to determine whether to bring an infringement action in compliance with Rule 11 of the Federal Rules of Civil Procedure,¹¹⁶⁵ because this bill did not require a biosimilar applicant to provide the reference product sponsor with confidential access to the biosimilar application.¹¹⁶⁶

Ms. Stanek Rea also criticized H.R.’s 1427 list it or lose it provision, which states that failure to identify a patent to the applicant would render that patent unenforceable.¹¹⁶⁷ In her view, this provision “would likely create an entirely new unenforceability defense that would parallel the inequitable conduct defense in terms of the amount of discovery required,” particularly because the requirement to list would be tied to the reference product sponsor’s “good faith” and would require “inquiries into the subjective intent of reference product holder employees.”¹¹⁶⁸ Furthermore, because this “forfeiture provision apparently attache[d] to the patent itself . . . it could have profound implications” for all biotechnology patent litigation (not just pre-launch litigation) and transactions.¹¹⁶⁹ Litigants and potential purchasers or licensees would be required to engage in expensive and time-consuming inquiries to determine whether the involved patents had been rendered unenforceable based on failure to identify the patents in response to a single listing request.¹¹⁷⁰ Ms. Stanek Rea also expressed concern about the effect of the list it or lose it provision on third party patent holders: “a non-exclusive licensee of a university patent . . . could forfeit the university’s right to enforce the patent against any party, even if the university never received the follow-on applicant’s patent notification statement, and even if the reference product holder is not using the licensed method in its reference product or for any purpose.”¹¹⁷¹ She added that “there is a strong argument” that the list it or lose it provision would violate the Due Process Clause of the U.S. Constitution because “the request for information is directed only to

¹¹⁶¹ *Id.* at 209 (emphasis omitted).

¹¹⁶² *Id.* at 210.

¹¹⁶³ *Id.*

¹¹⁶⁴ *Id.* at 197.

¹¹⁶⁵ Rule 11 provides that the legal contentions in a complaint must be “warranted by existing law or by a nonfrivolous argument” for changing the law. FED. R. CIV. P. 11(b)(2). It also requires “the factual contentions [to] have evidentiary support” or to be “likely [to] have evidentiary support after a reasonable opportunity for further investigation or discovery.” FED. R. CIV. P. 11(b)(3). Courts may impose harsh penalties for failure to abide by this Rule. *See* FED. R. CIV. P. 11(c).

¹¹⁶⁶ *See Biologics and Biosimilars: Balancing Incentives for Innovation, supra* note 1109, at 208 (statement of Ms. Stanek Rea).

¹¹⁶⁷ *Id.* at 207-08; *see supra* notes 400 and 985 and accompanying text.

¹¹⁶⁸ *Biologics and Biosimilars: Balancing Incentives for Innovation, supra* note 1109, at 207 n.3 (statement of Ms. Stanek Rea).

¹¹⁶⁹ *Id.* at 208.

¹¹⁷⁰ *Id.*

¹¹⁷¹ *Id.* at 214.

the reference product holder.”¹¹⁷² In Ms. Stanek Rea’s view, patent provisions of biosimilar legislation should provide for “all [then] available remedies, including damages and injunctive relief, should patent infringement be found.”¹¹⁷³

7. Energy & Commerce Committee Passage of Eshoo Amendment

On July 13, members of the New Democrat Coalition wrote to the Speaker of the House, Nancy Pelosi (D-CA), noting their support for the second Eshoo bill (H.R. 1548) and urging that this language be included in the final version of the House health care reform bill.¹¹⁷⁴ According to the letter, the signatories were “concerned that without a clear position from the House, the final product from the conference committee could reduce the period of data protection under the legislation and upset the balance of procedures for both innovators and generics that will lead to timely resolution of patent disputes.”¹¹⁷⁵ Thus, according to the letter, “[a]n express endorsement by the House is necessary to demonstrate support for the underlying policy [of H.R. 1548] prior to conference negotiations.”

On July 14, several House Democrats — including Representatives Waxman and Pallone — unveiled their proposed health care reform legislation without biosimilars language or even a placeholder.¹¹⁷⁶ Representative Eshoo then filed an amendment that borrowed heavily from the regulatory provisions of the Hatch/Enzi/Hagan amendment while maintaining nearly all of the patent provisions from H.R. 1548.¹¹⁷⁷ More specifically, she offered the Hatch/Enzi/Hagan language with three changes.¹¹⁷⁸ First, she included the pediatric exclusivity language from H.R. 1548.¹¹⁷⁹ The Eshoo amendment thus offered a twelve-year period without any supplemental exclusivity other than pediatric exclusivity. Second, she included the provision from the second Eshoo bill that would have prohibited FDA from licensing a biosimilar containing a select agent or toxin without first consulting with national security and drug enforcement agencies and determining that there would be no increased risk to the security or health of the public from licensing the biosimilar.¹¹⁸⁰ Third, she included the naming provision from the second Eshoo bill, which would have required FDA to “ensure” that a biosimilar’s labeling and packaging bore a name that “uniquely identif[ie]d” it and that distinguished it from both the reference product and other products licensed as biosimilar to that reference product.¹¹⁸¹

¹¹⁷² *Id.*

¹¹⁷³ *See id.* at 200.

¹¹⁷⁴ Letter from Rep. Crowley (D-NY) et al. to Speaker Pelosi, at 3 (July 13, 2009).

¹¹⁷⁵ *Id.*

¹¹⁷⁶ H.R. 3200, 111th Cong. (2009). According to the trade press, this move was expected. *Eshoo Borrows from HELP Bill in Challenge to Waxman on Biologics*, FDA WEEK, July 17, 2009. *FDA Week* reported that “[l]obbyists believe[d] that [Representative Waxman] would [have] prefer[red] not to include any follow-on biologics proposal, even his own, in the reform bill prior to conference” and preferred to “knock down the Senate’s exclusivity period in conference” because this approach “would avoid the risks of compromising with (or losing to) Eshoo.” *Id.*

¹¹⁷⁷ *See generally* Amendment Offered by Ms. Eshoo of California, Mr. Inslee of Washington, and Mr. Barton of Texas, stamped F:\PI\NH\TRICOMM\MAMDS\ESHOO_001.XML, available at http://energycommerce.house.gov/Press_111/20090731/hr3200_eshoo_2.pdf, § __ (a)(2) (proposed PHSA § 351(k)); *see also* *Eshoo Borrows from HELP Bill in Challenge to Waxman on Biologics*, FDA WEEK, July 17, 2009.

¹¹⁷⁸ *See generally* Amendment Offered by Ms. Eshoo of California, Mr. Inslee of Washington, and Mr. Barton of Texas, *supra* note 1177, § __ (a)(2) (proposed PHSA § 351(k)).

¹¹⁷⁹ *Id.* (proposed PHSA § 351(k)(8)).

¹¹⁸⁰ *Id.* (proposed PHSA § 351(k)(5)(D)).

¹¹⁸¹ *Id.* proposed PHSA § 351(k)(10)).

