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

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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. 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.

Patient Protection and Affordable Care Act, Pub. L. No. 111-148, Title V, 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. 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. 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. 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. This statute prohibited the adulteration and misbranding of drugs marketed in interstate commerce, but these terms were defined narrowly, 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." 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. The apparent overlap between the drug statute and the biologics statute has
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. Early bills did not contain an explicit safety or premarket review requirement, 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, members of Congress added both to the pending legislation. 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.” 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. 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. When sufficient safety data were obtained from these trials, the sponsor could submit a new drug application (NDA), which would take effect in sixty days unless the government rejected the application.

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. 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). 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. Following enactment of the 1938 law, a number of manufacturers concluded that their products were not new drugs and distributed those products without NDAs. We now use the term “generic” to refer not to the active ingredient but to the finished drug product. See infra note 54.

\[\text{footnotes}~10~S.~1944,~73rd~Cong.~(as~introduced~by~Mr.~Copeland,~June~12,~1933).\]
\[\text{footnotes}~11~See,~e.g.,~S.~2000,~73rd~Cong.~(as~introduced~by~Mr.~Copeland,~Jan.~4,~1934);~S2858,~73rd~Cong.~(as~introduced~by~Mr.~McCarran,~Feb.~21,~1934);~H.R.~7964,~73rd~Cong.~(as~introduced~by~Mrs.~Jenckes,~Feb.~14,~1934).\]
\[\text{footnotes}~12~See~Paul~A.~Offit,~The~Cutter~Incident~157-58~(2005).~Because~the~Food~and~Drugs~Act~contained~no~safety~requirement,~the~government~had~been~forced~to~proceed~against~elixir~sulfanilamide~on~a~misbranding~theory—specifically,~that~it~was~incorrectly~labeled~as~an~“elixir”~but~contained~no~alcohol.~See~id.~at~158.\]
\[\text{footnotes}~13~S.~5,~75th~Cong.~(as~reported~to~the~House,~Apr.~14,~1938).\]
\[\text{footnotes}~14~Pub.~L.~No.~75-717,~§~201(g),~52~Stat.~1040,~1041~(1938).\]
\[\text{footnotes}~15~Id.~§~201(p),~52~Stat.~at~1041-42.\]
\[\text{footnotes}~16~Id.~§§~505(a),~(b),~and~(i),~52~Stat.~at~1052-53.\]
\[\text{footnotes}~17~See~id.~§~505(b),~52~Stat.~at~1052~(requiring~submission~to~contain~“full~reports~of~investigations”~performed~to~determine~whether~the~new~drug~was~safe~for~use).\]
\[\text{footnotes}~18~Id.~§~505(c),~52~Stat.~at~1052.\]
\[\text{footnotes}~19~Id.~§~201(p),~52~Stat.~at~1041-42.\]
\[\text{footnotes}~20~We~now~use~the~term~“generic”~to~refer~not~to~the~active~ingredient~but~to~the~finished~drug~product.~See~infra~note~54.\]
\[\text{footnotes}~21~Pub.~L.~No~75-717,~§~201(p)(1),~52~Stat.~at~1041-42.\]
\[\text{footnotes}~22~40~Fed.~Reg.~26142,~26143~(June~20,~1975).\]
In some cases the manufacturer made its own determination that the drug was GRAS, and in others the manufacturer relied on a “not new drug” opinion issued by the agency. The agency kept no record of these opinions.

2. Implementation of the Kefauver-Harris Amendments

In 1962, following the thalidomide tragedy, Congress substantially reworked the drug provisions of the FDCA. 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. The “effectiveness” requirement was subject to a “substantial evidence” standard. 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. Second, it converted the premarket notification process to a premarket approval process, and it required FDA to review for effectiveness all products with NDAs that had become effective since enactment of the FDCA.

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. 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. FDA also revoked all of its old drug opinions. 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.
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.
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]mplied 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 Evaluation\(^{43}\) and, following litigation,\(^{44}\) published in the Federal Register.\(^{45}\)


\(^{38}\) 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.”).


\(^{40}\) 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).

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. FDA intended to add to the eligibility period over time and then shift the end date by one year each year. ANDAs would be permitted only if the pioneer product had been marketed for at least sixteen years. A proposed rule was leaked to the press in 1982, 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 regulation, was also considered at one point. 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. 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.

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, 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).


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.


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. 1337, 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. The Hatch-Waxman amendments were supported by members of Congress in both parties, and both the Pharmaceutical Manufacturers Association (PMA) and the Generic Pharmaceutical Industry Association (GPIA) endorsed the final legislation.

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. 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. Indeed, as under the prior ANDA policy, the agency may not request preclinical or clinical data to support the generic drug’s approval. 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. 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. 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.

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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).


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. 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).
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. 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. It may state that there are no such patents listed or that the patent(s) have expired. 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. The latter is a paragraph IV certification and requires notice to be sent to the NDA holder and the patent owner, if different. 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. Filing an ANDA with a paragraph IV certification is an act of patent infringement creating federal court jurisdiction for litigation. For forty-five days after the noticed 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.

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. 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). 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. 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. 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.

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).
70 FDCA § 505(j)(5)(B)(iii).
71 Id. § 505(j)(5)(B)(ii).
72 Id. § 505(j)(5)(B)(iii).
73 Id.
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)(i)(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 approval . . . .

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. 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. 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. 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

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76 FDCA § 505(b)(2).
77 Id. § 505(b)(2)(A).
78 Id. § 505(c)(3)(C).
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. 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. FDA regulations also generally provided for nondisclosure of preclinical and clinical data in NDAs. These regulations dated to the early 1970s and were predicated on section 301(j) of the FDCA, the Federal Trade Secrets Act, and exemption 4 of the Freedom of Information Act. 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. 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). 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.

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. There was an exception for generic applications containing paragraph IV certifications, which could be submitted after four years. 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. 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.

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80 See supra at I.A.3.
81 See supra at I.A.3.
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).
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)(vi)(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(i) 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 EDGA. 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 Procardia 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 Procardia did not receive exclusivity).
93 FDCA § 505(j)(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, 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. 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. Following incidents where these two biologics were contaminated with tetanus and resulted in the death of children, Congress passed the Biologics Act of 1902. 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. As a condition of licensure, the government retained the right to inspect the facility. 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. 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). 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. It would have been possible to read this provision differently, the new language was interpreted as requiring both an approved establishment license application...
(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

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106 Id.
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.
114 Pub. L. No. 78-410, § 351(g), 58 Stat. at 703.
115 37 Fed. Reg. 4004 (Feb. 25, 1972); see FDCA § 201(g).
by conducting the "Biologics Review," which was modeled on the DESI review and involved an assessment of every marketed biological product for effectiveness.\footnote{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.").} 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.\footnote{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 1920s\footnote{119} 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,\footnote{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.\footnote{121} After the FDCA was enacted in 1938, however, insulin NDAs were submitted and took effect under the sixty-day rule.\footnote{122} Human growth hormone, derived from the pituitary gland of cadavers, was approved in the mid 1970s.\footnote{123} Various other hormones, including conjugated estrogens derived from the urine of pregnant mares, were available by the 1950s and regulated under NDAs.\footnote{124} Thus by the time of the biotechnology

\footnote{117} Pub. L. No. 105-115 § 123(g), 111 Stat. at 2324 (enacting 42 U.S.C. § 262(j)).
\footnote{118} Michael Bliss, The Discovery of Insulin 133-141 (1982).
\footnote{119} 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.
\footnote{120} 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.
\footnote{121} 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).
\footnote{122} See, e.g., FDA, Ever Approved Drug Products, supra note 122, at 4513.
\footnote{123} FDA, Ever Approved Drug Products, supra note 122, at 4513.
\footnote{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(b)(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.
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)." 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. 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. 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."

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. Premarin, the reference product, "is derived from the urine of pregnant mares and contains a number of different estrogens." Precisely how each of the various estrogens contributes to the drug's overall effectiveness has not been determined. FDA has announced and apparently still maintains that it will not approve an ANDA due to the inability to fully characterize the reference product. Instead it approved a 505(b)(2) application for Cenestin, a synthetic conjugated estrogen derived from plant material.

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. 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.
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 Re-Inventing 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. 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. 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. 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. It was also evident in a more robust review of proposed manufacturing changes and, at times, the requirement that manufacturing changes be implemented through an entirely new application rather than a supplement.

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

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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.").
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.
premarket approval of medicines on the basis of safety, efficacy, and quality.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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


\textsuperscript{153} Id at Article 4.8(a).


\textsuperscript{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. 1-7967).
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. In 1995, a “centralized” procedure replaced the concertation procedure and also provided ten years of protection. 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. 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 (EMEA).

In 2001, much of the EU’s directive-based legislation was codified as Directive 2001/83/EC. 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. In addition to defining the phrase “biological medicinal product,” 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. 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

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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.


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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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,\textsuperscript{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.


\textsuperscript{170} Directive 2004/27/EC, supra note 167, at Article 10.5.


