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INTERESTS IN THE BALANCE

FDA REGULATIONS UNDER THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

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I. Introduction

Recent advances in biotechnology are yielding increasingly prevalent and diverse biological products made from a variety of natural sources intended to diagnose, treat, and prevent disease.[1] The Food and Drug Administration (FDA) continues to increase the number of biologics for which it grants approval, and biologics are being used to treat an increasing variety of conditions.[2] Yet, Americans do not have equitable and inexpensive access to these potentially life-saving products. These products' high prices prevent many patients from obtaining the biologic treatments they require.[3] Many believe that these prohibitive costs are the result of weak competition from generic biologic products, also known as follow-on biologics (FOBs).[4]

Much like the current problem facing biologics manufacturers, traditional generic pharmaceutical manufacturers struggled to compete with brand name manufacturers until Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly referred to as the Hatch-Waxman Act.[5] The Hatch-Waxman Act created an expedited pathway for FDA approval of generic pharmaceuticals. Under the Hatch-Waxman Act, generic drug manufacturers could obtain FDA approval for drugs before expiration of the associated brand

[1] *See infra* Part II.
[2] *Id.*
[3] *Id.*
[4] *Id.*
[5] *See infra* Part III.

name drug's patent term and could rely on the brand name drug's preclinical safety and efficacy testing results.[6]

Biologic products, as opposed to traditional pharmaceuticals, were originally regulated under the Hatch-Waxman Act. However, by the early 2000's, the difficulties associated with FDA regulation of biologic products had evinced the need for legislation dedicated specifically to FOBs.[7] First, reference product and FOB manufacturers disagree over whether biologic products' inherent complexity compared to traditional pharmaceuticals should require FOB manufacturers to conduct expensive clinical trials to prove their products' safety and potency.[8] Second, reference product and FOB manufacturers disagree on the extent to which reference products should be afforded exclusivity to recoup their front-end investment in innovative products.[9] Third, FOB manufacturers fear that brand name biologics manufacturers may engage in "evergreening," an anti-competitive strategy whereby manufacturers strategically alter their brand name drugs to eliminate demand for FOBs.[10] Fourth, critics argue that, unlike traditional pharmaceuticals, biologics should not be interchangeable with one another due to safety concerns, while supporters believe that interchangeability and automatic pharmacy substitution are essential to increasing FOB competition.[11]

Three specific provisions within the Biologics Price Competition and Innovation Act (BPCIA) were designed to address the regulatory and policy concerns associated with an abbreviated biologics approval pathway: exclusivity, biosimilarity, and interchangeability. Throughout the BPCIA's legislative history, Senators and Representatives proposed eight major

[6] *Id*.
[7] *See infra* Part IV.A.
[8] *See infra* Part IV.B.1.
[9] *See infra* Part IV.B.2.
[10] *See infra* Part IV.B.3.
[11] *See infra* Part IV.B.4.

bills, nine amendments, and numerous discussion drafts, all with different provisions on exclusivity, biosimilarity, and interchangeability.[12]

It is important to track the evolution of biosimilarity, interchangeability, and exclusivity provisions throughout the BPCIA's legislative history and distill Congress' intent to balance reference product sponsors' interest in protecting their investments and consumers' and FOB manufacturers' interest in bringing less expensive competing biological products to market.[13]Yet, the BPCIA alone is not enough. As it stands, the limited entry of competing FOBs in conjunction with the significant costs incurred by companies in the manufacture of both brand name and follow-on biologics make significant price reductions for biologic products under the BPCIA unlikely.[14] Because the biologics market is likely to remain hostile to FOB market entry even after the BPCIA's enactment, it is imperative that the FDA promulgates regulations designed to facilitate strong FOB competition while maintaining incentives for brand name manufacturers to produce innovative biologic products.[15]

This Comment analyzes the BPCIA's legislative history and identifies the extent to which Congress intended the Act's biosimilarity, interchangeability, and exclusivity provisions to protect reference product versus FOB interests. Part II provides an overview of biologics and their increasing use. Part III reviews how the Hatch-Waxman Act was enacted to deal with the inherent conflict between a need for brand name patent protection and a need for generic competition in the traditional pharmaceutical sector. Part IV introduces the major practical and policy issues driving biologics legislation. Part V details the BPCIA's legislative history and highlights crucial differences between proposed versions of the Act, and Part VI details the

[12]*See infra* Parts V and VI.
[13]*See infra* Part VII.A.
[14]*See infra* Part VII.B.
[15]*See infra* Part VII.C.

provisions of the BPCIA. Part VII then extracts Congress' intent in enacting the BPCIA's specific provisions and proposes regulations through which the FDA can most cogently effectuate Congress' intent.

II. A Primer on Biologics

Recent advances in biotechnology are yielding increasingly prevalent and diverse biologic products.[16] Biologics are medicinal products comprised of complex protein molecules produced using living cells and recombinant DNA technology.[17] Biologics include vaccines, hormones, human growth factors, enzymes, clotting and anti-clotting factors, and recombinant protein products.[18] Oftentimes, biologics are used therapeutically to replace or alter the proteins our bodies produce naturally.[19]

As of late 2008, biologics accounted for approximately one in eight prescriptions worldwide, with more than $10 billion in biologics scheduled to come off patent by 2016.[20] In addition, biologics are the fastest growing and most expensive class of prescription

[16] Ingrid Kaldre, *The Future of Generic Biologics: Should the United States "Follow-On" the European Pathway?*, 9 DUKE L. & TECH. REV. ¶¶ 1-2 (2008). Although the prevalence and diversity of biologics has increased dramatically in recent years, it is important to note that not all biologics are new. Biologics have existed for centuries. The smallpox vaccine, one of the most commonly recognized biologic products, was first administered in the late eighteenth century. Alexandra J. Stewart & Phillip M. Devlin, *The History of the Smallpox Vaccine*, 52 J. OF INFECTION 329, 329 (2006). Patients in the eighteenth century were inoculated for smallpox by subcutaneously introducing fresh material from a ripe smallpox pustule into a nonimmune individual. Stefan Riedel, *Edward Jenner and the History of Smallpox and Vaccination*, 18 BAYLOR U. MED. CENTER PROC. 21, 22 (2005).