Although the Eshoo amendment used the Hagan/Enzi/Hatch regulatory provisions (with the three changes just noted), it used the patent provisions from the second Eshoo bill, with two provisions deleted. These were: (1) the provision limiting declaratory judgment actions by the applicant to the last three years before expiry of the data exclusivity period;¹¹⁸² and (2) the artificial act of infringement, *i.e.*, the amendment to 35 U.S.C. § 271(e)(2) providing that it would be an act of infringement for a biosimilar applicant to provide to the reference product sponsor or an interested third party a statement challenging a patent that entity had identified.¹¹⁸³

Once it became apparent that Representative Eshoo had sufficient support in the Energy and Commerce Committee to secure passage of her amendment in the markup, a broad-based group including GPhA, AARP, health insurance companies, and unions stated that, rather than the Hatch/Enzi/Hagan language, they would prefer that no biosimilar language be included in the health care reform legislation.¹¹⁸⁴ During the Energy and Commerce Committee markup of H.R. 3200 on July 31, 2009, Representative Eshoo offered her amendment, and it was adopted by a vote of 47 to 11.¹¹⁸⁵

8. *Developments After Markup*

As noted, in September the HELP Committee reported its health care reform bill, with the Hatch/Enzi/Hagan language comprising Title VI, Subtitle A. Later that month, Representative Waxman, speaking at a GPhA conference, stated that “the war [was] not over.”¹¹⁸⁶ He said “[t]here are a lot of opportunities to revisit these issues. It may be in conference, it may be in other bills that we’ll be considering, it may be another way.”¹¹⁸⁷ Nevertheless, in late October, GPhA wrote to President Obama requesting that he “urge congressional leaders to strike the biogeneric language from pending health care reform legislation unless the provisions [were] materially altered.”¹¹⁸⁸ GPhA stated that the existing bills were “little more than camouflaged protection of the unacceptable and unsustainable status quo.”¹¹⁸⁹

On the same day, the House released its health care reform bill. It contained the Eshoo amendment, although three changes had been made.¹¹⁹⁰ First, any agreement between a reference product sponsor and biosimilar manufacturer or among multiple biosimilar manufacturers regarding manufacture, sale, or marketing of the biosimilar(s) or reference product would have needed to be reported to the FTC by each party to the agreement.¹¹⁹¹ Second, the draft included the artificial act of infringement that had been omitted when the Eshoo amendment had passed the Energy and Commerce Committee.¹¹⁹² Third, this version amended section 271(e)(4)

¹¹⁸² See *supra* note 878 and accompanying text.

¹¹⁸³ Compare Eshoo Amendment, § 602(a)(2) (proposed PHSA § 351(l)) with H.R. 1548, 111th Cong. § 101(a)(2) & 201 (proposed PHSA § 351(l)(6) & 35 U.S.C. 271(e)(2)(C)).

¹¹⁸⁴ *Generics, AARP, Unions Prefer No Biosimilars Path to 12-Year Exclusivity*, FDA WEEK, July 24, 2009.

¹¹⁸⁵ Alex Wayne, *House Health Compromise Includes Biologics Drug Competition*, CQ TODAY ONLINE NEWS — HEALTH, July 31, 2009.

¹¹⁸⁶ *Waxman Offers Generic Pledge to Keep Fighting on Biologics*, FDA WEEK, Sept. 25, 2009.

¹¹⁸⁷ *Id.*

¹¹⁸⁸ Letter from Kathleen Jaeger, President & CEO, GPhA, to Pres. Obama (Oct. 27, 2009).

¹¹⁸⁹ *Id.*

¹¹⁹⁰ House Health Care Reform Bill stamped F:\P11\NH\TRICOMM\HCAA_001.XML, §§ 2575-77 (Oct. 29, 2009).

¹¹⁹¹ *Id.* § 2575(a)(2) (proposed PHSA § 351(l)(6)).

¹¹⁹² *Id.* § 2577(a) (proposed 35 U.S.C. § 271(e)(2)(C)).

of title 35. This section of the Patent Act provides for the availability of damages, injunctions, and a stay on FDA approval of the biosimilar application in the event of a finding of patent infringement in the Hatch-Waxman setting. The biosimilar title in the House healthcare reform legislation would have provided that this section did not apply to remedies in patent litigation regarding biosimilars.¹¹⁹³ The bill passed the House on November 7, 2009.¹¹⁹⁴

In mid-November, the HELP-passed bill was consolidated with the bill that the Senate Finance Committee passed.¹¹⁹⁵ The consolidated health care reform package was known as the Patient Protection and Affordable Care Act (PPACA) and was drafted as an amendment (Amendment 2786) in the nature of a substitute to H.R. 3590. The biosimilars language, comprising Subtitle A of Title VII, was almost identical to the HELP-reported language. There was one significant difference: the released bill included pediatric exclusivity provisions identical to those in Kennedy's proposed language stamped 9151, circulated in late March.¹¹⁹⁶

9. Additional Proposed Amendments in the Senate

In early December, Senator Brown filed an amendment to Amendment 2786 that would have provided that reference product exclusivity expired on the earlier of: (1) twelve years after first licensure of the reference product, and (2) the date on which the gross sales from the reference product equaled \$3.5 billion.¹¹⁹⁷ At about the same time, Senator Sanders (I-VT) filed an amendment to Amendment 2786 that would have required FDA to establish a system for "cost-sharing arrangements," under which ANDA and biosimilar applicants could have obtained access to clinical data submitted by innovators for a fee payable to the innovators but set by FDA.¹¹⁹⁸

Later in December, Senator McCain offered an amendment that would have changed the Senate language in three major respects.¹¹⁹⁹ First, the amendment would not have permitted FDA to waive the clinical study requirement for biosimilars, and it would have allowed the agency to waive the analytical and animal study requirements only after public notice and comment.¹²⁰⁰ Second, the amendment would have

¹¹⁹³ *Id.* § 277(b) ((proposed 35 U.S.C. § 271(e)(4)).

¹¹⁹⁴ See H.R. 3962, 111th Cong. §§ 2575-77 (as passed by the House, Nov. 7, 2009). In making floor statements on the bill, several Representatives suggested that clinical studies would be necessary to support a finding of interchangeability for a biosimilar. See, e.g., 155 Cong. Rec. H 12623, H 12896 (daily ed. Nov. 7, 2009) (statement of Rep. Pascrell (D-NJ)) ("The legislation under consideration establishes a framework for allowing biosimilar competition in this country The creation of this new class of medicines comes with requirements for new clinical research and testing, especially in the area of new biosimilars' interchangeability with innovator products."); *id.* at H 12891 (statement of Rep. Payne (D-NJ)); *id.* at H 12911 (statement of Rep. Fillner (D-CA)).

¹¹⁹⁵ Amendment No. 2786 in the Nature of a Substitute to H.R. 3590, Title VII, Subtitle A (introduced Nov. 19, 2009), 155 Cong. Rec. S11794-S11799 (daily ed. Nov. 19, 2009); Mercedes Varasteh Dordeski, Senate Unveils Consolidated Health Care Reform Bill, Health Care Lawyer Blog (Nov. 19, 2009), http://www.healthcarelawyerblog.com/2009/11/senate_unveils_consolidated_he.html.