\textsuperscript{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). 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.

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.” 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. The amendment to the Annex took effect in October 2003 and was

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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.


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 original 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.

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later confirmed by an amendment to the Directive itself.¹⁷ 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,¹⁷¹ as well as a series of guidelines specific to individual product classes.¹⁷² 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.¹⁷³ 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

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¹⁷ One 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 1 and the related detailed guidelines. The results of other tests and trials from the reference medicinal product’s dossier shall not be provided.


¹⁷³ See, e.g., EMEA, Guideline on Comparability of Biotechnology-Derived Medicinal Products after a Change in the Manufacturing Process (EMEA/CHMP/BWP/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). 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.").

See, e.g., EMEA, Guidance on Similar Medicinal Products containing Recombinant Interferon Alpha (EMEA/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.").

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 (Omnitrope\(^{184}\) and Valtropin\(^{185}\)). 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 Abseamed\(^{189}\)), and two epoetin zeta products were approved in December 2007 (Retacrit\(^{190}\) and Silapro\(^{191}\)). 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

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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, Guidance on Similar Medicinal Products containing Recombinant Interferon Alpha (EMEA/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 (EMEA/CHMP/BMWP/14327/2006), adopted December 2007.

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

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


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

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

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

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

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

approved in September 2008 (Biogastim, Filgrastim ratiopharm, Ratiograstim, and Tevagrastim), and two more were approved in February 2009 (Filgrastim Hexal and Zarzio). An interferon beta-1a application was withdrawn in May 2009 after the CHMP issued a negative opinion in February 2009. An application for an epoetin theta product (Ratiorhoe), which had received a positive opinion from the CHMP, was withdrawn for an epoetin theta product (Ratioepo), which had received a positive opinion from Hexal and approved in September 2008. co-marketing partner was identified at the time of adoption of the opinion of the CHMP due to the fact that no withdrawal its application for a marketing authorization for Biferonex, at 1 (June 15, 2008) was 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. 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

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193 CT Arzneimittel GmbH (Germany) received a marketing authorization for Biogastim, 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.


199 On February 25, 2010, ratiopharm GmbH officially notified the CHMP that it wished to withdraw its application for a marketing authorization for Ratiorhoe, 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. 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. 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. 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. 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. 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

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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."); 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) ("When 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. "To 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).
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. 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. Previously, courts issued permanent injunctions virtually as a matter of course once infringement and validity had been determined. The Hatch-Waxman amendments provided an automatic permanent injunction, 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. 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. 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. 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.

208 See, e.g., *Amado v. Microsoft Corp.*, 517 F.3d 1353, 1361 (Fed. Cir. 2008) ("[C]oncluding 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.
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. The generic industry, to the extent it addressed this question directly, took the same position. 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. 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. The Generic Pharmaceutical Association (GPhA)

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 PHSAct 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. FDA, however, took the position that legislative authority was required. The question was also mooted by the bipartisan decision in 2007 to proceed with legislative amendment. 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, 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, 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. FDA responded at length to the petitions and legal argument, when it approved Omnitrope, 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

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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).


\(^{229}\) FDA Accepts Data Sets on Therapeutic Equivalence of Biotech Drugs, FDA WEEK, Mar. 23, 2001, at 6.


\(^{231}\) CBER Chief: Generic Biologics A Problem From Scientific Standpoint, FDA WEEK, Apr. 20, 2001, at 18.


\(^{233}\) Id. at 25-29.


\(^{235}\) 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.” Also in 2003, the U.S. Pharmacopeia (USP) announced the goal of publishing official reference standards for biological products, although it would later disclaim the inference that these monographs would themselves make biosimilar applications feasible.

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. The agency had released a comparability guidance for human biological products more generally in 1996. 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. 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. 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.

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...
before April 2004, and she told the trade press that the agency hoped to release the document in the spring. 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. 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.

Dr. 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. 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. 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." 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. 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.

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 of GENOTROPIN® (somatropin [rDNA origin] for injection) to approve GENOTROPIN® under section 505(b)(2).

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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 PHSAs 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® (somatropin [rDNA origin] for injection) to approve Omnitrope." 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).
of protein products. And it projected the document would be released by the end of the year. 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. 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.

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. 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. In October 2005, Dr. Galson again indicated that the agency was working on guidance and expected to issue it “soon,” 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.”).


255 FDA May Work with Mexico on Biogenerics 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 biogenerics 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 biogenerics regulatory system. Agency officials hope to start combining the scientific and legal issues of biogenerics into a draft guidance following the FDA public workshop in February on the science of biogenerics, Winkle said.”).


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 Biogenerics 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 biogenerics 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.”).

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

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. 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. At that time, the trade press reported that the immunogenicity guidance was being circulated among top CDER officials. 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. In 2002 and 2003, key members of Congress openly discussed the need for legislation. 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..."
products to the public when patents expire. 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.

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. These views are discussed in subsection D. Other Judiciary Committee hearings were expected, 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). Within a few months, however, he would signal that he was not prepared to introduce this legislation in the immediate term.

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.” 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 application had “helped take the steam out of the issue on Capitol Hill.”

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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 Senate 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.


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.”).


274 See supra section 1.C.2.

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). 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.

On January 26, 2006, the EMEA recommended approval of Omnitrope. 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. (The states of Kansas, Minnesota, Vermont, and Wisconsin would file a citizen petition in August asking the same thing.) 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. 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.").


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 more 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. 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. 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." 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). 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. 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. 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.

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281 See, e.g., id., at 7 (Nov. 12, 2004).
283 Id., at 6-7.
284 Id., at 10, 11.
285 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.).
286 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.” 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. PhRMA similarly argued that “the identity of each biological product — whether innovator or follow-on — is inseparable from the process used to manufacture it.”

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. 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. 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.

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. Individual companies made the same point. 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-

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290 Id. at 19-29.
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 these 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.”).
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.
change and post-change protein products will have comparable effects. 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).

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." 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 profiles 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.

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. 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. The generic industry also pointed to publication of

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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 11; 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.\textsuperscript{304} SICOR, a subsidiary of Teva Pharmaceuticals, disputed claims that current scientific analytical techniques were incapable of fully characterizing proteins.\textsuperscript{305} Indeed, it stated, "the results of analytical characterization are often more sensitive to product changes than are clinical studies."\textsuperscript{306}

2) \textit{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."\textsuperscript{307} Amgen stated that current analytical techniques provide, at most, an incomplete snapshot of a protein product.\textsuperscript{308} Pfizer argued that analytical techniques used to characterize small molecules are "generally insufficient to fully characterize most protein products."\textsuperscript{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.\textsuperscript{310}

3) \textit{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.\textsuperscript{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."\textsuperscript{312} The guidance document also

\begin{itemize}
\item \textsuperscript{305} Letter from Suzanne M. Sensabaugh, \textit{supra} note 282, at 12.
\item \textsuperscript{306} \textit{Id.} at 11.
\item \textsuperscript{307} Letter from Caroline J. Loew, \textit{supra} note 291, Attachment B, at 10.
\item \textsuperscript{308} \textit{See The Law of Biologic Medicine, \textit{supra} note 217, at 84 (statement of David Beier, Senior Vice President, Global Government Affairs, Amgen Inc.).}
\item \textsuperscript{309} Letter from Frederick W. Telling, \textit{supra} note 293, at 7.
\item \textsuperscript{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).
\item \textsuperscript{311} \textit{See FDA, Guidance for Industry, Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Aug. 1999).}
\item \textsuperscript{312} \textit{See id.} at 3-5.
\end{itemize}
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. 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. 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."

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. 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). 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,

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

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 pharmacologically 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." In 2006, 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. 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. 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." This, they argued, would prevent "inappropriate substitutions." 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 same-ness 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 nonproprietary 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.” 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. 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.” 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.

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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. 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." 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 physiochemical biological and PK characterization." 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." 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. 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."

\section*{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.

\subsection*{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. If analytical

\begin{itemize}
\item \textsuperscript{328} Generic Biologics on FDA Fast Track?: 'Follow-On' Process Under Debate, \textit{The Pink Sheet}, May 26, 2003.
\item \textsuperscript{329} See supra note 327.
\item \textsuperscript{330} Some Follow-On Biologics May Get 'AB' Rating Without Clinical Study, \textit{FDA Week}, June 20, 2003.
\item \textsuperscript{331} FDA Says It Would be Difficult to Assign 'Equivalence' to Biogenerics, \textit{FDA Week}, Sept. 17, 2004.
\item \textsuperscript{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. \textit{Id.} at 158-59; see also \textit{Follow-On Protein 505(b)(2) Applications Do Not Require PharmiTox Studies, The Pink Sheet}, Feb. 21, 2005.
\item \textsuperscript{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).
\item \textsuperscript{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).
\end{itemize}
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. 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. 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. The Plasma Protein Therapeutics Association also took the position that "questions regarding immunogenicity cannot be identified solely with current analytical technology." 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." Biogen Idec and Pfizer made similar arguments. In its Citizen Petition urging rejection of Sandoz’s NDA for Omitrope, 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." 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."
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. 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.” 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 “San
doz implemented changes to the drug product to address this immunogenicity.”