[17] Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 535 (2010). The Biologics Price Competition and Innovation Act (BPCIA) defines the term "biological product" as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i)(1) (2010). According to FDA regulations, a biologic product is any "virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man." 21 C.F.R. § 600.3 (2010).

[18] U.S. Food and Drug Administration, What Are "Biologics" Questions and Answers, Apr. 30, 2009, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm. One example of an extremely successful biologic is Amgen's EPOGEN, a genetically engineered form of the human hormone erythropoietin used to treat anemia in patients with chronic kidney disease. Epogen, http://www.epogen.com/ (last visited Oct. 24, 2010).

[19] Kaldre, *supra* note 16, ¶ 2.

[20] Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U. L. REV. 555, 555 (2008).

therapeutics.[21] It was estimated in 2008 that biologics earned approximately forty-four percent of global profits from all prescription drugs,[22] and biologics generate $50 billion annually in the U.S. alone.[23] As the Food and Drug Administration (FDA) continues to increase the number of biologics for which it grants approval, biologics are being used to treat an increasing variety of conditions, resulting in increasing profit margins for biologics manufacturers.[24] It is clear, therefore, that the market share for biologics will continue to expand.[25]

The complexity of the manufacturing process and of the biologics themselves has led manufacturers to demand a significant premium for their products.[26] Biologics are often twenty times more expensive per patient than traditional pharmaceuticals,[27] and such pricing has prevented many patients from obtaining the biologic treatments they require.[28] Many believe that these prohibitive costs are the result of weak competition from generic biologic products, also known as follow-on biologics (FOBs).[29]

III. Traditional Pharmaceutical Regulation Under the Hatch-Waxman Act

Much like the current problem facing biologics manufacturers, traditional generic pharmaceutical manufacturers struggled to compete with brand name manufacturers until 1984. In that year, Congress passed the Drug Price Competition and Patent Term Restoration Act,

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[21] LESLIE TUCKER, NAT'L HEALTH POLICY FORUM, PHARMACOGENOMICS: A PRIMER FOR POLICYMAKERS 11 (2008), http://www.nhpf.org/library/details.cfm/2593.
[22] PRICEWATERHOUSECOOPERS, PHARMA 2020: MARKETING THE FUTURE—WHICH PATH WILL YOU TAKE? 13-14 (2009), http://www.pwc.com/en_GR/gr/surveys/assets/pharma-2020-marketing-future.pdf.
[23] David E. Adelman & Christopher M. Holman, *Misplaced Fears in the Legislative Battle Over Affordable Biotech Drugs*, 50 IDEA 565, 566 (2010).
[24] *Id*. at 567 (citing Michael Lanthier*et al.*, *Economic Issues with Follow-On Protein Products*, 7 NATURE REV. DRUG DISCOVERY 733, 733-34 (2008)).
[25] *Id.*
[26] Andrew Wasson, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products*, 4 DUKE L. & TECH. REV. 4, ¶¶ 1-2 (2005).
[27] William L. Warren, et al., *Abbreviated Approval of Generic Biologics*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS Dec. 2006, at 10.
[28] Alan J. Morrison, *Biosimilars in the United States: A Brief Look at Where We Are and the Road Ahead*, 26 BIOTECHNOLOGY L. REP. 463, 464 (2007).
[29] Gitter, *supra* note 20, at 562.

commonly referred to as the Hatch-Waxman Act.[30] Traditional drugs and biologics must obtain FDA approval before being marketed to consumers.[31] The Hatch-Waxman Act was created to address the lengthy FDA approval process and the resulting delays in bringing both brand name and generic pharmaceuticals to market.[32] Before the Hatch-Waxman Act, all traditional pharmaceuticals had to go through the New Drug Application (NDA) process, which required drug manufacturers to conduct expensive and time-consuming preclinical testing to ensure the safety and efficacy of any new drug.[33] The Hatch-Waxman Act created the Abbreviated New Drug Application (ANDA) process, an expedited pathway for FDA approval of generic pharmaceuticals that allows generic drug manufacturers to bring their products to market without conducting costly preclinical testing.[34] Using an ANDA, generic manufacturers can obtain FDA approval of generic drugs before expiration of the associated brand name drug's patent term.[35] Also, under the ANDA, generic drug manufacturers who establish their generic drug's "bioequivalence" to the brand name reference drug can rely on the preclinical safety and efficacy testing conducted for the brand name drug.[36] These provisions together allow a generic drug to obtain FDA approval before expiration of the brand name drug's patent term without incurring

[30] 21 U.S.C. § 355 (1984).
[31] Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission That Biotech Patents Fail Enablement*, 11 VA. J. L. & TECH. 8, ¶ 25 (2006).
[32] Wing Yan Tam, *supra* note 17, at 540. On average, it takes eight and a half years from preclinical testing to FDA approval for a traditional pharmaceutical, and it can take up to twenty years for some drugs. *Id*. at 539 (citing Michael Dickson & Jean Paul Gagnon, *Key Factors in the Rising Cost of New Drug Discovery and Development*, 3 NATURE REVS. 417, 418 fig. 1 (2004)).
[33] *See generally* 21 U.S.C. § 355 (2006); *see, e.g.,*aaiPharma Inc. v. Thompson, 296 F.3d 227, 230-31 (4th Cir. 2002).
[34]*See generally* 21 U.S.C. § 355(j) (2006).
[35]Mandel, *supra* note 31, ¶ 26.
[36] 21 U.S.C. § 355(j)(2)(A)(i)-(v) (2006). Establishing therapeutic equivalence requires information showing equivalence between the drugs' conditions of use, active ingredients, route of administration, dosage form, strength, and labeling. *Id*. In addition, the applicant must establish the drugs' bioequivalence. 21 U.S.C. 355(j)(2)(A)(iv) (2006). A generic drug is "bioequivalent" to a reference drug if the two "do not differ significantly with respect to the rate and extent to which their active ingredients become available at their site of action on or in the body." Wing Yan Tam, *supra* note 17, at 540-41 (citing David Bickart, *Developments in Pharmaceutical and Biotech Patent Law,* PRACTISING LAW INSTITUTE, PHARMACEUTICAL AND BIOTECH PATENT LAW 208, 218 (2008)).