¹¹⁹⁶ Compare Amendment No. 2786 in the Nature of a Substitute to H.R. 3590, Title VII, Subtitle A (introduced Nov. 19, 2009), 155 Cong. Rec. S11794-S11799 (daily ed. Nov. 19, 2009) (proposed PHSA § 351(m)) with Draft stamped O:\KER\KER09151.xml __ (a) (proposed PHSA § 351(m)).

¹¹⁹⁷ Brown Amendment, No. 2895 to Amendment 2786, stamped WHI09B15 (Dec. 4, 2009).

¹¹⁹⁸ Sanders Amendment, No. 2858 to Amendment 2786, stamped KER09A11 (Dec. 2, 2009).

¹¹⁹⁹ The amendment also reflected changes to the short title of the biosimilars provisions (to the "Patient Access to Safe and Competitive Biologics Act"), cross-references, other minor editorial changes, and it clarified that the clinical study or studies generally required to show biosimilarity must be "conducted by the applicant." McCain Amendment, No. 3293, stamped KER09B55, § 7002(a)(2) (Dec. 20, 2009) (proposed PHSA § 351(k)(2)(A)(i)(I)(cc)).

¹²⁰⁰ See *id.* (proposed PHSA § 351(k)(2)(A)(i)(I) & (ii)).

made several changes to the interchangeability provisions, including substitution of the phrase “therapeutic equivalence” for “interchangeability” throughout the draft. It would have struck the definition of “interchangeable,” and it would have defined “therapeutic equivalence” as the situation where a biosimilar has “been determined to meet the standards described in subsection (k)(4).”¹²⁰¹ The amendment also would have inserted new paragraph (4)(B) providing that, “[n]otwithstanding any other provision of law, no biological product determined to be therapeutically equivalent to a reference product under subparagraph (A) shall be deemed to be therapeutically appropriate with respect to an individual unless so determined by a health care professional treating such individual.”¹²⁰²

Third, the amendment contained new data exclusivity provisions. The amendment would have provided for a four-year bar on submission and a ten-year bar on approval of a biosimilar application.¹²⁰³ The ten-year period could have been extended by two years if the sponsor submitted “a subsequent application for a change (not including a modification to the structure of the reference product) that results in a new indication for the reference product.”¹²⁰⁴ A separate provision stated that where the reference product “represent[ed] a significant therapeutic advancement (including a modification that results in a new dosage form, new dosing regimen, or new route of administration of such biological product)” of a product previously licensed to the “sponsor or manufacturer,” the data exclusivity period would be the sum of two years and “the remaining period of exclusivity under clause (i) for [the] biological product on which the reference product representing the significant therapeutic advancement was based.”¹²⁰⁵ This period could not be extended.¹²⁰⁶ Finally, the McCain amendment contained first licensure language identical to that in the Senate bill as reported in 2008. In other words, the first licensure date would not have included “the date of approval of a supplement or of a subsequent application for a new indication, route of administration, dosage form, or strength for the previously licensed reference product.”¹²⁰⁷

None of these amendments gained traction, and when the Senate passed H.R. 3590 on December 24, 2009, the biosimilar provisions were identical to those in the Senate consolidated healthcare reform bill.¹²⁰⁸

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On January 15, 2010, the trade press reported that the White House was urging “significant changes to [the] biosimilars provisions in health care reform legislation.”¹²⁰⁹ The requested changes supposedly included “a shorter exclusivity period” and changes to the language “believe[d] [to] allow drug makers to secure additional 12-year periods by making minor changes to their products.”¹²¹⁰ On January 19, the Governors of Colorado, Delaware, Massachusetts, Maryland,

¹²⁰¹ *Id.* § 7002(b)(3) (proposed PHSA § 351(i)(4)).

¹²⁰² *Id.* § 7002(a)(2) (proposed PHSA § 351(k)(4)(B)).

¹²⁰³ *Id.* (proposed PHSA § 351(k)(7)(A)(i) & (B)).

¹²⁰⁴ *Id.* (proposed PHSA § 351(k)(7)(A)(ii)).

¹²⁰⁵ *Id.* (proposed PHSA § 351(k)(7)(A)(iii)).

¹²⁰⁶ *Id.* (proposed PHSA § 351(k)(7)(A)(iv)).

¹²⁰⁷ *Id.* (proposed PHSA § 351(k)(7)(C)).

¹²⁰⁸ H.R. 3590, 111th Cong., Title VII, Subtitle A (as passed by Senate Dec. 24, 2009).

¹²⁰⁹ *White House Pressing for New Biosimilars Policy in Reform Talks*, FDA WEEK, Jan. 15, 2010.

¹²¹⁰ *Id.*

North Carolina, and Rhode Island wrote President Obama expressing concern about the White House's efforts.¹²¹¹ These Governors indicated they opposed changes to the data exclusivity period and first licensure provision, because these provisions "represent[ed] critical element[s] needed to ensure appropriate incentives for continued biomedical innovation."¹²¹² The signatories "urge[d]" the President to "continue working with the congressional leaders to carefully evaluate the product of the extensive work that they have already done on this matter and retain the provisions that were passed in both chambers of Congress."¹²¹³

The same day, Republican Scott Brown won the Massachusetts Senate seat left vacant after the August 2009 death of Senator Kennedy.¹²¹⁴ He had campaigned as the forty-first vote against health care reform in the Senate, depriving Democrats of a filibuster-proof majority.¹²¹⁵ And his victory was seen as "put[ting] the entire [health care] reform effort in jeopardy."¹²¹⁶ On February 22, the White House released a blueprint for health care reform that called for a biosimilars pathway but provided no specifics about the proposed exclusivity period or other aspects of the proposal.¹²¹⁷ The reform outline generally was framed as a package of changes to the Senate health care reform bill, and it was unclear whether the Administration's reference to a biosimilars pathway was meant to refer with approval to the biosimilars language in H.R. 3590.¹²¹⁸

The plan forward soon became clear: "in a legislative two-step, the House would approve the original Senate bill and a package of changes through [the budget] reconciliation [process]."¹²¹⁹ On March 21, the House passed H.R. 3590 and on March 23, the President signed it.¹²²⁰ The bill became Public Law 111-148. The reconciliation bill had been introduced on March 17 and did not affect the biosimilars language.¹²²¹ The reconciliation bill was passed by the House on March 21 and the Senate on March 25, and it became Public Law 111-152 on March 30.¹²²²

IV. BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009

In this section, the authors describe the current law, as revised by the BPCIA; the section thus uses current PHSA section numbers.

¹²¹¹ Letter from Governor O'Malley (D-MD) et al. to Pres. Obama, Jan. 19, 2010, at 1.

¹²¹² *Id.*

¹²¹³ *Id.*

¹²¹⁴ Michael Cooper, *G.O.P. Senate Victory Stuns Democrats*, N.Y. TIMES, Jan. 19, 2010.