Second, FDA issued a not-approvable letter to Nastech Pharmaceutical for its follow-on version of Novartis’s Miacalcin (calcitonin-salmon nasal spray). The letter cited concerns about potential immunogenicity resulting from interactions of the calcitonin and the chlorobutanol preservative in Nastech’s nasal spray.

III. PROPOSED LEGISLATION AND OTHER DEVELOPMENTS, 2006-2010


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. 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. Instead, stakeholders generally understood that Representative Waxman intended the bill to start discussion of the issues related to biosimilars legislation. The trade press reported that Representative Waxman planned to collect cosponsors and make the bill a legislative priority in 2007.

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
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.”
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 bio-
similars. First, under section 351(k)(1) of the PHSA, FDA could have licensed
“comparable” biological products. 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. 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, pu-
urity, and potency “relative to the reference product” was shown. 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 prod-
ucts, 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). 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. 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.

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-

4, 2006; see also New Democrats Support Brand-Backed Follow-on Biologic Bill, FDA Week, May 25,
2007.

\[351\] H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)).

\[344\] See supra note 240 and accompanying text.

\[350\] 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. 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." Any clinical studies required were to be "designed to avoid duplicative and unethical clinical testing." FDA could not require postmarketing studies as a condition of approval.

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." 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." 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." The list of examples seems to have been drawn from a similar list in FDA's regulations implementing the Orphan Drug Act. 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. This provision drew criticism from innovators, who believed it would "force[e] the agency to say something is comparable that scientifically is not."
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. 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. Although this approach of permitting "extrapolation" from data for one indication was used by FDA in the Omnitrope approval, 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. 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. 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. 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." No equivalent language is found in section 505(j) of the FDCA.

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360 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 [were] labeled." 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. 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.

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. 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]." 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. Omnitrope did not receive an AB rating.
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 "approval [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.


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. 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.” 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. The BLA holder would have had to update this list within thirty days of issuance or licensure of a new relevant patent.

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. 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. As under the Hatch-Waxman amendments, however, providing the notice would have constituted an act of patent infringement as to patents identified in it, 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.

The BLA holder or patent owner could have brought an infringement suit within forty-five days of receiving the notice. 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. 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.

\[\text{References}\]

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(i)(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(i)(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.


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, it could have recovered only a “reasonable royalty” from the infringing applicant or a person found to have induced or contributed to the infringement. **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. 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.

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.

### 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). FDA and BIO opposed inclusion of biosimilars in PDUFA. FDA called for

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390 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.

391 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.

410 Id. § 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.

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

412 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.

413 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)).

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


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."

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. When the PDUFA legislation passed the Senate in May 2007, it included a placeholder for insertion of text on follow-on biologics. 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 biosimilars 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. The HELP Committee voted to pass the bill. 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. 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

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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:\KER\KER07721.xml (the 7721 Draft).
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.”

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.” 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.” 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. 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 produce the same clinical result in a given patient. 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)
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

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)).
424 Id.
patent protection for biologics” for several reasons. First, a biosimilar would “only have to be ‘highly similar’ to [rather than the ‘same as’] the innovator product.” 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.” 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.” 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.” 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.’”

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].” 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.” 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.” 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. BIO updated the paper to cite this finding.

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

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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.
hearing. This was followed by a March 26 hearing before the House Committee on Oversight and Government Reform and a May 2 hearing before the Subcommittee on Health of the House Energy and Commerce Committee. 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.

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." 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" of the HELP Committee hearing.

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

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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).
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).
biosimilars. 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." 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. 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." 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. 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." 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."

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. 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.
For example, Dr. Woodcock noted, "In 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-
Representative Waxman also expressed concern that statutory language requiring clinical trials would "freeze science as of the date of enactment." 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." 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.

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." 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."

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." 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." 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." 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." Inger Mollerup, Ph.D., Vice President of Regulatory Affairs at Novo Nordisk A/S, added that the provision "go[es] far beyond the science." Dr. Mollerup explained that Novo Nordisk had studied two fast-acting

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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.
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. 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.”

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.” 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.” 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.”

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.” 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.” 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.”

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. Most, however, stated that issuance of product class-specific guidance should not be a prerequisite to licensure of biosimilars. 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.
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, Insmed 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 . . . it 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."\(^{494}\)

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\(^{485}\) 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 guideline 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.” Dr. Hussain stated that interchangeability could be shown in either an initial biosimilar application or a later supplement after the biosimilar had been marketed. He also suggested that “switching clinical studies” or postmarketing data from the already-marketed biosimilar could be used to support interchangeability. 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.”

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. Dr. Siegel expressed concern that interchangeability designations “could lead to inappropriate assumptions of sameness and substitution . . . [that could] have potentially serious health consequences.” 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.

Dr. Woodcock expressed concerns about interchangeability and switching, particularly with respect to products with different immunogenicity. 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. 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.” She noted, however, that these studies could present “ethical issues” requiring careful assessment. 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. 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.

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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).

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.
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.
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.\footnote{Hussain Testimony, at 36.} 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).\footnote{Id.}

### 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.\footnote{FDA Releases Long-Awaited ‘White Paper’ on Follow-On Biologics, FDA WEEK, Apr. 27, 2007.} 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.”\footnote{Woodcock et al., supra note 226, at 438.} 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.”\footnote{Id. at 438, 441.} 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.”\footnote{Id. at 438.} 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.\footnote{Id. at 438, 441.} For recombinant proteins, establishing a high degree of structural similarity to the reference product was viewed as “crucial” by the authors.\footnote{Id. at 441.} 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
integrate this new information into its review of proteins. 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.

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. 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." 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. 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.

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. Even if the legislation passed, according to Dr. von Eschenbach, FDA would not be able to implement it unless scientific issues were resolved. 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. 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 422.
541 Id. at 440 (citing First Woodcock Testimony, supra note 445).
543 Id.
544 Id.
545 Id.
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 biologicals, SCRIP NEWS, Mar. 23, 2007, at 13; Von E opposes generic biologics legislation, DICKINSON'S FDA REVIEW, Mar. 2007, at 10.
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. On April 19, 2007, Representative Jay Inslee introduced the "Patient Protection and Innovative Biologic Medicines Act of 2007," otherwise known as H.R. 1956. 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." Just over a month later, Senator Gregg introduced a somewhat similar bill, known as the "Affordable Biologics for Consumers Act," S. 1505. 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.

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. 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. 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.


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). This approach was broader than the approach in the first two Waxman bills, because it permitted FDCA approved proteins 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). 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 505(b)(2).
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 PHSA 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 address 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 PHSA § 351(k)(4)).
563 Id. (proposed PHSA § 351(k)(4)(C)(vii)).
564 See supra Section I.C.3.
565 S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(3)(A)).
566 Id. (proposed PHSA § 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.\(^5\)

These requirements would have been generally consistent with the data requirements that have been established in Europe through guidelines.\(^5\) 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.\(^5\) 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.”\(^5\)

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.\(^5\) 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.\(^5\) 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.\(^5\) Second, the applicant would have needed to demonstrate that “the biosimilar [wa]s 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.”\(^5\)

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

Both bills would have prohibited FDA from designating biosimilars as therapeutically equivalent to their reference products. 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. 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.

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.

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. 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. Under both bills,

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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)).
approval of the section 351(k) application could not be made effective until fourteen years after approval or licensure of the reference product. 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.

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.” Under H.R. 1956, FDA would have had to determine whether the significant clinical benefit had been shown “in comparison with existing therapies.” This language tracks the supplemental exclusivity language used in Europe.

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. 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. In Europe, the period is one year.

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. S. 1505 contained an additional supplemental exclusivity provision absent from H.R. 1956, modeled on three-year exclusivity under the Hatch-Waxman amendments.

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. 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. This exclusivity could have been obtained at any time after approval of the reference product application. 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. The Inslee bill would have provided no such exclusivity.
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," 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. To be "unique," the USAN could not have been adopted for any protein manufactured by a different entity. 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. 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.

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. Such a product would have been required to be labeled with a brand name or "phrasing . . . approved by [FDA] that adequately distinguishes[d] it from other approved . . . proteins with the same proper name." 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." 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.

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." 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 product."

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

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.


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. 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.” 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. 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.

Under the Gregg bill, FDA could have approved the biosimilar application once the data exclusivity period expired, regardless of whether patent litigation had concluded. 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. 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

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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)).
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\BAI07574 (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.
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)(1)(bb), using term “comparative”); 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. In other words, the bill did not permit a biosimilar to serve as a reference product. All five discussion drafts had taken this approach, and it is the approach taken in Europe.

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. “Product class” was not defined in the bill. 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. The moratorium approach was abandoned late in the process for the guidance provision.

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 use the PHSA pathway for biosimilars, a transition provision would have applied.

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 Biologies 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. After the transition period, all biological products with approved applications under the FDCA would have been "deemed approved" under section 351 of the PHSA.