the cost of clinical trials, thus allowing generic manufacturers to offer equivalent drugs at significantly lower prices immediately after the reference product's patent expires(?).[37]

Ultimately, the Hatch-Waxman Act addressed the inherent tension between promoting drug discovery and innovation through patent protection and a need to increase market entry of lower-cost generic pharmaceuticals.[38] Between its enactment in 1984 and mid-2007, use of generic pharmaceuticals increased from 19% of all prescriptions to 67%.[39] This marked increase in generic pharmaceuticals established the Hatch-Waxman Act as a highly successful tool for providing cost savings to consumers while continuing to encourage pharmaceutical innovation.[40]

IV. The Need for Biosimilars Legislation

Confusion over regulation of biologics within the existing pharmaceutical regulatory framework and several policy concerns regarding biologic regulation have driven development of the Biologics Price Competition and Innovation Act (BPCIA).

A. Biologics Under the Hatch-Waxman Act

By the early 2000's, the difficulties associated with FDA regulation of biologic products had elucidated the need for legislation dedicated specifically to biosimilars.[41] Since 1906, overlap between the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Services Act (PHSA) had caused confusion regarding federal regulation of biologic products.[42] It was unclear whether the FDA had the authority to approve FOBs under an abbreviated pathway and whether approval, if authorized, should proceed under the FDCA or the PHSA.[43] Even if

[37] Mandel, *supra* note 31, ¶ 27.
[38] 21 U.S.C. §§ 271(e), 335 (2006).
[39] Michelle L. Ethier, *Permissible Product Hopping: Why a Per Se Legal Rule Barring Antitrust Liability is Necessary to Protect Future Innovation in the Pharmaceutical Industry*, 3 AKRON INTELL. PROP. J. 323, 332 (2009).
[40] Wing Yan Tam, *supra* note 17, at 540.
[41] Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 698 (2010).
[42] *Id*.
[43] *Id*. Some members of Congress and the generics industry took the position that the FDA already had the authority to approve FOBs under an abbreviated pathway, but the innovator industry obviously disagreed, *id*.

such authority was assumed, it was still unclear whether FOB applicants could rely on reference product preclinical and clinical safety data.[44] As a result of this confusion, the FDA took the position that new legislative authority on biologics regulation was required.[45]

B. Major Policy Concerns

In addition to FDA confusion over regulatory authority to approve biologics, several policy concerns have driven the development of the BPCIA.

1. Inherently Elevated Costs and Complexity of Producing Biologic Products

The safety, purity, and potency of a traditional generic pharmaceutical depend on the specific chemical composition and purity of the drug, both of which can be reliably determined using existing technological methods.[46] Absolute characterization is standard for traditional pharmaceuticals and involves an exhaustive but routine analysis of the drug at the molecular level.[47] The state of the art in biologics, however, does not always allow equivalence testing for biologics similar to such testing for traditional drugs.[48] Determining the three-dimensional structure of biologics, which is integral to verifying safety and potency, is difficult.[49] In addition, difficulties arise in predicting whether minor changes in a biologic will detrimentally affect its function or its safety.[50] These issues make comparative characterization—as opposed to absolute characterization—the standard for biologic comparison.[51] Further, comparative characterization to determine the identity, potency, safety, quality, and purity of a FOB may only be possible for

[44] *Id*. at 698-99.
[45] *Id*. at 699.
[46] 21 U.S.C. § 355(j) (2006); Adelman & Holman, *supra* note 23, at 581.
[47] Gitter, *supra* note 20, at 592.
[48] Adelman & Holman, *supra* note 23, at 580.
[49] *Id.* (citing David M. Dudzinski et al., *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 NEW. ENG. J. MED. 843, 847 (2008)).
[50] *Id.*
[51] Gitter, *supra* note 20, at 591-92.

simpler biologics.[52] For characterization of more complex biologics, animal or human clinical trials may be required.[53]

Clinical trials are, however, costly and time-consuming. Requiring clinical trial data from FOB manufacturers largely eliminates the cost savings envisioned under an abbreviated approval pathway. Increased production costs in turn prevent generic drug manufacturers from bringing competing products to market at significantly discounted prices.[54] Whereas the cost of developing a traditional generic pharmaceutical is estimated at $1-$2 million per drug, the cost of developing a follow-on biologic is estimated at $10-$80 million.[55] If FOB manufacturers are unable to realize significant cost savings under biosimilars legislation, it is likely that significantly fewer FOB products will make it to market.[56]

Beyond production costs, several factors contribute to the financial infeasibility of bringing a follow-on product to market. FDA approval for follow-on biologics is likely to take longer than approval of traditional generic pharmaceuticals under the Hatch-Waxman Act, effectively extending the brand name biologic's market monopoly.[57] In addition, manufacturing and producing biologics in living cells presents unique challenges for which not all companies are equipped.[58] The substantial costs of developing follow-on biologics, conducting any necessary clinical trials, and obtaining FDA approval has severely curtailed the number of

[52] Wing Yan Tam, *supra* note 17, at 543; Gitter, *supra* note 20, at 595.
[53] Adelman & Holman, *supra* note 23, at 581 (citing Janet Woodcock et al., *The FDA's Assessment of Follow-On Protein Products: A Historical Perspective*, 6NATURE REV. DRUG DISCOVERY 437, 438 (2007)).
[54] *See supra* Part III.
[55] Suzanne M. Sensabaugh, *Biological Generics: A Business Case*, 4 J. GENERIC MED. 186, 189 (2007), *available at* http://hartmannwillner.com/yahoo_site_admin/assets/docs/Biological_generics_a_business_case.11495232.pdf.
[56] *See infra* Part VII.B.
[57] Wing Yan Tam, *supra* note 17, at 558.
[58] Richard Gayle, *Healthcare Reform Gave Biotech Everything It Wanted, and More*, XCONOMY (Mar. 24, 2010), http://www.xconomy.com/national/2010/03/24/healthcare-reform-gave-biotech-everything-it-wanted-and-more/2/.