¹²¹⁵ *Conservative Grassroots Strategy Propels Brown to Senate*, WASHINGTON INDEPENDENT, Jan. 20, 2010.

¹²¹⁶ *New Doubts About Health Reform Compound Uncertainty on Biosimilars*, FDA WEEK, Jan. 22, 2010.

¹²¹⁷ *Obama Health Reform Plan Includes Vague Statement on Biosimilars*, FDA WEEK, Feb. 26, 2010.

¹²¹⁸ *See id.*

¹²¹⁹ Sheryl Gay Stolberg, Jeff Zeleny, and Carl Hulse, *Health Vote Caps a Journey Back From the Brink*, N.Y. TIMES, Mar. 20, 2010. Because the BPCIA had been included in the healthcare reform legislation, the plan that emerged following the Massachusetts election meant there would be no further opportunities to revisit the Senate biosimilar language.

¹²²⁰ 156 Cong. Rec. H2152-53 (daily ed. Mar. 21, 2010); Remarks on Signing the Patient Protection and Affordable Care Act, 2010 Daily Comp. Pres. Doc. (Mar. 23, 2010).

¹²²¹ H.R. 4872, 111th Cong. (2010).

¹²²² 156 Cong. Rec. H2168-69 (daily ed. Mar. 21, 2010); Remarks on Signing the Health Care and Reconciliation Act of 2010 in Alexandria, Virginia, 2010 Daily Comp. Pres. Doc. (Mar. 30, 2010).

A. Pathway

1. Definitions and Scope

Under current law, the phrase “biological product” includes proteins, except chemically synthesized polypeptides.¹²²³ This means that naturally derived and recombinant proteins with approved NDAs are biological products. Once the ten-year transition period described below has ended, all proteins except chemically synthesized polypeptides will need to be the subject of BLAs.¹²²⁴ Only a “single biological product licensed under subsection (a)” may serve as a reference product for a biosimilar that is the subject of “an application submitted under subsection (k).”¹²²⁵ In other words, a biosimilar may not serve as a reference product for a 351(k) application, nor may an FDCA protein.¹²²⁶ The new biosimilar pathway is not limited to therapeutic products or to recombinant products; on its face, it applies also to vaccines and blood products, among other things.

2. Application Contents

Four years after approval of a biological product licensed under section 351(a), any person may submit a biosimilar application under section 351(k), using that biological product as its reference product.¹²²⁷ Each application must show that: first, the biological product that is the subject of the application is “biosimilar” to a reference product; second, the biological product and reference product use the same mechanism(s) of action for the condition(s) of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism(s) of action are known for the reference product; third, the reference product was previously licensed for the condition(s) of use prescribed, recommended, or suggested in the labeling proposed for the biological product; fourth, the biological product has the same route of administration, dosage form, and strength as the reference product; and finally, “the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.”¹²²⁸

A product is “biosimilar” to its reference product if it is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and if there are no “clinically meaningful differences” between the biological product that is the subject of the application and the reference product “in terms of safety, purity, and potency of the product.”¹²²⁹ A biosimilarity showing must be based on analytical studies, animal studies, and a clinical study or studies.¹²³⁰ The analytical studies should show that the proposed product is “highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and the animal studies should include an assessment of toxicity.¹²³¹ The clinical work should include an assessment of immunogenicity and pharmacokinetics or pharmacodynamics that

¹²²³ PHSA § 351(i)(1).

¹²²⁴ Pub. L. No. 111-148 § 7002(e).

¹²²⁵ PHSA § 351(i)(4).

¹²²⁶ As discussed below, on March 23, 2010, biological products approved under section 505 of the FDCA will be deemed licensed under section 351 of the PHSA. Until that time, they cannot be “reference products” for applications submitted under section 351(k) of the PHSA.

¹²²⁷ PHSA § 351(k)(7)(B).

¹²²⁸ *Id.* § 351(k)(2)(A)(i).

¹²²⁹ *Id.* § 351(i).

¹²³⁰ *Id.* § 351(k)(2)(A)(i)(I).

¹²³¹ *Id.* § 351(k)(2)(A)(i)(I)(aa) & (bb).

is “sufficient to demonstrate the safety, purity, and potency” of the product for one or more “appropriate” conditions of use for which licensure is sought and for which the reference product is licensed and intended to be used.¹²³²

A biosimilar application must also include publicly available information about FDA’s previous determination that the reference product is safe, pure, and potent.¹²³³ The applicant may also provide: (1) “any additional information in support of the application,” including publicly available information about the reference product or other biological products; and (2) information demonstrating that the biological product meets the legislation’s standards for interchangeability with the reference product.¹²³⁴ The latter may also be submitted in a supplement to the application.¹²³⁵ A biosimilar biological product that FDA has not determined meets the separate standard for “interchangeability” is considered to have a new active ingredient for purposes of section 505B of the FDCA.¹²³⁶ This means that the application must contain a pediatric assessment, unless this requirement has been waived or deferred.¹²³⁷

3. FDA Review and Standard of Approval

Every application for licensure of a biosimilar biological product must be reviewed by the FDA division that was responsible for review and approval of the reference product application.¹²³⁸ There are transitional user fee provisions. Until 2012, the prescription drug user fee system that applies to applications submitted under section 351(a) applies also to applications under section 351(k).¹²³⁹ FDA must adjust the user fee to account for differences between the cost of reviewing 351(a) applications and the cost of reviewing 351(k) applications.¹²⁴⁰ Following a process that is described in an uncodified version of the BPCIA, and no later than January 15, 2012, FDA must submit recommendations on performance goals for the biosimilar application review process to Congress.¹²⁴¹ User fees for biosimilar applications will be considered as part of PDUFA re-authorization.

FDA must license a biosimilar biological product if: (1) FDA determines that the information in the application (or supplement) “is sufficient to show that” the proposed product either (a) “is biosimilar to the reference product,” or (b) meets the legislation’s standards for interchangeability and “therefore is interchangeable with the reference product”; and (2) the applicant (or another appropriate person) consents to “inspection of the facility that is the subject of the application.”¹²⁴² As noted, a product is biosimilar if it is “highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and if there are no “clinically meaningful differences” between the biological product that is

¹²³² *Id.* § 351(k)(2)(A)(i)(I)(cc). FDA may determine that any of these elements is “unnecessary” in an application. *Id.* § 351(k)(2)(A)(ii). Under section 505(b) of the FDCA, a biosimilar applicant may use the special protocol assessment process to discuss with FDA the clinical study or studies “necessary” to support its application.

¹²³³ *Id.* § 351(k)(2)(A)(iii).

¹²³⁴ *Id.* § 351(k)(2)(A)(iii) and (B).

¹²³⁵ *Id.* § 351(k)(2)(B).

¹²³⁶ FDCA § 505B(n).

¹²³⁷ *Id.* § 505B(a)(1).

¹²³⁸ PHSA § 351(k)(5)(B).

¹²³⁹ Pub. L. 111-148, § 7002(f)(3).

¹²⁴⁰ *Id.*

¹²⁴¹ *Id.* § 7002(f)(1).