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). 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. 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. 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. 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. 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" 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." The clinical data would have needed to include immunogenicity data and an assessment of either pharmacokinetics or pharmacodynamics. 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. The clinical studies in question would also have been required to be "designed to avoid needlessly duplicative or unethi-
cal clinical testing." 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." S. 1695's sparse legislative language on application requirements paralleled the approach in Europe. The general requirements to provide analytical, animal, and clinical data also paralleled the approach laid out in CHMP guidance. Although the S. 1695 data requirements are less specific than CHMP guidance, FDA would have had the discretion to ask for the analytical, animal, and clinical data when determining the extent to which animal and clinical studies were necessary. 

Professor Rossignol notes that clinically relevant immunogenicity could be excluded through other means. Except for the requirement to test immunogenicity, and then only upon a showing that clinically relevant immunogenicity could be excluded through other means, the first discussion draft did not contain language directing FDA to avoid requiring duplicative and unethical testing. This language was added in the second draft and retained in subsequent drafts and the introduced version of the bill, but as noted below, it was dropped from S. 1695 when the bill was reported.

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." FDA Week suggested that the change "appear[ed] to lower the bar for determining comparability." 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. 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. Fourth, the first discussion draft did not contain language directing FDA to avoid requiring duplicative and unethical testing. This language was added in the second draft and retained in subsequent drafts and the introduced version of the bill, 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."

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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.
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)).
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


d. 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, BOCENTURY, 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 § 2(a)(2) (proposed PHSA § 351(k)(2)(A)); 7641 Discussion Draft § 2(a)(2) (same); 7645 Discussion Draft § 2(a)(2) (proposed PHSA § 351(i)(2)(A)); 7655 Discussion Draft § 2(a)(2) (proposed PHSA § 351(i)(2)(A)) (language is bracketed).

664 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(2)(A)); 7669 Discussion Draft § 2(a)(2) (same); 7669 Discussion Draft § 2(a)(2) (same).

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

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

667 S. 1695, 110th Cong. § 2(a)(2) (proposed PHSA § 351(k)(5)(C)).

668 7574 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(5)(C)); 7641 Discussion Draft § 2(a)(2) (proposed PHSA § 351(k)(5)(C)).

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

another biologic. This language was not proposed until the 7669 Discussion Draft, just before agreement was reached. 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.

Under S. 1695, FDA could have issued general or specific guidance on the submission and licensure processes for 351(k) applications. 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). 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. 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. 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. 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, 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." 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

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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)).
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 § 2(a)(2) (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. 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.

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. This early draft
   would not have permitted interchangeability designations until either FDA issued
   a required guidance on the interchangeability standard or two years elapsed.

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. Some trade press
characterized this change as lowering the bar for interchangeability. 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.

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. 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.

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." This language
did not appear in most discussion drafts and was added toward the end of the
drafting process.
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. Pediatric exclusivity would not have been available. 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).

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. 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.

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. 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.

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. In either case, exclusivity would block submission, not approval, of section 351(k) applications. An extension (of unspecified length)

602 S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(7)(A) & (B)).
603 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.
604 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.
605 S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(6)).
606 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.
607 7574 Discussion Draft § _ (a) (proposed PHSA § 351(l)(1)(A)).
608 Id. (proposed PHSA § 351(l)(1)(A)(i) & (ii)).
609 Generic Biologics May See Life After PDUFA; Senate Mark-Up Possible in May, The Pink Sheet, Apr. 23, 2007, at 6.
610 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." 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.

Pediatric exclusivity would have been available to extend data exclusivity and orphan exclusivity. The 7574 Discussion Draft also provided that, where the reference product had been orphan-designated, section 351(k) would have "appl[ied] to" biosimilars only after expiration of the seven-year period of orphan exclusivity. 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. 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. 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.

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...
“not” conducted or sponsored “solely” by the applicant. Third, in the supplemental exclusivity provision, the “significant clinical benefit” standard was changed to one of “clinical superiority,” and a reference product could receive no more than three extensions. 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. 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.” 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. It would not have provided pediatric exclusivity, nor would it have addressed the relationship between data exclusivity and orphan drug exclusivity.


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

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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)(II) & (iii)).

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.\textsuperscript{713} Generic applicants must address patents meeting the listing criteria when submitting their applications.\textsuperscript{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.\textsuperscript{715} The applicant could also have, in "its sole discretion" provided additional information it deemed appropriate, including information requested by the reference product sponsor.\textsuperscript{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 process;\textsuperscript{717} 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.\textsuperscript{718}

S. 1695 provided a default procedure for confidential access, but would have allowed the parties to agree to use a different procedure.\textsuperscript{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."\textsuperscript{720} Although language comparable to this had been considered,\textsuperscript{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.\textsuperscript{722} These individuals could not have disclosed any of this confidential information to "any other person or entity" without the biosimilar

\textsuperscript{713} FDCA § 505(b)(1)(G).

\textsuperscript{714} FDCA §§ 505(b)(2)(A), 505(j)(2)(A)(vii).

\textsuperscript{715} S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(1) & (2)).

\textsuperscript{716} Id. (proposed PHSA § 351(l)(I)(B)(i) & (I)(2)(B)).

\textsuperscript{717} See, e.g., 7669 Discussion Draft § 2(a)(2) (proposed PHSA § 351(l)(2)).

\textsuperscript{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)).

\textsuperscript{719} S. 1695 § 2(a)(2) (proposed PHSA § 351(l)(1)(A)).

\textsuperscript{720} FDCA §§ 505(c)(3)(D)(i)(III), 505(j)(5)(C)(i)(II). 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)(II)).

\textsuperscript{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)).

\textsuperscript{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." Other employees of the reference product sponsor, outside scientific consultants, and other outside counsel could not have accessed the application without such consent. 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 relevant and a mandatory information exchange process. 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. This list would need to include all patents as to which the reference product sponsor believed it "could reasonably assert[i]" a claim of patent infringement if an unlicensed person commercially marketed the biosimilar. 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 "believed[d] in good faith" claimed the reference product or biosimilar. 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.

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. 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.

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-
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. 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.

(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.

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. If no agreement were reached during this time, an alternative procedure would apply. The applicant first would be required to notify the reference product sponsor of the number of patents it planned to list for immediate litigation. 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. 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.

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. 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)).
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. 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. This provision was added just prior to introduction of the bill.

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. 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. 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. Both discussion drafts provided that a court could not otherwise extend the data exclusivity period.

743 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)(I) & (II)).

744 Id. (proposed PHSA § 351(l)(6)(C)).

745 Id. (proposed PHSA § 351(l)(8)(A)).

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. 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. 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.

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. 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. 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. These two provisions were similar to those proposed in the first and second Waxman bills.

The drafters considered the reasonable royalty provision early in the drafting process 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

Id. (proposed PHSA § 351(1)(7)); 754 Discussion Draft § ___(a) (same).

754 754 Discussion Draft § ___(a), (c)(1)(B)(iii) (proposed PHSA § 351(1)(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. 754 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.

Id. § 2(c)(1)(B)(ii) (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)(ii) (proposed PHSA § 351(l)(6) & 35 U.S.C. § 271(e)(4)(D)).

754 Id. § 2(c)(1)(C) (proposed 35 U.S.C. § 271(e)(6)(C)).

744 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.

7646 See supra notes 398-400 and accompanying text.

7647 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). 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.”

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. 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. Finally, if the biosimilar applicant failed to provide its application and manufacturing information, only the reference product sponsor could bring a declaratory judgment action as to a patent that claimed the biological product or a use of the biological product.

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.

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, 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. GPhA argued in favor of a shorter period applicable only to innovative products licensed after enactment.

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. First, the...
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. 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. 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. 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. The letter also stated the Administration's "belief[f] that the legislation should be amended to require a predictable and public product-class guidance process prior to acting on any follow-on applications." Fourth, the letter stated that preapproval immunogenicity data should not be waivable because these data are "critical." Fifth, according to the letter, S. 1695 should require applicants to show biosimilarity for each reference product condition of use. 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." 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." 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. 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). 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.

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761 Id. at 2, 3.
762 Id. at 3.
763 Id. at 2.
764 Id. at 3-4.
765 Id. at 3.
766 Id. at 4.
767 Id.
768 Id. at 4.
769 Id. at 5.
770 Id. at 5-6.
771 Id. at 6.
772 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. 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.” 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, 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.

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. 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. 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.

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). 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 part patent owner that had granted it an exclusive license, whereas the introduced version of the bill had required listing of only those patents that reasonably could be asserted by the reference product sponsor.

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. According to the trade press, Senator Kennedy said that the HELP Committee planned to work on several aspects of the draft.  