companies financially able to bring a follow-on biologic to market, and FOB development to date has not resulted in significant price discounts or shifts in market share for biologics.[59]

2. Innovation vs. Competition: Marketing Exclusivity Periods

The conflict between brand name and FOB manufacturers is, at its root, one of the most fundamental inherent conflicts of the patent system. While patent rights encourage innovation by granting inventors a limited monopoly over their respective discoveries, antitrust laws foster competition by prohibiting any attempt to monopolize.[60] Patents are important to promote the progress of science but must remain "exception[s] to the general rule against monopolies and to the right of access to a free and open market."[61]

In the context of biologics, extended development and FDA approval timelines often erode a reference product's patent term. The average biologic product requires ten to fifteen years from discovery to FDA approval.[62] In addition, brand name biologics manufacturers spend $10-$80 million per product to bring a new biologic to market,[63] partially because for every brand name product that makes it to market, 5,000 to 10,000 attempted products fail.[64] At the same time, however, biologic products have the potential to be reverse engineered, and FOB manufacturers can bring competing drugs to market at costs lower than those incurred by brand name manufacturers.[65] Therefore, exclusivity periods independent of a product's patent term are crucial to protect drug manufacturers' very significant front-end investment in innovative biologic products.[66] Without the limited monopoly granted under exclusivity periods, companies

[59] FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION iii (2009), http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.
[60] *See generally* 35 U.S.C.A. § 154 (West 2011); 15 U.S.C. § 2 (2006).
[61] In re Ciprofloxacin Hydrochloride Antitrust Litig., 544 F.3d 1323, 1333 (Fed. Cir. 2008).
[62] Linfong Tzeng, *Follow-On Biologics, Data Exclusivity, and the FDA*, 25 BERKELEY TECH. L.J. 135, 154 (2010).
[63] Sensabaugh, *supra* note 55.
[64] *Id*. at 11.
[65] *Id*. at 4.
[66] Ethier, *supra* note 39, at 329.

may not be able to recoup the initial investment in research required to bring a new biologic to market.[67] Innovation may thus be frustrated and consumers would not have the opportunity to benefit from new biologics.

In tension with reference product sponsors' need to recoup investment, there exists a competing social need for access to less expensive biologic products. The cost of biologic products has become inconvenient for many and prohibitive for many more. By bypassing the significant research and development costs associated with reference product innovation, FOB manufacturers may be able to provide drugs that drive down the high prices brand name manufacturers charge for their products, to the benefit of all consumers.[68] Because consumers benefit both from increased innovation by brand name manufacturers and from the cost savings associated with increased FOB competition, it is apparent why FOB regulation has become a contentious issue.

3. Potential for Product "Evergreening"

In addition to spurring generic competition for traditional small-molecule drugs, the Hatch-Waxman Act has had some unintended anti-competitive consequences that may begin to arise in the biologics arena as well. In response to the success of generic drug manufacturers under the Hatch-Waxman Act, some brand name pharmaceutical companies have begun engaging in an anti-competitive tactic called "evergreening." A desire to prevent this anti-

[67] *Id*.
[68] Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 COLUM. L. REV. 1471, 1495 (2008). Because the first generic market entrant's 180-day exclusivity period under the Hatch-Waxman Act, the first generic drug is generally offered at only a 20% discount over its name brand equivalent. Arie M. Michelsohn, *"Follow-On" Biologics: What Will It Take?*, 5, No. 2, THE SCITECH LAWYER 4, 6 (2008). However, entry of the second generic drug generally doubles the price discount of the first generic entrant and three or more generic alternatives can decrease the product price by fifty to eighty percent of the brand name price. David A. Balto, *Pharmaceutical Patent Settlements: The Antitrust Risks*, 55 FOOD & DRUG L.J. 321, 325 (2000); Wing Yan Tam, *supra* note 17, at 556.

competitive behavior under the BPCIA was integral to development of the Act's exclusivity provisions.

Evergreening is a burgeoning anti-competitive strategy whereby a brand name pharmaceutical manufacturer strategically alters its brand name drug so that the old and new formulations are no longer bioequivalent.[69] As a result, under the provisions of the Hatch-Waxman Act, any generic versions of the old brand name drug are no longer bioequivalent to the new brand name drug. [70] The generic manufacturer can then choose to (1) enter the market as a brand name drug itself, or (2) begin the ANDA process anew based on the brand name drug's new formulation.[71] The first option is potentially prohibitively expensive because without a brand name corollary the FDA must consider the once generic drug a "new" drug, which requires approval under an NDA supported by extensive preclinical testing.[72] The second option, while more realistic, provides no assurance that the brand name manufacturer will not repeat the evergreening process, potentially in perpetuity.[73] Both options continue the brand name pharmaceutical's monopoly and prevent customers from realizing the cost savings for which the Hatch-Waxman Act was designed.[74]