¹²⁴² PHSA § 351(k)(3).

the subject of the application and the reference product “in terms of safety, purity, and potency of the product.” As discussed in the next section, a product is “interchangeable” only if an additional showing is made.

Section 351(k) states that FDA’s authority with respect to risk evaluation and mitigation strategies (REMS) applies to biosimilar biological products licensed under section 351(k) “in the same manner” as it applies to biological products licensed under section 351(a).¹²⁴³ This allows FDA to impose a REMS at the time of licensure or any time after, if the standard in section 505-1 of the FDCA has been met. Section 505-1 already applies to applications “approved under section 351 of the Public Health Service Act,” so this provision of section 351(k) is probably superfluous.¹²⁴⁴

4. *Interchangeability*

FDA must determine that a biological product is interchangeable with a reference product if it determines that the information submitted in the application (or supplement) is sufficient to show that: (1) the product “is biosimilar to the reference product;” (2) the product “can be expected to produce the same clinical result as the reference product in any given patient;” and (3) if the product “is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between” the two products “is not greater than the risk of using the reference product without alternating or switching.”¹²⁴⁵ Under section 351(i) of the PHSA, which lays out definitions, if a biosimilar is “interchangeable,” then it “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”¹²⁴⁶

5. *Guidance Documents*

Section 351(k) of the PHSA authorizes but does not require FDA to issue guidance documents on the licensure of biosimilar biological products.¹²⁴⁷ This guidance must be issued in accordance with section 701(h) of the FDCA except that the agency must provide the public with a chance to comment on any proposed guidance document before adopting the guidance in final form.¹²⁴⁸ In addition, the agency must establish a process through which the public may provide input on priorities for issuing guidance.¹²⁴⁹ Issuance of guidance, or non-issuance of guidance, does not preclude review of, or action on, an application submitted under the section.¹²⁵⁰

¹²⁴³ *Id.* § 351(k)(5)(C).

¹²⁴⁴ Section 505(o), which was also added to the statute in 2007 and which gives FDA authority to require postmarketing studies, postmarketing trials, and safety-related labeling changes, similarly applies to applications approved under section 351.

¹²⁴⁵ PHSA § 351(k)(4).

¹²⁴⁶ *Id.* § 351(i).

¹²⁴⁷ *See id.* § 351(k)(8).

¹²⁴⁸ *Id.* § 351(k)(8)(A). Section 701(h) requires FDA to develop guidance documents “with public participation” and to ensure that information identifying the existence of such documents and the documents themselves are made available to the public both in written form and, as feasible, through electronic means. Guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, must be the subject of public participation prior to implementation, unless prior public participation is not feasible or appropriate. For guidance documents that set forth existing practices or minor changes in policy, FDA must provide for public comment upon implementation.

¹²⁴⁹ *Id.* § 351(k)(8)(B)(ii).

¹²⁵⁰ *Id.* § 351(k)(8)(C).

Guidance documents may be generally applicable or specific to a product class. If FDA issues a class-specific guidance, it must describe the criteria it will use to determine whether a biological product is “highly similar” to a reference product in that product class, as well as the criteria “if available” that will be used to determine whether a biological product is interchangeable with a reference product.¹²⁵¹ FDA may indicate in a class-specific guidance that current science and experience do not allow licensure of biosimilar applications with respect to a particular product or product class, except the agency may not do so with respect to recombinant proteins.¹²⁵² Any such statement may be modified or reversed in subsequent guidance.¹²⁵³ Section 351(k) adds that the authority to issue a guidance document stating that particular biosimilar products cannot be licensed may not be construed to mean that if FDA has not done so, any particular biosimilar application must be approved.¹²⁵⁴

6. FDCA Transition Provisions

Unlike the Hatch-Waxman amendments, the BPCIA did not contain special exclusivity rules for products licensed prior to its enactment. Because it changed the definition of “biological product” to include proteins, however, it contained transitional provisions to govern biosimilar versions of FDCA proteins. Specifically, under a section of the public law that was not codified, any application for a “biological product” (now defined to include “proteins”) must be submitted under section 351 of the PHSA.¹²⁵⁵ Under another uncodified provision, however, an application for a biological product (including a protein) may be submitted under section 505 of the FDCA if: (1) the product is in a product class for which a biological product in that class is the subject of an application approved under the FDCA before enactment of the Act, *i.e.*, March 23, 2010; and (2) the application was submitted before enactment, *i.e.*, March 23, 2010; or is submitted no later than ten years after enactment, *i.e.*, March 23, 2020.¹²⁵⁶ Notwithstanding this rule, an application may not be submitted under section 505 if there is “another biological product” licensed under section 351(a) of the PHSA that could serve as the reference product for that application.¹²⁵⁷ Finally, ten years after enactment, *i.e.*, March 23, 2020, any approved new drug application (NDA) for a biological product will be deemed a license under section 351 of the PHSA.¹²⁵⁸

B. Exclusivity

1. Exclusivity for Interchangeable Biosimilars

Section 351(k) of the PHSA provides a kind of exclusivity for the first biosimilar to be found interchangeable with a particular reference product. Although modeled on the 180-day exclusivity provision of the Hatch-Waxman amendments, its connection to patent challenges is more tenuous. The first biological product determined to be interchangeable with a particular reference product for any condition of use

¹²⁵¹ *Id.* § 351(k)(8)(D).

¹²⁵² *Id.* § 351(k)(8)(E)(i).

¹²⁵³ *Id.* § 351(k)(8)(E)(ii).

¹²⁵⁴ *Id.* § 351(k)(8)(E)(iii).

¹²⁵⁵ Pub. L. 111-148 § 7002(e)(1).

¹²⁵⁶ *Id.* § 7002(e)(2).

¹²⁵⁷ *Id.* § 7002(e)(3).

¹²⁵⁸ *Id.* § 7002(e)(4).

receives a period of exclusivity, during which no other product may be deemed interchangeable to that reference product for any condition of use.¹²⁵⁹ The exclusivity period terminates on the earlier of: (1) one year after “first commercial marketing of the first interchangeable biosimilar;” (2) if a patent infringement case has been brought against the applicant for the first interchangeable biosimilar biological product under section 351(l)’s provisions for “immediate” patent litigation, eighteen months after either a final court decision on all patents in suit or the dismissal of the patent action with or without prejudice; (3) forty-two months after licensure of the first interchangeable biosimilar biological product, if a patent action was commenced against the applicant under these provisions and the litigation is still ongoing; or (4) eighteen months after licensure of the first interchangeable biosimilar biological product, if the applicant was not sued under these provisions.¹²⁶⁰

2. Data Exclusivity

Under subparagraph (A) of section 351(k)(7), no biosimilar application may be submitted until four years after approval of the reference product BLA. Under subparagraph (A), no biosimilar application may be approved until twelve years after approval of the reference product BLA.¹²⁶¹ Both periods run from “the date on which the reference product was first licensed under subsection (a)” of section 351.¹²⁶² Subparagraph (C) provides that “[s]ubparagraphs (A) and (B) shall not apply to a license for or approval of” the following: (1) any supplement to a reference product BLA; (2) any “subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity)” for either: (a) “a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength”; or (b) “a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.”¹²⁶³

3. Pediatric Provisions

Six months of pediatric exclusivity are available for reference biological products under section 351(m) of the PHSa. A reference product sponsor is entitled to this exclusivity if: (1) FDA has determined that information relating to use of the reference product in pediatric patients “may produce health benefits in that population;” (2) the agency has made a written request for pediatric studies, which includes a timeframe for completing those studies; (3) the reference product sponsor agreed to the request; (4) the studies were completed, within the specified timeframe, using appropriate formulations for each age group for which they were

¹²⁵⁹ PHSa § 351(k)(6).