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760 S. 1695 § 2(a)(2) (proposed PHSA § 351(k)(7)(A)).
761 7721 draft § 2(a)(2) (proposed PHSA § 351(k)(7)(C)).
763 7721 draft § 2(i).
764 Id. § 2(b)(3) (proposed PHSA § 351(i)(2)).
765 Id. § 2(a)(2) (proposed PHSA § 351(k)(2)(A)(i)(I)(bb) & (cc)).
766 Id. (proposed PHSA § 351(k)(3)(B)).
767 Id. § 2(a)(2) (proposed PHSA § 351(l)(1)(B)(iii)).
768 Id. (proposed PHSA § 351(l)(3)(A)(ii)).
769 See supra note 728 and accompanying text.
770 Senate Panel Passes Biogenerics 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.\textsuperscript{791} As noted, the Senate had passed the PDUFA legislation in May 2007 with a placeholder for insertion of text on biosimilars.\textsuperscript{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.\textsuperscript{793} According to the trade press, Senator Clinton responded that the bill would not require substitution so the amendment was not needed.\textsuperscript{794} After Senator Kennedy agreed to work with Senator Coburn on the issue, the amendment was withdrawn.\textsuperscript{795} Senator Alexander (R-TN) proposed an amendment to provide pediatric exclusivity for biologics, but this amendment did not pass.\textsuperscript{796} Senator Sherrod Brown (D-OH) offered and then withdrew an amendment that would have reduced the data exclusivity period to seven years.\textsuperscript{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,\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{801} According to its press release, GPhA was informed by the Senate staff that “this is not the true intent of the compromise.”\textsuperscript{802} GPhA pledged to “work with the negotiators to craft language that addresses this issue.”\textsuperscript{803}

BIO also expressed its intent to continue working with Congress to improve the legislation, but identified different aspects of the legislation for improvement.\textsuperscript{804}

\textsuperscript{793} Id.
\textsuperscript{794} Id.
\textsuperscript{795} Id.
\textsuperscript{796} Id.
\textsuperscript{800} Id.
\textsuperscript{801} Id.
\textsuperscript{802} Id.
\textsuperscript{803} Id.

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\textsuperscript{793} Id.
\textsuperscript{794} Id.
\textsuperscript{795} Id.
\textsuperscript{796} Id.
\textsuperscript{800} Id.
\textsuperscript{801} Id.
\textsuperscript{802} Id.
\textsuperscript{803} Id.

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While BIO was "pleased that the bill made 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." 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." 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." 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."

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. The signatories emphasized that the biosimilars legislation "had not passed the full Senate" and that the House Committee on Energy and Commerce "had not had the opportunity to deliberate and consider the compl-
cated scientific, legal, and economic issues" implicated by the legislation. These legislators stated their belief that Congress should consider biosimilars legislation after "full deliberation, hearings, and markup by appropriate committees. 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." 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. Although it was briefly considered possible that the legislation would be included in the Patent Reform Act under consideration in September 2007, this did not happen, and in late October, House lawmakers agreed to wait until 2008 to pursue biosimilars legislation.

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.”

C. 110th Congress, Second Session

The Senate waited for the House to act. Thus in early 2008, the major negotiations on biosimilars took place in the House of Representatives. Representatives Eshoo and Barton introduced a bill in March (H.R. 5629 or “the first Eshoo bill”). 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. 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.

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. 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].” Ultimately,
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.\textsuperscript{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,”\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{829}

a. Regulatory Pathway

1) Scope

H.R. 5629 would have created a pathway for licensure of products “biosimilar” to a “reference product.”\textsuperscript{830} Unlike every other bill introduced in the 109th and 110th Congress, however, the Eshoo bill did not define “reference product.”\textsuperscript{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.\textsuperscript{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


\textsuperscript{825} BIO “Ferociously Lobbying” for a Biosimilar Bill This Year, FDA Week, Feb. 1, 2008, at 3.

\textsuperscript{826} See Senate Biosimilars Bill Reported 1 1/2 Years After Committee Passed It, FDA Week, Nov. 28, 2008.

\textsuperscript{827} Id.

\textsuperscript{828} H.R. 5629, § 1.

\textsuperscript{829} See Barton’s Decision to Back Eshoo on Biogenerics May Hurt House Negotiations, FDA Week, Feb. 15, 2008.

\textsuperscript{830} H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)).

\textsuperscript{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).

\textsuperscript{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. 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. 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. 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. 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.

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.” The clinical data would have needed to include immunogenicity data and an assessment of either pharmacokinetics or pharmacodynamics. 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.” 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. 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 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)(II)).
839 Id. (proposed PHSA § 351(k)(2)(A)(i)(II)).
840 Id. (proposed PHSA § 351(k)(2)(A)(i)(II)); 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,"\textsuperscript{846} whereas the issuance of guidance on biosimilars was optional under the HELP bill.\textsuperscript{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.\textsuperscript{848} Moreover, FDA also could not have accepted a biosimilar application until the guidance development process for that product class had been initiated.\textsuperscript{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.\textsuperscript{850}

3) \textit{Interchangeability and Naming}

The first Eshoo bill's interchangeability provisions largely tracked the language of the HELP bills. There were, however, several important differences. \textbf{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.\textsuperscript{851} \textbf{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.\textsuperscript{852} \textbf{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.\textsuperscript{853}

\textsuperscript{842} Id. (proposed PHSA § 351(k)(2)(A)(ii)-(v)).
\textsuperscript{843} Id. (proposed PHSA § 351(k)(2)(C)).
\textsuperscript{844} Id. (proposed PHSA § 351(k)(2)(C)).
\textsuperscript{845} Id. (proposed PHSA § 351(k)(3)).
\textsuperscript{846} Id. (proposed PHSA § 351(k)(9)(A)).
\textsuperscript{847} See supra note 674 and accompanying text.
\textsuperscript{848} H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(9)(E)).
\textsuperscript{849} Id.
\textsuperscript{850} Id. (proposed PHSA § 351(k)(9)(D)).
\textsuperscript{851} H.R. 5629, § 101(a)(2) (proposed PHSA § 351(k)(4)(A)(i)(I)).
\textsuperscript{852} Id. (proposed PHSA § 351(k)(4)(A)(g)(II)).
\textsuperscript{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 identified” 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.\(^{863}\)

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\(^{854}\) 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)).

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. 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. 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.

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.

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. 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. “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. 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. 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.
in the previous paragraph. 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. 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.

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. Submission of the latter certification (a paragraph (4)(D)(ii) certification) would have constituted an act of patent infringement, 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. 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.

After introduction of the first Eshoo bill, GPhA issued a press release calling the bill "a pathway to the wrong destination." In particular, GPhA opposed the data exclusivity provisions of H.R. 5629, which it called "unjustifiable." 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 ..." GPhA reiterated its support for the second Waxman bill in the press release.

In contrast, BIO wrote to Representatives Eshoo and Barton to "offer [its] support" for the bill. 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 permitt[ed] interchangeability for a specific class of products." 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-
able from that of the innovative product, to avoid confusion and inadvertent substitution without patient and physician knowledge.\textsuperscript{885} BIO reiterated its “belie[f] 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.\textsuperscript{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 . . . .”\textsuperscript{887} According to BIO, these “mechanisms will serve to protect the intellectual property rights of innovators and other third parties such as academic institutions.”\textsuperscript{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.\textsuperscript{889} Responses came from thirty stakeholders, including trade associations BIO, PhRMA, and GPhA, as well as federal agencies the FTC and FDA.\textsuperscript{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.\textsuperscript{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 data\textsuperscript{892}; naming\textsuperscript{893}; applying the new pathway to FDCA proteins\textsuperscript{894}; requiring guidance development prior to FDA action on biosimilar applications\textsuperscript{895}; and data exclusivity.\textsuperscript{896} Both concluded, for example, that legislation should not at this time allow for interchangeability determinations and that a patient should

\textsuperscript{885} Id.
\textsuperscript{886} Id.
\textsuperscript{887} Id. at 3.
\textsuperscript{888} Id.
\textsuperscript{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).
\textsuperscript{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.
\textsuperscript{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).
\textsuperscript{895} Id. at 8 (noting that requiring a public product class guidance process prior to action on biosimilar applications “would be beneficial”).
\textsuperscript{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)).
\textsuperscript{897} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{899} The Leavitt letter had stated that biosimilarity should be shown for each condition of use.\textsuperscript{900}

The Torti letter was considered by some trade press to “take[] several positions favored by biotech manufacturers.”\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{903} Johnson & Johnson took the position that “an immunogenicity assessment should be required in any premarket approval package” for a biosimilar,\textsuperscript{904} a viewpoint consistent with the testimony of Dr. Siegel at the 2007 hearing.\textsuperscript{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.”\textsuperscript{906} Other generic stakeholders, such as Barr, agreed.\textsuperscript{907}

\textsuperscript{897} Id. at 9.
\textsuperscript{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.
\textsuperscript{899} Torti Letter, at 2.
\textsuperscript{900} See supra note 774.
\textsuperscript{902} Id.
\textsuperscript{903} BIO Response to Questions on Biosimilars from the U.S. House of Representatives Energy & Commerce Committee, Subcommittee on Health 6 (May 2, 2008).
\textsuperscript{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).
\textsuperscript{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.”).
\textsuperscript{906} GPhA Response to House Energy & Commerce Committee Questionnaire on Biogenerics 1 (May 6, 2008).
\textsuperscript{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 biologies 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 "beliefs[ ]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

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 [agency 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 guidance or promulgate regulations before accepting, reviewing, or acting on generic applications. As is the case for brand products, the use of guidelines 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.").
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]." With respect to data exclusivity, Novartis stated "a minimum of 12 years of exclusivity is essential and there may be sound arguments for more." GPhA supported a data exclusivity period of, at most, five years, 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." GPhA's statements on the patent provisions were generally consistent with its previous support for the second Waxman bill, and Barr's patent comments generally were consistent with Mr. Downey's prior testimony on these issues.