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[69] Cheng, *supra* note 68. Methods of reformulation include changing the drug's molecular structure, method of delivery, or indication of use. Rebecca S. Yoshitani & Ellen S. Cooper, *Pharmaceutical Reformulation: The Growth of Life Cycle Management*, 7 HOUS. J. HEALTH L. &POL'Y 379, 388 (2007).
[70] Cheng, *supra* note 68.
[71] *Id*.
[72] Ethier, *supra* note 39, at 335.
[73] Alan Devlin, *Exclusionary Strategies in the Hatch-Waxman Context*, 2007 MICH. ST. L. REV. 631, 657.
[74] *Id*. For example, in *Abbott Labs. v. Teva Pharms. USA, Inc.*, Abbott Laboratories and Fournier Industrie et Sante marketed the drug fenofibrate under the brand name TriCor as a cholesterol-lowering drug in capsule form. 432 F. Supp. 2d 408, 415 (D. Del. 2006). Abbott began marketing TriCor in 1998 and has reported sales of approximately $750 million per year. Second Amended Answer, Affirmative Defenses, and Counterclaims at 16, *Abbott Labs.*, 432 F. Supp. 2d 408 (No. 02-1512 (KAJ)) [hereinafter Teva, Second Amended Answer]; Reply Brief in Support of Teva Pharmaceuticals USA, Inc.'s and Teva Pharmaceutical Industries Ltd.'s Motion to Supplement and Amend Their Answers to Assert Antitrust Counterclaims at 2, *Abbott Labs.*, 432 F. Supp. 2d 408 (No. 02-1512-KAJ) [hereinafter Teva, Reply]. In 2000, Teva filed an ANDA paragraph IV application to sell a generic version of TriCor. Teva, Reply, *supra*, at 121. In 2001, Abbott made its first product hop from TriCor in capsule form to a new tablet formulation, simultaneously removing the capsule formulation from the market. *Abbott Labs.*, 432 F. Supp. 2d at 416. In addition, Abbott changed the National Drug Data File (NDDF) code for the old capsule formulation to "obsolete," preventing pharmacists from substituting prescriptions for the new as well as the old

Those defending so-called evergreening, however, believe that discussions of innovation in the biologics and pharmaceuticals industries are inherently more complex because "incremental innovation" in the form of new dosages, formulations, and indications is the key to advances in the treatment and prevention of disease.[75] While such incremental changes are often the types of changes used by evergreening drug manufacturers to exclude generic competitors from the market,[76] such improvements comprise a significant share of drug utilization and associated profits for manufacturers.[77] If biologics companies were prevented from gaining protection for and profiting from such incremental improvements, proponents argue, biotechnological innovation would likely be stifled.[78] Much of the debate over the BPCIA's exclusivity provisions revolved around the potential for such anti-competitive behavior in the biologics sector and how legislators could design the Act to prevent evergreening.

4. The Advantages of Automatic Pharmacy Substitution

The Hatch-Waxman Act allows pharmacists to automatically substitute generic equivalents for prescribed brand name drugs without physician consent or consultation.[79] Similarly, follow-on biologics products that receive an interchangeability rating could be automatically substituted in pharmacies for a physician prescribed reference biologic, unless the

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brand name formulations with the generic version. *Id.*; Teva's Answering Brief in Opposition to Abbott's and Fournier's Motion to Dismiss Counterclaims, at 14-15, *Abbott Labs.*, 432 F. Supp. 2d 408 (No. 02-1512 (KAJ)) [hereinafter Teva, Answer]. In 2002, Teva followed Abbott's hop by developing generic TriCor tablets and applying for FDA approval. Teva's, Answer *supra*, at exhibit A. Abbott then hopped a second time developing a version of TriCor that need not be taken with food. *Abbott Labs.*, 432 F. Supp. 2d at 418. As a result, once Teva obtained FDA approval to market its generic version, it was unable to rely on generic substitution at pharmacies and was, instead, forced to market Fenofibrate as a brand name drug called Lofibra. *Id.* at 416; Teva, Second Amended Answer, *supra*, at 37. Brand name Lofibra was then only able to earn about $4 million per year, as opposed to TriCor's $750 million per year. *Abbott Labs.*, 432 F. Supp. 2d at 416; Teva, Second Amended Answer, *supra*, at 37.

[75] Ernst R. Berndt et al., *The Impact of Incremental Innovation in Biopharmaceuticals*, 24 PHARMACOECONOMICS 69 (Supp. 2, 2006); Ethier, *supra* note 39, at 19.

[76] *See supra* Part IV.B.3.

[77] Berndt et al., *supra* note 75; Ethier, *supra* note 39, at 19.

[78] Ethier, *supra* note 39, at 343.

[79] Cheng, *supra* note 68, at 1488. *See also* Loren Gelber, *Obtaining Approval of a Generic Drug*, *in* THE PHARMACEUTICAL REGULATORY PROCESS 415, 416-17 (Ira R. Berry ed., 2005).

prescribing physician specifically indicates that only the brand name product should be distributed.[80]

Critics of interchangeable FOBs, however, argue that due to their inherent complexity and diversity, biologics are uniquely sensitive to changes in environmental and manufacturing conditions.[81] Two biologics with similar formulations may behave very differently in each individual, and substitution for a brand name biologic may have adverse and unintended effects.[82] In addition, biologic products are often mixtures of different proteins and impurities, all of which contribute to the product's function and safety.[83] How these different components function together to produce the desired result is often poorly understood and difficult to reproduce.[84] Critics argue, therefore, that follow-on biologics should not be interchangeable with one another.[85]

Interchangeability supporters, however, argue that without an interchangeability rating, follow-on biologics cannot be automatically substituted for brand name biologics. Lack of automatic substitution will hinder the rate at which a follow-on product acquires market share from the reference product, and thus, will limit the follow-on's ability to increase revenue and return on investment. Such an entry barrier may discourage follow-on manufacturers and decrease competition for brand name biologics.[86]

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[80] FED. TRADE COMM'N, *supra* note 59, at iv.
[81] Wing Yan Tam, *supra* note 17, at 542 (citing Michael Kleinberg & Kristen Wilkinson Mosdell, *Current and Future Considerations for the New Classes of Biologicals*, 61 AM. J. OF HEALTH-SYSTEM PHARMACY 695, 695 (2004)).
[82] *Id.* (citing Scott Gottlieb, *Biosimilars: Policy, Clinical, and Regulatory Considerations*, 65 AM. J. OF HEALTH-SYSTEM PHARMACY S2, S5 (2008)).
[83] David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 224 (2005).
[84] *Id*.
[85] Gitter, *supra* note 20, at 560-61.
[86] FED. TRADE COMM'N,*supra* note 59, at iv.