¹²⁶⁰ *Id.* § 351(k)(6). “Final court decision” means a final decision of a court from which no appeal (other than a petition for a writ of certiorari to the United States Supreme Court) has been or can be taken. *Id.*

¹²⁶¹ *Id.* § 351(k)(7)(A) & (B).

¹²⁶² *Id.* If a reference product has been orphan-designated, “a biological product seeking approval for [the orphan indication] under [section 351(k)] as biosimilar to, or interchangeable with, such reference product may be licensed by [FDA] only after the expiration for such reference product of the later of”:[] (1) the seven-year orphan exclusivity period; and (2) the 12-year period under section 351(k)(7) of the PHSa. Pub. L. 111-148, § 7002(h) (2010).

¹²⁶³ PHSa § 351(k)(7)(C).

requested; and (5) FDA accepted the reports in accordance with section 505A(d) (3) of the FDCA.¹²⁶⁴ If pediatric exclusivity is obtained, it extends by six months the four-year bar on submission of a biosimilar application, the twelve-year bar on approval, and (if applicable) the seven-year period of orphan exclusivity for the biologic.¹²⁶⁵ It will do so, however, only if FDA accepted the study reports no later than nine months prior to the expiration of the period in question.¹²⁶⁶

Section 351(m)(1) of the PHS Act states that certain subsections of FDCA section 505A “apply with respect to extension of a period . . . to the same extent and in the same manner as such provisions apply with respect to the extension of a period under . . . section 505A.”¹²⁶⁷ The cross-referenced subsections are: (a), (d), (e), (f), (i), (j), (k), (l), (p), and (q).¹²⁶⁸ Subsection (a) provides definitions.¹²⁶⁹ Subsection (d) relates to FDA’s issuance of written requests for pediatric studies and applicants’ responses to written requests.¹²⁷⁰ It also provides that FDA’s only responsibility in deciding whether to accept the reports is to determine whether the studies “fairly respond” to the request, were “conducted in accordance with commonly accepted scientific principles and protocols,” and comply with FDA filing requirements.¹²⁷¹ Subsection (e) requires FDA to publish notices of determinations to accept study reports.¹²⁷² It also directs the agency to publish notices of drugs for which pediatric formulations were found to be safe and effective in a pediatric population, if—within a year after FDA published its determination that it would accept the reports—a pediatric formulation for the drug is not marketed.¹²⁷³ Subsection (f) relates to agency review of written requests and pediatric studies and to making related information publicly available.¹²⁷⁴ Subsection (i) applies to labeling changes resulting from a pediatric study conducted under section 505A.¹²⁷⁵ Subsection (j) requires FDA to order additional information to appear in a drug’s labeling if it finds that a pediatric study conducted under section 505A does or does not demonstrate that the drug is safe and effective in pediatric populations.¹²⁷⁶ Subsection (k) concerns public dissemination of pediatric information.¹²⁷⁷ Subsection (l) relates to adverse event reporting.¹²⁷⁸ Subsection (p) requires FDA to enter into a contract with the Institute of Medicine (IOM) for a study on written requests.¹²⁷⁹ Subsection (q) provides that the pediatric exclusivity provisions will sunset in 2012.¹²⁸⁰

¹²⁶⁴ PHS Act § 351(m)(2) & (3).

¹²⁶⁵ *Id.* § 351(m)(2)(A) & (B), (m)(3)(A) & (B).

¹²⁶⁶ *Id.* § 351(m)(4).

¹²⁶⁷ *Id.* § 351(m)(1).

¹²⁶⁸ *Id.*

¹²⁶⁹ FDCA § 505A(a).

¹²⁷⁰ *Id.* § 505A(d).

¹²⁷¹ *Id.* § 505A(d)(3).

¹²⁷² *Id.* § 505A(e).

¹²⁷³ *Id.*

¹²⁷⁴ *Id.* § 505A(f).

¹²⁷⁵ *Id.* § 505A(i).

¹²⁷⁶ *Id.* § 505A(j).

¹²⁷⁷ *Id.* § 505A(k).

¹²⁷⁸ *Id.* § 505A(l).

¹²⁷⁹ Section 505A(p) of section 505A was also revised. It now requires that the IOM study consider, among other things, certain issues relating to biological products being tested for pediatric use and recommendations for ensuring pediatric testing of biological products.

¹²⁸⁰ FDCA § 505A(q).

C. Patent Provisions

1. Notification and Information Exchange Processes

Section 351(l) of the PHSA provides a default process for exchange of information prior to patent litigation. The parties may agree to a different process. The statutory process involves several steps.

First, the biosimilar applicant must provide a copy of its application and information about the manufacturing process to the reference product sponsor. The biosimilar applicant must do so within twenty days after FDA notifies the applicant that the application has been accepted for review.¹²⁸¹ Outside counsel and one in-house lawyer for the reference product sponsor, neither of which have participated in patent prosecution relating to the reference product, may review the application and other information provided.¹²⁸² Also, a representative of a third-party patent owner may review these materials.¹²⁸³ Any materials provided may not be disclosed without the prior written consent of the biosimilar applicant and may be used only to identify relevant patents to assert.¹²⁸⁴ These confidentiality restrictions govern until a court enters a protective order.¹²⁸⁵

Second, the reference product sponsor must, within sixty days of receiving the biosimilar application, provide the biosimilar applicant with a list of patents for which it believes it (or a third-party patent owner that has granted an exclusive license to it) could reasonably assert a claim of infringement and indicate which of those patents it would be prepared to license.¹²⁸⁶ This list must be supplemented within thirty days of the subsequent issuance or exclusive licensing of a patent satisfying the same criterion.

Third, within another sixty-day period, the biosimilar applicant must provide to the reference product sponsor a detailed statement as to each patent either: (1) that it will not market its product prior to patent expiry or (2) on a claim-by-claim basis, why the patent is invalid, unenforceable, or not infringed.¹²⁸⁷ It must also respond to any offer to license, and it may respond with its own list of patents as to which it believes the reference product sponsor (or a third-party patent owner that has granted an exclusive license to it) could reasonably assert a claim of infringement.¹²⁸⁸

Fourth, within a further sixty days, the reference product sponsor must provide a response to the detailed statement that the biosimilar applicant provided, consisting of a detailed, claim-by-claim statement as to why the patent will be infringed, or is valid and enforceable (as appropriate).¹²⁸⁹

¹²⁸¹ PHSA § 351(l)(2).