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." 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." 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." 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." 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."

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. No committee report accompanied the reported

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917 Id. at 30.
918 GPhA Response to House Energy & Commerce Committee Questionnaire on Biogenerics 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 Biogenerics 16 (May 6, 2008).
921 See Written Responses From Barr Pharmaceuticals, Inc. 10-11 (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. In addition, some considered the timing of this action to be “curious.” 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.

D. 111th Congress, First Session

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.” 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.’” 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. 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.

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

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928 See Senate Biosimilars Bill Reported 11/2 Years After Committee Passed It, FDA WEEK, Nov. 28, 2008.
929 Id.
930 Id.
932 Id.
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 reintroducing it as H.R. 1548 (or “the second Eshoo bill”). 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. The first Eshoo bill had not included the “reduced or enhanced potency” language. 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.” 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.

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. The third bill used, for the first time, the term “biosimilar” rather than the term “comparable.” 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. 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.” The new language was criticized on the ground

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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 alteration 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.
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


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
been required to submit information showing the extrapolation was "scientifically appropriate." 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. The previous bills did not contain this submission requirement or exception from extrapolation.

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. The first two Waxman bills had instead provided that the applicant could submit any information, "including publicly-available information," in the application. 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.

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. 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."

c. Data Exclusivity

The third Waxman bill proposed tiered data exclusivity; the period could be five or three years, depending on the circumstances. 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.

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...
period. The list of exclusions again seemed to have been drawn from the similar list in FDA’s regulations implementing the Orphan Drug Act. As noted, the previous Waxman bills used the same list to describe products that were deemed comparable as a matter of law. 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. 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. FDA also could have designated, by regulation, additional products not eligible for five-year exclusivity.

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.” 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.

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. In another respect, however, the provision was like three-year exclusivity in the Hatch-Waxman amendments; it offered the exclusivity only

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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.


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. 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.” 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. Only one extension would have been permitted for a reference product.

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. 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. 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].”


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. 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]
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 Coalition 991 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(f)(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)).
reported that a Waxman aide said that Representative Waxman was “disappointed” at this development. By May 1, the second Eshoo bill had fifty-six co-sponsors, and twelve more were added in June. 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. 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.”

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. 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.” Products in the first group would have received twelve years of exclusivity. Data exclusivity for products in the second group would have expired when data exclusivity for the previously licensed product expired. 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. 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).

993 Coalition of Moderate Dems Backs Eshoo Biosimilars Bill, FDA WEEK, May 1, 2009.
995 Letter from Rep. Waxman to President Obama (June 8, 2009), at 1.
996 Id.
998 See generally Discussion Draft stamped O:\KER\KER09127.xml (2009).
999 Id. (A)(ii).
1000 Id. (B)(ii)(II).
1001 Id. (B)(ii)(I) & (II).
1002 Id. (B)(ii)(I)(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. 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. 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. Finally, the HELP Committee was “weighing a series of technical corrections” to the bill.

b. 9374 Discussion Draft

On June 9, the HELP Committee released its draft health care reform bill with a placeholder for biosimilars language. 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. Option B was identical to the exclusivity language of S. 1695, as reported. Option C would have provided the same four-year bar on submission of a biosimilar application and twelve-year bar...
on approval as S. 1695, as reported, but it contained a different first licensure provision. 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." The discussion draft included pediatric exclusivity language nearly identical to the draft stamped O:\KER\KERO9151.xml, as described in the previous section.

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."

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.

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, to provide that an "exclusive licensee" (not just the patent owner) would be subject to this prohibition. 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. 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. The 9374 Discussion Draft instead provided that a newly issued or licensed patent would

\[^{1010}\] 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)).
\[^{1015}\] See supra note 753 and accompanying text.
\[^{1016}\] Proposed PHSA § 351(k)(6)(C).
\[^{1017}\] Id. § 602(a)(2) (proposed PHSA § 351(k)(6)(B)).
\[^{1018}\] S. 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.\textsuperscript{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.\textsuperscript{1020} Prior to preparing the report, the FTC had held a public workshop and invited stakeholder comments on these issues.\textsuperscript{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.\textsuperscript{1022} Michael S. Wrobleski, 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.\textsuperscript{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.\textsuperscript{1024} Second, the FTC determined that biosimilars legislation need not establish special procedures to resolve patent issues prior to FDA approval of biosimilar applications.\textsuperscript{1025} Third, according to the FTC, there was no need for exclusivity as an incentive for development of interchangeable biosimilars.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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]."\textsuperscript{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..."
costs to obtain FDA approval” and the significant fixed costs of the necessary manufacturing capacity.\textsuperscript{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.\textsuperscript{1031} Third, physicians may be reluctant to switch patients to biosimilars based on concerns that patients may react differently.\textsuperscript{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.”\textsuperscript{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.\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{1036} Instead, the FTC asserted, innovative biologics are “covered” by more patents and more “varied” patents . . . than “small-molecule branded products.”\textsuperscript{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.”\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
applicants to expend resources on litigation challenging patents.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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-fifteen-year data exclusivity period was unnecessary. Representative Baldwin (D-WI) pointed out that, at the time, innovative biologics “enjoy[ed] infinite data exclusivity.”\textsuperscript{1044} Representative Inslee agreed, stressing that companies “[r]ight now . . . have an incentive to investment [in biotechnology] in part because of data exclusivity.”\textsuperscript{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.”\textsuperscript{1046} When Representative Inslee asked if the FTC study examined how the lack of data exclusivity would affect investment in new products, Mr. Wrobleski responded “We did not evaluate that in particular . . . because patent protection has been very, very strong.”\textsuperscript{1047}

Mr. Wrobleski 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.”\textsuperscript{1048} According to Mr. Wrobleski, patents have been sufficiently strong that they have “even kept out a branded competitor from doing just that.”\textsuperscript{1049} “If 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.”\textsuperscript{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?”\textsuperscript{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 . . . ?”\textsuperscript{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.\textsuperscript{1053}

\textsuperscript{1041} Id. at ix.
\textsuperscript{1042} Id.
\textsuperscript{1043} Id.
\textsuperscript{1044} Preliminary Transcript, supra note 1022, at 53 (statement of Rep. Baldwin).
\textsuperscript{1045} Id. at 132 (statement of Rep. Inslee).
\textsuperscript{1046} Id. at 133-134 (statement of Commissioner Harbour).
\textsuperscript{1047} Id. at 134 (statement of Mr. Wrobleski).
\textsuperscript{1048} Id. at 103.
\textsuperscript{1049} Id.
\textsuperscript{1050} Id. at 104.
\textsuperscript{1051} Id. at 102 (statement of Rep. Christensen).
\textsuperscript{1052} Id. at 117 (statement of Rep. Eshoo).
\textsuperscript{1053} Id. at 116.
c. Reactions to the Report

Numerous Representatives expressed "disappointment" that they had received the report fewer than twenty-four hours earlier and that only one witness had been called.\textsuperscript{1054} Subcommittee Chair Pallone indicated that additional hearings would be held, but that a date had not yet been determined.\textsuperscript{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."\textsuperscript{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.”\textsuperscript{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.’”\textsuperscript{1058}

In contrast, BIO called the report “fundamentally flawed” for five reasons.\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{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.\textsuperscript{1064}

\textsuperscript{1054}E.g. id. at 17-18 (statement of Rep. Eshoo); id. at 22 (statement of Rep. Burgess).
\textsuperscript{1055}Id. at 21 (statement of Rep. Pallone).
\textsuperscript{1056}FTC Says Generic Biologics Pathway Would Reduce Costs of Biologic Drugs, PHARM. L. & IND. REPORT, June 12, 2009.
\textsuperscript{1058}Id.
\textsuperscript{1059}Press Release, BIO, FTC Report on Biosimilars Is Fundamentally Flawed (June 10, 2009).
\textsuperscript{1060}BIO, FTC Biosimilars Report Rebuttal (2009), at 1.
\textsuperscript{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)).
\textsuperscript{1062}Id.
\textsuperscript{1063}Id. at 3.
\textsuperscript{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.\textsuperscript{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."\textsuperscript{1066} At that time, the second Eshoo bill had 100 co-sponsors.\textsuperscript{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."\textsuperscript{1068} The letter, signed by White House Office of Health Reform\textsuperscript{1069} 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."\textsuperscript{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."\textsuperscript{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."\textsuperscript{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.\textsuperscript{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-