C. Potential Provisions

Three specific provisions within the BPCIA were designed to address the regulatory and policy concerns associated with an abbreviated biologics approval pathway: biosimilarity standard, interchangeability standard, and exclusivity. The FDA's interpretation of these provisions will ultimately foster or destroy the success of the BPCIA in creating a competitive FOB market.

1. Biosimilarity

The BPCIA and its predecessor drafts would all have used some sort of standard to determine whether an FOB could be approved under an abbreviated pathway using reference product data. While the individual requirements for these standards differed from bill to bill, every piece of legislation leading up to the BPCIA's enactment had one thing in common. Simply put, biologic products that met a particular bill's biosimilarity standard could have been approved under the bill's abbreviated pathway, and those products that did not meet the standard could not. For this reason, each bill's biosimilarity standard provides insight into how aggressively its drafters intend biosimilar approval to be used to stimulate FOB competition in the biologics market.

2. Interchangeability

As discussed, interchangeability is a heightened standard beyond biosimilarity that provides certain FOB products with competitive advantages, depending on the specific legislation.[87] The BPCIA's predecessor drafts differed significantly on standards of interchangeability, and some would not have recognized the concept at all. Others would have recognized interchangeability but would have allowed substitution of the FOB for a reference

[87] The concept of interchangeability is derived from the Hatch-Waxman's "bioequivalence" standard. *See supra* Part III. Under the Hatch-Waxman Act, because traditional pharmaceutical molecules could be easily compared to determine equivalence, generic pharmaceuticals were automatically considered interchangeable with their reference products.

product only at a physician's explicit request. The stringency of a given interchangeability provision combined with a bill's position on automatic pharmacy substitution will influence the rate at which a follow-on product acquires market share from the reference product, increases revenue, and earnsa return on investment. Therefore, a bill's interchangeability provisions indicate its drafters' intent to either facilitate FOB market competition or to protect reference product interests.

3. Exclusivity

During the term of market exclusivity for both brand name and follow-on biologics, the FDA may not grant approval of a competing application for the same product,[88] and competing drug or biologic products cannot be marketed until the term of the market exclusivity expires.[89] Each bill in the BPCIA's legislative history contained market exclusivity provisions of varying duration for various stakeholders: reference product sponsors, reference product sponsors applying for supplemental exclusivity, or interchangeable FOB manufacturers. The types of products protected and the duration of exclusivity provisions within a given bill indicate how aggressively drafters intended to protect certain interests with a guaranteed limited monopoly.

V. Legislative History of the BPCIA: 2006-2009

Throughout the BPCIA's legislative history, Senators and Representatives proposed eight major bills, nine amendments, and numerous discussion drafts, all with different provisions on biosimilarity, interchangeability, and exclusivity. This section provides a high-level summary of these bills, amendments, and discussion drafts and highlights those differences crucial to understanding Congress' intent in enacting the BPCIA. For a more detailed description of these documents' provisions, see Appendix: Proposed Legislation in the BPCIA's Legislative History.

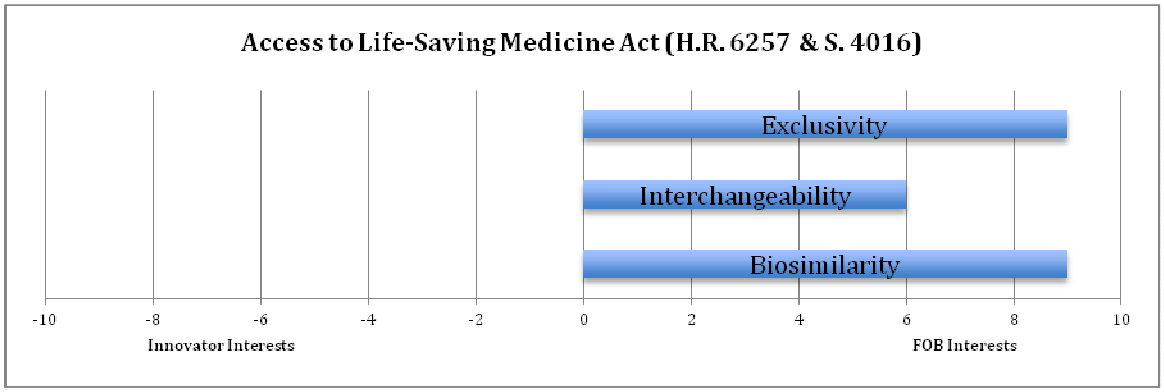
[88] Wing Yan Tam, *supra* note 17, at 552-53.
[89] For an analysis of motivations behind market exclusivities, see Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 357-58 (2007).

A. 109th Congress, Second Session

1. Access to Life-Saving Medicine Act (H.R. 6257 & S. 4016)

On September 29, 2006, Representative Waxman and Senator Schumer introduced the Access to Life-Saving Medicine Act (ALSMA) into the House and Senate as H.R. 6257 and S. 4016 respectively. These bills were nearly identical and, as expected, did not pass. They did, however, succeed at broaching the critical issues surrounding biosimilars legislation. See Appendix: Table 1 for a detailed summary of the bill's provisions.

The ALSMA would have established two regulatory pathways for approval and licensure of biologic products. The bill would have allowed approval of both comparable biologic products and biologic products not comparable to the reference product so long as the applicant established the product's safety, purity, and potency relative to the reference product for its proposed conditions of use.[90]



a) Biosimilarity

The ALSMA's biosimilarity provisions would have imposed liberal testing and data requirements for approval and would have given the FDA discretion to determine whether clinical testing would be required for a given FOB on a case-by-case basis. First, the ALSMA would have allowed FDA approval of products exhibiting an "absence of clinically meaningful

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

differences" based on non-clinical laboratory studies and clinical studies but only when necessary to establish the product's safety, purity, and potency.[91] Second, the ALSMA would have required FOB applicants to establish "thorough characterization" in addition to several other measures of comparability that survived largely unchanged in the BPCIA.[92] Third, the ALSMA would have established a broad class of biological products defined within the section as inherently comparable while reserving the FDA's discretion to find comparability between other products.[93] Fourth, the ALSMA would have explicitly forbid the FDA from requiring any additional post-marketing studies as a "condition of approval."[94] Finally, for FOBs with a known mechanism of action, the ALSMA would have required the FDA to approve the FOB for "*all* conditions of use of the reference product,"[95] not just the condition of use for which the