¹²⁸² *Id.* § 351(l)(1)(B)(ii).

¹²⁸³ *Id.* § 351(l)(1)(B)(iii).

¹²⁸⁴ *Id.* § 351(l)(1)(C), (D).

¹²⁸⁵ *Id.* § 351(l)(1)(F).

¹²⁸⁶ *Id.* § 351(l)(3)(A).

¹²⁸⁷ *Id.* § 351(l)(3)(B).

¹²⁸⁸ *Id.* If a relevant patent issues or is licensed to the reference product sponsor after it provides its initial patent list, then it must supplement the list within thirty days and the biosimilar applicant must provide its detailed statement explaining why the patent is not infringed or is invalid or unenforceable within a further thirty days. *Id.* § 351(l)(7). Absent agreement of the parties, such patents will not be part of the first phase of patent litigation. If the reference product sponsor fails to supplement its list, it cannot bring suit on that patent against the biosimilar applicant.

¹²⁸⁹ *Id.* § 351(l)(3)(C).

2. *First Phase of Patent Litigation*

The BPCIA establishes a two-phase litigation process that represents a radical departure from traditional patent litigation. For fifteen days after the reference product sponsor provides its response, the biosimilar applicant and the reference product sponsor must negotiate upon a list of patents that should be litigated immediately.¹²⁹⁰ If they agree, the reference product sponsor has thirty days to bring suit on the listed patents.¹²⁹¹ If the parties cannot agree, the BPCIA prescribes a procedure for determining which patents will be litigated immediately. The biosimilar applicant is to specify the number of patents it intends to list in a subsequently exchanged list of patents.¹²⁹² No more than five days later, the parties exchange lists of patents that they want litigated immediately.¹²⁹³ The reference product sponsor may not list more patents than the number provided by the biosimilar applicant, with the exception that it is always allowed to list at least one patent.¹²⁹⁴ The reference product sponsor must then bring suit on the listed patents within thirty days.¹²⁹⁵ Once the complaint is served, the biosimilar applicant has thirty days to provide FDA with notice and a copy of the complaint.¹²⁹⁶ FDA then publishes the notice in the Federal Register.¹²⁹⁷

3. *Notice of Commercial Marketing: Second Phase of Patent Litigation*

The biosimilar applicant must provide notice to the reference product sponsor 180 days before commercial marketing of its biosimilar product.¹²⁹⁸ At that time, the reference product sponsor may seek a preliminary injunction on any patent identified in the initial lists that was not included in the immediate litigation phase,¹²⁹⁹ as well as any patent identified in a supplement to the list.¹³⁰⁰

4. *Available Remedies and Potential Limitations on Those Remedies*

The Patent Code mandates an injunction if: (a) a patent was litigated in the first phase of patent litigation, (b) there is a final court decision that the patent is infringed, and (c) the data exclusivity period has not expired.¹³⁰¹ Under all other

¹²⁹⁰ *Id.* § 351(l)(4)(A), (B).

¹²⁹¹ *Id.* § 351(l)(6)(A).

¹²⁹² *Id.* § 351(l)(5)(A).

¹²⁹³ *Id.* § 351(l)(5)(B).

¹²⁹⁴ *Id.* § 351(l)(5)(B)(ii).

¹²⁹⁵ *Id.* § 351(l)(6)(B). The Patent Code provides that submitting an application for a biosimilar product is an act of infringement with respect to any patent on the patent lists provided by the reference product sponsor or biosimilar applicant or on any supplement to that list. 35 U.S.C. § 271(e)(2)(C)(i). If the applicant does not provide its application and manufacturing information to the reference product sponsor, then submission of its application constitutes an act of infringement as to any patent that could have been identified by the reference product sponsor in its initial patent list. *Id.* § 271(e)(2)(C)(ii).

¹²⁹⁶ PHS § 351(l)(6)(C).

¹²⁹⁷ *Id.* § 351(l)(6)(C)(ii).

¹²⁹⁸ *Id.* § 351(l)(8)(A).

¹²⁹⁹ *Id.* § 351(l)(8)(B).

¹³⁰⁰ *Id.* § 351(l)(7).

¹³⁰¹ 35 U.S.C. § 271(e)(4)(D).

circumstances, an injunction is not mandatory and presumably will issue only if the reference product sponsor satisfies the traditional four-part test.¹³⁰² An injunction will not be available, and the reference product sponsor and third party patent owner will be limited to a reasonable royalty, if the reference product sponsor did not initiate patent litigation within thirty days of the creation of the list of patents for immediate patent litigation or it did initiate litigation on time, but the suit was dismissed without prejudice or was not prosecuted in good faith.¹³⁰³ Moreover, if the patent should have been, but was not, included on the reference product sponsor's initial or supplemental list, the owner of the patent (whether or not the reference product sponsor) may not bring suit on that patent with respect to that biosimilar product.¹³⁰⁴

The usual rule is that prior to the 180-day notice of commercial marketing neither the reference product sponsor nor the biosimilar applicant may bring an action for a declaratory judgment with respect to any patent that was on the initial lists but was not part of the immediate litigation phase.¹³⁰⁵ If the biosimilar applicant fails to timely provide a copy of its application and manufacturing information to the reference product sponsor, only the reference product sponsor may bring a declaratory judgment action with respect to a patent that claims the biological product or a use of that product.¹³⁰⁶ Moreover, if the biosimilar applicant fails to take any of the following required steps, the reference product sponsor may bring a declaratory judgment action on any patent on its own initial or supplemental list: (1) provide a detailed statement in response to the reference product sponsor's initial or supplemental lists; (2) provide a list of patents for immediate litigation after agreement could not be reached; (3) provide notice of the litigation and a copy of the complaint to FDA; or (4) provide notice to the reference product 180 days before commercial marketing.¹³⁰⁷

5. Key Differences between the BPCIA and the Hatch-Waxman Amendments

In several respects, the patent provisions of the BPCIA represented a radical departure from those contained in the Hatch-Waxman amendments. The information provided in the *Orange Book* for patent litigation proceeding under the Hatch-Waxman amendments — which patents cover which products — is instead provided through an information exchange process.¹³⁰⁸ Process patents, which may not be listed in the *Orange Book*, are addressed in, and clearly may be asserted during, litigation under the BPCIA.¹³⁰⁹ Bringing suit under the BPCIA does not stay approval of the biosimilar application as occurs under the Hatch-Waxman amendments when suit is timely brought against the generic drug applicant.¹³¹⁰ Similarly,

¹³⁰² See *supra* at section I.D (discussing *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 394 (2006), which held that a court should apply the traditional four-factor test when determining whether a permanent injunction should issue in a patent infringement action).

¹³⁰³ 35 U.S.C. § 271(e)(6)(A), (B).

¹³⁰⁴ *Id.* § 271(e)(6)(C).

¹³⁰⁵ PHS § 351(l)(9)(A).

¹³⁰⁶ *Id.* § 351(l)(9)(C).

¹³⁰⁷ *Id.* § 351(l)(9)(B).