\footnotesize{1065} Letter from Rep. Eshoo et al. to Chairman Waxman and Chairman Pallone, at 1 (June 16, 2009).
\footnotesize{1066} Id.
\footnotesize{1067} Id.
\footnotesize{1068} See supra note 995-996 and accompanying text.
\footnotesize{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, \textsection 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. \textsection 2(b).
\footnotesize{1070} Letter from Nancy-Ann DeParle, Director, Office of Health Reform & Peter Orszag, Director, Office of Management & Budget (June 24, 2009), at 1.
\footnotesize{1071} Id.
\footnotesize{1072} Id.
\footnotesize{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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."\textsuperscript{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.\textsuperscript{1080}

\textbf{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.\textsuperscript{1081}

As in S. 1695, a biosimilar application could not have been submitted until four years after licensure of the reference product.\textsuperscript{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

\begin{itemize}
  \item \textsuperscript{[1074]} Senate Democrats' Biosimilars Deal Falls Apart in Meeting, FDA \textit{Week}, July 10, 2009.
  \item \textsuperscript{[1075]} Id.
  \item \textsuperscript{[1076]} Biotech Drug Copies Could Be Held Up 13 Years Under Senate Plan, \textit{Bloomberg}, July 8, 2009; see also \textit{New Bill Limits Exclusivity to Biologics Approved After Enactment}, FDA \textit{Week}, July 10, 2009.
  \item \textsuperscript{[1077]} Panel Considers Abortion-Related Amendments to Health Care Overhaul Bill, \textit{CQ Committee Coverage}, July 13, 2009, at 2.
  \item \textsuperscript{[1078]} Brown to Seek Exclusivity Cuts When Senate Health Bill Hits the Floor, \textit{FDA Week}, July 17, 2009.
  \item \textsuperscript{[1079]} \textit{HELP Approves Biosimilars Provision With 12 Years of Exclusivity}, \textit{FDA Week}, July 17, 2009.
  \item \textsuperscript{[1080]} [\textsuperscript{602}(a)(2) (proposed PHSA § 351(k)(7)(A)).
  \item \textsuperscript{[1081]} Kennedy Amendment to Senate Health Care Reform Legislation, stamped O:\KER\KER09653.xml, § 602(a)(2) (proposed PHSA § 351(k)(7)(A)).
  \item \textsuperscript{[1082]} Id. (proposed PHSA § 351(k)(7)(G)).
\end{itemize}
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.¹⁰⁰³ 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.¹⁰⁰⁴

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.”¹⁰⁰⁵

Like the third Waxman bill, the 9653 Kennedy proposal provided for supplemental exclusivity under certain conditions.¹⁰⁰⁶ 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.”¹⁰⁰⁷ 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).¹⁰⁰⁸ Only two supplemental periods were permitted.¹⁰⁰⁹

The 9653 Kennedy proposal omitted the Waxman language calling for a reduction

¹⁰⁰³ Id. (proposed PHSA § 351(k)(7)(B)(i)).
¹⁰⁰⁴ Id. (proposed PHSA § 351(k)(7)(B)(ii)). The list was modified in the Kennedy proposal to read as follows: (1) “protein biological products that differ in structure solely due to minor post-translational changes or minor changes in amino acid sequence”; (2) “polysaccharide 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 minor changes in the structure or number of saccharide moieties”; and (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).” Id.
¹⁰⁰⁵ 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)).
¹⁰⁰⁶ Id. (proposed PHSA § 351(k)(7)(D)).
¹⁰⁰⁷ 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)).
¹⁰⁰⁸ Id. (proposed PHSA § 351(k)(7)(E)).
¹⁰⁰⁹ 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.  

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. 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.”

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.” 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 bringing a significant clinical benefit, in comparison with existing therapies.” That benefit could have been improved safety or improved efficacy, but it was required to constitute a major contribution to patient care. Only one extension would be allowed. 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.” 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. 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. The ten-year period could be extended by two years if there were “significant therapeutic advancements with respect to the reference product.”

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.”

**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.” 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.”

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. 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. This amendment also included pediatric
exclusivity provisions virtually identical to those in the 9653 Kennedy proposal. AARP supported this amendment.\textsuperscript{106}

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.\textsuperscript{107} Second, the exclusivity adjustment (i.e., loss of ninety days for major substances with annual gross sales over $1 billion) was omitted.\textsuperscript{108}

6. \textit{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.\textsuperscript{109} The discussion focused on the length and structure of data exclusivity provisions and the patent resolution process.

a. \textit{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.”\textsuperscript{110} 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.”\textsuperscript{111} Representative Eshoo noted that her legislation would end the status quo under which “innovators [at the time had] infinite data protection,” but would “maintain[] an 12-year period . . . of concurrent data protection as a backstop to existing patent protections.”\textsuperscript{112}

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.\textsuperscript{113} Bruce A. Leicher, Senior Vice President and General Counsel of Momenta, supported the third Waxman bill's five-year exclusivity period.\textsuperscript{114} 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.”\textsuperscript{115} 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

\textsuperscript{106} Press Release, Senator Brown's Office, Brown Calls Committee Vote a Missed Opportunity to Lower Costs and Improve Medical Care (July 14, 2009).

\textsuperscript{107} Second Brown Amendment to Senate Health Care Reform Legislation, stamped O:\WHI\WHI09723.xml, (proposed PHSA § 351(k)(7)(A)(i)(I)).

\textsuperscript{108} See id. (proposed PHSA § 351(k)(7)(D)).


\textsuperscript{110} Id. at 8 (statement of Rep. Eshoo).

\textsuperscript{111} Id.

\textsuperscript{112} Id. at 9.

\textsuperscript{113} Id. at 9.

\textsuperscript{114} Id. at 190, 194 (statement of Larry McNeely, Healthcare Reform Advocate, U.S. Public Interest Research Groups).

\textsuperscript{115} Id. at 14 (statement of Bruce Leicher, Senior Vice President and General Counsel of Momenta).

\textsuperscript{116} Id. at -15.
reward [products] that have extended data exclusivity.” 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.” In Mr. Leicher’s view, delays in biosimilar market entry caused by data exclusivity would similarly delay this innovation. 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.”

Alex M. Brill, Research Fellow, American Enterprise Institute, supported a seven-year exclusivity period. 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 ren[s] . . . and provide no additional benefit to consumers.” 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. 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. According to Mr. Brill, “[a]n improvement that enlarges market share would increase profits further, thereby mitigating the amount of needed exclusivity.”

Jeffrey P. Kushan, an attorney at Sidley Austin, LLP, testifying on behalf of BIO, supported Representative Eshoo’s proposed twelve-year exclusivity period. 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. First, patents on biotechnology-derived drugs are narrower than patents on chemically synthesized drugs. 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. 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.” He was referring specifically to the

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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. 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." 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."

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."

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. Mr. Lasersohn noted that different stakeholders had very different views on the strength of biotechnology patents.

He noted that, to venture capitalists, "what matters . . . most is that [this disagreement] creates uncertainty, which is what actually affects our investment decisions."

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."


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." 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."

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." 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. 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." 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."

Mr. Leicher again supported Representative Waxman's approach. 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. He also noted that "numerous countries like Germany . . . permit the filing of nullity actions in court seeking to invalidate patents that are improvidently granted." 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." 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." Second, Mr. Leicher stated, the second Eshoo bill compels "disclosure of critical confidential information" about the biosimilar "that is not related to" demonstrating infringement. Third, in
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. Mr. Leichner 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. Ms. Stanek Rea agreed that the three-year period might not allow for resolution of patent litigation.

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.” 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.” 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.” 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.”

Ms. Stanek Rea expressed concern that H.R. 1427 would permit pre-launch litigation related only to patents selected by the applicant. 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.” 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.

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

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1151 See supra note 878 and accompanying text.
1152 Biologies 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." 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."

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. 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." 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. 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 paten provisions from H.R. 1548. More specifically, she offered the Hatch/Enzi/Hagan language with three changes. First, she included the pediatric exclusivity language from H.R. 1548. 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. 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 identify[d]" it and that distinguished it from both the reference product and other products licensed as biosimilar to that reference product.