[91]H.R. 6257, 109th Cong. § 2(2) (2006) (proposed PHSA §§ 351(i)(2)(A), (i)(2)(B), (i)(4)).
[92]The bill defined "thorough characterization" as an "analysis of structural features based upon appropriate analytical and functional testing sufficient to identify differences . . . relevant to safety, purity or potency." H.R. 6257, 109th Cong. § 2(2) (2006) (proposed PHSA § 351(i)(5)). In addition to thorough characterization, the ALSMA would have required that: 1) the two products used "the same mechanism or mechanisms of action for the conditions of use . . . but only to the extent the mechanism or mechanisms of action are known for the reference product," 2) the FOB's condition or conditions of use had previously been approved for the reference product, 3) the products had the same route of administration, dosage form, and strength, 4) all FOB facilities met relevant standards, and 5) the two products contained "comparable principal molecular structural features . . . notwithstanding minor differences." H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA §§ 351(k)(1)(B)-(F)). It is important to note two of the bill's underlying features: 1) its focus on the product's safety, as opposed to its precise physical comparability, and 2) the bill's reliance on analytical studies for characterization, as opposed to clinical studies.
[93] First, two "protein biological products with differences in structure between them solely due to post-transitional events, infidelity of translation or transcription, or minor differences in amino acid sequence." H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)(i)). Second, two "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." H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)(ii)). Third, "glycosylated protein products with differences in structure between them solely due to post-transitional 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 differ and even if there were differences in post-polymerization." H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)(iii)). Fourth, two "polynucleotide biological products with identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone." H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)(iv)). Fifth, any "[c]losely related, complex, partly definable biological products with similar therapeutic intent, such as two live viral products for the same indication." H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)(v)).
[94]H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(2)) ("The Secretary shall not, as a condition of approval, propose any additional postmarketing studies.").
[95]H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(5)) (emphasis added).

application established comparability. This broad approval mechanism has since been dubbed "extrapolation."

b) Interchangeability

The ALSMA defined an "interchangeable" biological product as one with a comparable molecular structure that could be expected to produce the same results in patients as the reference product.[96]

c) Exclusivity

Although limited, the ALSMA's exclusivity provisions would have favored FOB applicants more than the BPCIA or any other legislation considered before the BPCIA's enactment. The ALSMA would have provided up to 180 days of exclusivity to the first interchangeable FOB and no reference product exclusivity.[97] Eliminating reference product exclusivity would have left the door wide open for FOB applicants to submit applications for licensure to the FDA, conduct necessary testing, gain FDA approval, and begin market their FOBs the day a reference product's patent term expired.

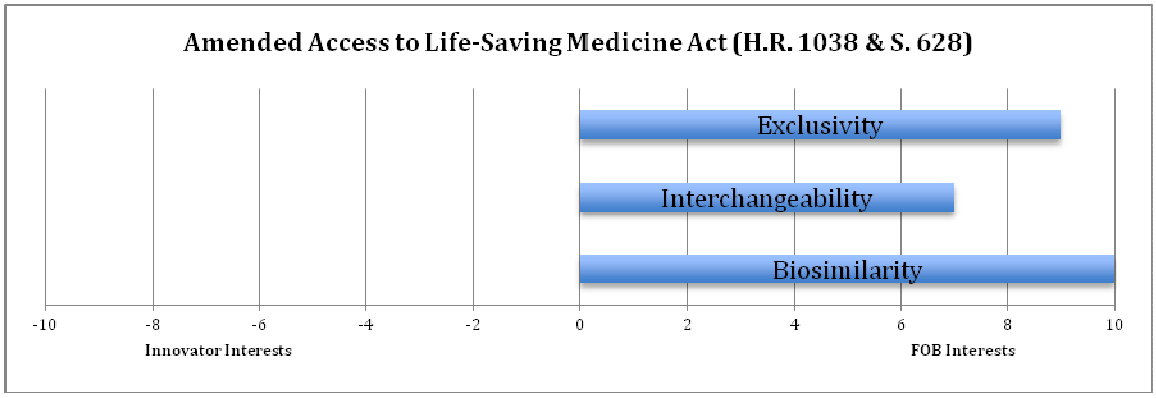
B. 110th Congress, First Session

1. Amended ALSMA (H.R. 1038 & S. 623)

On February 14, 2007, Representative Waxman and Senator Schumer introduced a second version of the ALSMA (the Amended ALSMA) into the House and Senate as H.R. 1038 and S. 623 respectively. These bills were identical, and like the ALSMA, both would have established approval pathways for both comparable and non-comparable biologic products. [98] However, the Amended ALSMA differed substantively from the original ALSMA on the required data to establish product comparability and on product interchangeability. These bills,

[96]H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(6)).
[97]H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(9)(A))(ii).
[98] H.R. 1038, 110th Cong. § 3(a)(2) (2007) (proposed PHSA § 351(k)(1), (2)).

again, passed neither the House nor the Senate. See Appendix: Table 2 for a detailed summary of the bill's provisions.



a) Biosimilarity

The Amended ALSMA's biosimilarity provisions, while nearly identical to those under the ALSMA, would have provided the FDA with significantly greater discretion in determining comparability. First, the Amended ALSMA replaced the term "comparable" with the phrase "highly similar" and removed the requirement that comparability be demonstrated by "thorough characterization."[99] Second, the Amended ALSMA would have allowed the FDA to determine both the clinical and non-clinical testing requirements for each FOB applicant on a case-by-case basis.[100] As opposed to requiring at least analytical and functional testing,[101] this less stringent requirement would have advantaged FOB applicants even more than the original ALSMA.[102]