¹³⁰⁸ See FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (30th ed. 2010).

¹³⁰⁹ PHS § 351(l)(2)(A) (providing that the applicant must provide information that “describes the process or processes used to manufacture the biological product that is the subject of the application”).

¹³¹⁰ See FDCA § 505(j)(5)(B)(iii) (providing for a thirty-month stay if the NDA holder sues the generic within forty-five days of the generic's notice letter).

there is no statutory bar on FDA approval even where the applicant indicates it will wait until patent expiry, or, except in very limited circumstances, where the reference product sponsor wins the patent suit.¹³¹¹ There also is no parallel in the BPCIA to the 180-day exclusivity provided by the Hatch-Waxman amendments as an incentive to challenge or design around patents.¹³¹² Perhaps the most important departure from the patent litigation regime established by the Hatch-Waxman amendments is the conduct of the litigation itself. Litigation under the Hatch-Waxman amendments remains traditional patent litigation, with patentees able to assert any patents as to which a reasonable claim of infringement could be made. In contrast, the BPCIA may operate to prevent patentees from asserting the relevant patents during the initial phase of litigation because the biosimilar applicant dictates how many patents can be asserted in the first instance.

V. CONCLUDING OBSERVATIONS

Assembling and setting down this informal, though voluminous, legislative history gave the authors an opportunity to consider in depth whether and to what extent the story of the BPCIA is like, and unlike, the story of the Hatch-Waxman amendments. Three conclusions emerged.

First, as was true of the Hatch-Waxman amendments, the BPCIA was enacted after many years of stakeholder discussions — within the industry, at the agency, through citizen petition dockets, in journals, in legislative hearings, in markups, and on the Hill more generally — of, as far as the authors can tell, every key scientific and policy issue that needed to be addressed. Every provision of the final legislation — from the clinical trial requirements to the data exclusivity term — had been publicly vetted for at least several years, and consensus on some points (such as the need for case by case determinations of the data requirements) had been evident for the better part of a decade. The purely scientific issues, of course, were discussed as early as the late 1990s, open stakeholder discussions of these issues occurred as early as 2001, and Congress began exploring them in earnest in 2004. FDA participated fully in these discussions. And even the basic policy issues — such as the length of the data exclusivity term and the nature of (and even advisability of) the patent litigation process — were thoroughly debated years before enactment of the legislation. For example, whether there would be data exclusivity was first raised in 2006. The number of years was debated as early as 2007, with even then some saying fourteen years, others saying ten, and others saying five. To give another example, whether there would be a connection between application approval and the status of any relevant patents (or patent infringement litigation) was openly discussed in 2007. The advisability of a public process to flesh out data requirements was considered in a hearing in 2007. And whether the statute should prohibit (or perhaps require) distinct nonproprietary names was first raised in 2006. While some issues (such as the “evergreening issue”) were not fully articulated until 2007, the authors are not aware of a single significant scientific or policy decision reflected in the final legislation that was not the subject of several years of bipartisan multi-stakeholder discussion.

Second, a variety of approaches to key issues were drafted, considered repeatedly, and in the end not adopted. This fact must influence interpretation of the final enacted provisions. Chief among them was the question whether the legislation should include a pathway comparable to FDA’s view of section 505(b)(2) of the FDCA, *i.e.*, a pathway for products that are different in some fashion from the reference product. Representative Waxman proposed this second pathway in 2006.

¹³¹¹ See *id.* § 505(j)(5)(B) (specifying the timing of approval for an ANDA).

¹³¹² See *id.* § 505(j)(5)(B)(iv).

He proposed it again in 2007 and yet again in 2009, and on July 31, 2009, the House Energy and Commerce Committee — which he chaired — voted 47 to 11 instead for a biosimilar scheme that contained only one biosimilar pathway. Equally important was the length of the exclusivity period for innovative biological products, and this too was vetted exhaustively. It is challenging to find, in the legislative history of the Hatch-Waxman amendments, extensive or evidence-focused discussion of the length of the chosen exclusivity period. The opposite is true in the history of the BPCIA. Opinions were offered by the generic industry, the innovative industry, venture capitalists, and AARP, among others. Economic scholarship linking exclusivity terms to the cost of research and development was considered. A key European government official offered his perspective. The Federal Trade Commission and the White House weighed in. Although Representative Waxman initially suggested zero years of exclusivity, the exclusivity terms seriously on the table during this multi-stakeholder discussion from 2006 to 2010 ranged from five years to fourteen years. And yet a genuinely bipartisan Member-level compromise of twelve years, reached in the summer of 2007, remained intact through three subsequent years of legislative debate and found its place in the final law. Equally important was the question whether and when subsequent applications would be entitled to a distinct twelve year period or instead treated as the continuation of a previously approved product. On this issue, discussions occurred from 2007 to 2010. The final legislation precludes a new twelve-year period for supplements and also for new applications for: (1) a change (not including a structural modification) that results a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength, and (2) a structural modification that does not result in a change in safety, purity, or potency. Considered *and rejected* were a variety of other proposals that would have precluded exclusivity for, among other things, changes in amino acid sequence, pegylation, glycosylation, and differences that render two products the same for orphan drug purposes.

Third, as was also true of the Hatch-Waxman amendments, the BPCIA represented a meaningful compromise between biosimilar industry and innovator industry interests. The Hatch-Waxman amendments had joined patent term restoration efforts, on the one hand, with a generic approval pathway, on the other hand. In 2010, there was no marriage of competing bills. But the final decisions on key issues were the subject of bipartisan agreement and represented a middle ground between innovator and generic interests. For example, the twelve-year exclusivity term was the subject of a bi-partisan member-level agreement, and it was neither as long (fourteen years) nor as short (five to seven years) as alternatives genuinely under consideration. To give another example, a statutory provision describing the interchangeability standard, but not requiring interchangeability determinations upon approval, was not what either industry initially urged. Many stakeholders would have preferred language that unambiguously required clinical trials, and others supported a waiver provision that extended even to immunogenicity data. There were no floor statements upon passage to solidify the impression that a compromise was reached on these and other key issues, but the extensive informal legislative history in the preceding sections shows one was.

This exercise also taught the authors that the European experience was enormously influential. Not only did the European approvals beginning in 2006 put pressure on FDA and Congress to act, but stakeholders repeatedly referenced the European scheme and experience, a European government official participated in the process, one Member offered exclusivity provisions clearly modeled on the European approach, and the final legislation in many respects track the European model. For example, it

assumes that the contents of biosimilar applications will vary from product class to product class and that the scientific regulator should have discretion to dictate those contents; it requires that analytical, preclinical, and clinical testing be comparative in nature; it permits only one reference product per biosimilar and requires that the reference product be one that was supported by a full marketing application; it suggests a public guidance process for development of scientific standards; and it raises the special issue of immunogenicity. Given the extent to which Members of Congress looked to the European experience for guidance, one would expect FDA to take a similar approach as it implements the regulatory pathway. As Mr. Rossignol observed in 2007, there is no obvious reason why scientific requirements should be different on one side of the Atlantic than on the other.