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:\PII\NH\TRICOMM\AMDS\ESHOO_001.XML, available at http://energycommerce.house.gov/Press_Releases/111/20090713/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;\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.""\textsuperscript{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.""\textsuperscript{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.""\textsuperscript{1188} GPhA stated that the existing bills were ""little more than camouflaged protection of the unacceptable and unsustainable status quo.""\textsuperscript{1189}

On the same day, the House released its health care reform bill. It contained the Eshoo amendment, although three changes had been made.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1192} Third, this version amended section 271(e)(4)

\textsuperscript{1182}See supra note 878 and accompanying text.
\textsuperscript{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)).
\textsuperscript{1184}Generics, AARP, Unions Prefer No Biosimilars Path to 12-Year Exclusivity, FDA WEEK, July 24, 2009.
\textsuperscript{1185}Alex Wayne, House Health Compromise Includes Biologics Drug Competition, CQ TODAY ONLINE NEWS — HEALTH, July 31, 2009.
\textsuperscript{1186}Waxman Offers Generic Pledge to Keep Fighting on Biologics, FDA WEEK, Sept. 25, 2009.
\textsuperscript{1187}Id.
\textsuperscript{1188}Letter from Kathleen Jaeger, President & CEO, GPhA, to Pres. Obama (Oct. 27, 2009).
\textsuperscript{1189}Id.
\textsuperscript{1190}House Health Care Reform Bill stamped F:\API\NHIRTRICOMMA\AHCAA_001.XML, §§ 2575-77 (Oct. 29, 2009).
\textsuperscript{1191}Id. § 2575(a)(2) (proposed PHSA § 351(l)(6)).
\textsuperscript{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

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1193 See id. § 271(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. Filner (D-CA)).
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:\KERIKER09151.xml ____(a) (proposed PHSA § 351(m)).
1198 Sanders Amendment, No. 2858 to Amendment 2786, stamped KERO9A11 (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 KERO9B55, § 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) & (iii)).
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)." 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."  

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. 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." 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." This period could not be extended. 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." 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.

**E. 111th Congress, Second Session**

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." 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." On January 19, the Governors of Colorado, Delaware, Massachusetts, Maryland,

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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)(i)).
1205 *Id.* (proposed PHSA § 351(k)(7)(A)(ii)).
1206 *Id.* (proposed PHSA § 351(k)(7)(A)(iii)).
1207 *Id.* (proposed PHSA § 351(k)(7)(A)(iv)).
1208 *Id.* (proposed PHSA § 351(k)(7)(C)).
1209 H.R. 3590, 111th Cong., Title VII, Subtitle A (as passed by Senate Dec. 24, 2009).
1211 *Id.*
North Carolina, and Rhode Island wrote President Obama expressing concern about the White House's efforts.\textsuperscript{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.”\textsuperscript{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.”\textsuperscript{1213}

The same day, Republican Scott Brown won the Massachusetts Senate seat left vacant after the August 2009 death of Senator Kennedy.\textsuperscript{1214} He had campaigned as the forty-first vote against health care reform in the Senate, depriving Democrats of a filibuster-proof majority.\textsuperscript{1215} And his victory was seen as “put[ting] the entire [health care] reform effort in jeopardy.”\textsuperscript{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.\textsuperscript{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.\textsuperscript{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].”\textsuperscript{1219} On March 21, the House passed H.R. 3590 and on March 23, the President signed it.\textsuperscript{1220} The bill became Public Law 111-148. The reconciliation bill had been introduced on March 17 and did not affect the biosimilars language.\textsuperscript{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.\textsuperscript{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.

\textsuperscript{1211}Letter from Governor O’Malley (D-MD) et al. to Pres. Obama, Jan. 19, 2010, at 1.
\textsuperscript{1212}Id.
\textsuperscript{1213}Id.
\textsuperscript{1216}New Doubts About Health Reform Compound Uncertainty on Biosimilars, FDA Week, Jan. 22, 2010.
\textsuperscript{1217}Obama Health Reform Plan Includes Vague Statement on Biosimilars, FDA Week, Feb. 26, 2010.
\textsuperscript{1218}See id.
\textsuperscript{1219}Sheryl Gay Stolberg, Jeff Zeleny, and Carl Hulse, *Health Vote Caps a Journey Back From the Brink*, NY 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.
\textsuperscript{1221}H.R. 4872, 111th Cong. (2010).
A. Pathway

1. Definitions and Scope

Under current law, the phrase “biological product” includes proteins, except chemically synthesized polypeptides. 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. 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).” In other words, a biosimilar may not serve as a reference product for a 351(k) application, nor may an FDCA protein. 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. 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.”

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.” A biosimilarity showing must be based on analytical studies, animal studies, and a clinical study or studies. 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. The clinical work should include an assessment of immunogenicity and pharmacokinetics or pharmacodynamics that

1223 PHSA § 351(i)(1).
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.  

A biosimilar application must also include publicly available information about FDA’s previous determination that the reference product is safe, pure, and potent. 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. The latter may also be submitted in a supplement to the application. 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. This means that the application must contain a pediatric assessment, unless this requirement has been waived or deferred.

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. 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). 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. 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. 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.” 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

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123 Id. § 351(k)(2)(A)(ii)(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)(i). (ii).

1234 Id. § 351(k)(2)(A)(ii).

1235 Id. § 351(k)(2)(B).

1236 FDCA § 505B(n).

1237 Id. § 505B(a)(1).

1238 PHS A § 351(k)(5)(B).


1240 Id.

1241 Id. § 7002(f)(1).

1242 PHS A § 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). 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.

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.” 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.”

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. 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. In addition, the agency must establish a process through which the public may provide input on priorities for issuing guidance. Issuance of guidance, or non-issuance of guidance, does not preclude review of, or action on, an application submitted under the section.
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.\textsuperscript{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.\textsuperscript{1252} Any such statement may be modified or reversed in subsequent guidance.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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

\textsuperscript{1251} Id. § 351(k)(8)(D).

\textsuperscript{1252} Id. § 351(k)(8)(E)(i).

\textsuperscript{1253} Id. § 351(k)(8)(E)(ii).

\textsuperscript{1254} Id. § 351(k)(8)(E)(iii).

\textsuperscript{1255} Pub. L. 111-148 § 7002(e)(1).

\textsuperscript{1256} Id. § 7002(e)(2).

\textsuperscript{1257} Id. § 7002(e)(3).

\textsuperscript{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. 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(i)’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.

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. Both periods run from “the date on which the reference product was first licensed under subsection (a)” of section 351. 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.”


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

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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{1266}

Section 351(m)(1) of the PHSA 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.”\textsuperscript{1267} The cross-referenced subsections are: (a), (d), (e), (f), (i), (j), (k), (l), (p), and (q).\textsuperscript{1268} Subsection (a) provides definitions.\textsuperscript{1269} Subsection (d) relates to FDA’s issuance of written requests for pediatric studies and applicants’ responses to written requests.\textsuperscript{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.\textsuperscript{1271} Subsection (e) requires FDA to publish notices of determinations to accept study reports.\textsuperscript{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.\textsuperscript{1273} Subsection (f) relates to agency review of written requests and pediatric studies and to making related information publicly available.\textsuperscript{1274} Subsection (i) applies to labeling changes resulting from a pediatric study conducted under section 505A.\textsuperscript{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.\textsuperscript{1276} Subsection (k) concerns public dissemination of pediatric information.\textsuperscript{1277} Subsection (l) relates to adverse event reporting.\textsuperscript{1278} Subsection (p) requires FDA to enter into a contract with the Institute of Medicine (IOM) for a study on written requests.\textsuperscript{1279} Subsection (q) provides that the pediatric exclusivity provisions will sunset in 2012.\textsuperscript{1280}

\textsuperscript{1264} PHSA § 351(m)(2) & (3).
\textsuperscript{1265} Id. § 351(m)(2)(A) & (B), (m)(3)(A) & (B).
\textsuperscript{1266} Id. § 351(m)(4).
\textsuperscript{1267} Id. § 351(m)(1).
\textsuperscript{1268} Id.
\textsuperscript{1269} FDCA § 505A(a).
\textsuperscript{1270} Id. § 505A(d).
\textsuperscript{1271} Id. § 505A(d)(3).
\textsuperscript{1272} Id. § 505A(e).
\textsuperscript{1273} Id.
\textsuperscript{1274} Id. § 505A(f).
\textsuperscript{1275} Id. § 505A(i).
\textsuperscript{1276} Id. § 505A(j).
\textsuperscript{1277} Id. § 505A(k).
\textsuperscript{1278} Id. § 505A(l).
\textsuperscript{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.
\textsuperscript{1280} FDCA § 505A(q).

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.\(^{1297}\)


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).
\(^{1296}\) PHSA § 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).
circumstances, an injunction is not mandatory and presumably will issue only if
the reference product sponsor satisfies the traditional four-part test. An in-
junction 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. 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.

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. 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. 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.

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 infor-
mation 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. Process patents, which may
not be listed in the Orange Book, are addressed in, and clearly may be asserted
during, litigation under the BPCIA. Bringing suit under the BPCIA does not stay
approval of the biosimilar application as occurs under the Hatch-Waxman amend-
ments when suit is timely brought against the generic drug applicant. 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).
1304 Id. § 271(e)(6)(C).
1305 PHSA § 351(j)(9)(A).
1306 Id. § 351(j)(9)(C).
1307 Id. § 351(j)(9)(B).
1308 See FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (30th ed.
2010).
1309 PHSA § 351(j)(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.\footnote{See id. § 505(j)(5)(B) (specifying the timing of approval for an ANDA).} 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.\footnote{See id. § 505(j)(5)(B)(iv).} 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.
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.