[99] Compare H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)) and H.R. 1038, § 3(a)(2) (proposed PHSA § 351(k)(1)(B)).
[100] During the 2007 hearings on the Amended ALSMA, representatives from the innovator industry criticized the bill's reservation of authority to determine necessary analytical requirements to the FDA. Industry representatives argued that "there will always be a need (in the foreseeable future) for some amount of clinical testing" to set a "floor" to the FDA and the biologics industry. Carver et al., *supra* note 41, at 731. The generic industry, however, argued that mandating clinical trials would "not be something that is scientific, but rather political," and that it would ultimately "slow the pace of scientific inquiry." *Id.* at 730-31.
[101] H.R. 6257, 109th Cong. § 3(a)(2) (2006) (proposed PHSA § 351(k)(1)(B)).
[102] In a February 14, 2007 press release, the GPhA "expressed its strong support" for the Amended ALSMA. Press Release, GPhA, GPhA Endorses Access to Life Saving Medicine Act – Legislation Would Create Safe, Abbreviated FDA Approval Pathway for Biogenerics (Feb. 14, 2007), *available at* http://www.gphaonline.org/media/press-releases/2009/gpha-endorses-access-life-saving-medicine-act-legislation-would-create-saf. The group stated that under the Act's "clear, efficient abbreviated FDA approval pathway," the "FDA will have the authority and flexibility it needs to request from generic companies the necessary data and tests on a product-by-product basis."

b) Interchangeability

The Amended ALSMA also would have created a less stringent standard for interchangeability determinations by requiring no additional showing beyond comparability to be deemed interchangeable.[103] This coupled with the bill's more relaxed biosimilarity standard would have forced the FDA to find significantly more FOBs interchangeable with their corresponding reference products.

c) Exclusivity

Despite the innovator industry's significant criticism of the original ALSMA,[104] the Amended ALSMA would have made no changes to the Act's exclusivity provisions. Drafters of both the ALSMA and the Amended ALSMA considered arguments for and against innovator exclusivity periods of both five and fourteen years and consciously chose not to allow any reference product exclusivity.

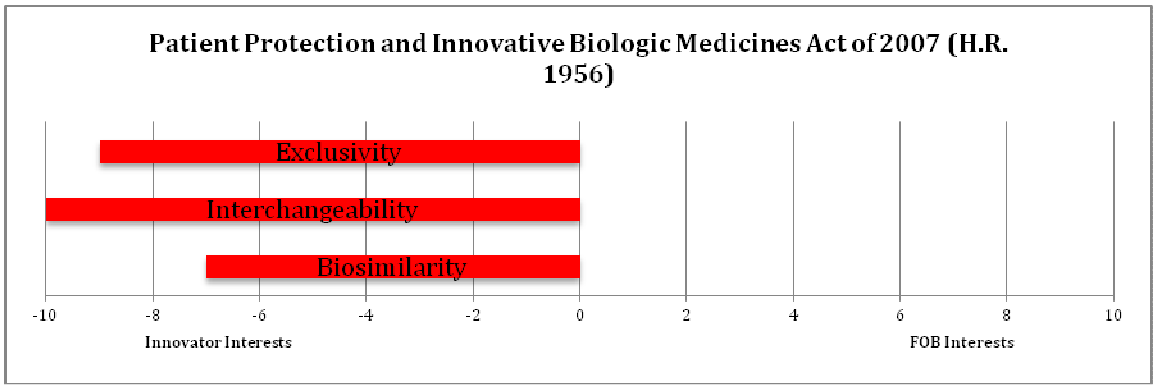
Id. However, on March 26, 2007, BIO issued a statement "strongly oppos[ing]" the ALSMA. Press Release, BIO, BIO Restates Opposition to H.R. 1038 (Mar. 26, 2007), *available at* http://www.bio.org/news/pressreleases/newsitem.asp?id=2007_0326_01. BIO stated that the Amended ALSMA would "restrict the ability of the FDA to require whatever clinical testing it believes appropriate" and that the Amended ALSMA would permit approval of unsafe follow-on biologic products. *Id*.

[103] In the 2007 hearings on the Amended ALSMA, generics industry representatives argued "without hesitation, that adequate scientific tools currently exist to assess and deem certain products interchangeable," and that interchangeability designations for biosimilars were the "natural next step" for the FDA. Carver et al., *supra* note 41, at 733-34. The innovator industry, however, that "in the foreseeable future, there is no realistic potential for scientifically valid determination of interchangeability" and that such determinations "could lead to . . . potentially serious health consequences." *Id*. Dr. Janet Woodcock, then FDA Deputy Commissioner and Chief Medical Officer agreed with generics representatives that interchangeability designations may be possible, but urged that additional clinical data would be required for such findings. *Id*. at 734.

[104] In a report issued by the Biotechnology Industry Organization, critics of the Amended ALSMA stated that any biosimilar legislation "must establish a substantial period of data exclusivity [for reference products] to preserve incentives for research development, manufacture, and approval of new biologic therapies." BIO, A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES, 1 (2007). Bio called for an innovator exclusivity period of no less than 14 years in order to stimulate innovative research and to allow reference product manufacturers to recoup the high costs of product development. *Id*. Bio argued that under the Amended ALSMA's "highly similar" standard, FOB manufacturers might be able to secure abbreviated regulatory approval using reference product clinical data while avoiding patent infringement litigation. *Id*. Bio cited a research paper finding that reference product companies typically recover the costs of investment in a particular product between 12.9 and 16.2 years after approval as support for innovator exclusivity as a type of "insurance policy" for reference product manufacturers. *Id*. at 4.

2. Patient Protection and Innovative Biologic Medicines Act of 2007(H.R. 1956)

On April 19, 2007, Representative Inslee introduced the Patient Protection and Innovative Biologic Medicines Act of 2007 (PPIBM) into the House as H.R. 1956. Unlike the Amended ALSMA, the PPIBM would have established only one regulatory pathway for approval and licensure of FOBs and would not have allowed the FDA to approve biologic products that did not satisfy FDA issued guidance on applicable reference products. The movement to a single regulatory pathway would have significantly decreased the number and types of FOB applicants the FDA could approve. The bill, however, did not pass the House. See Appendix: Table 3 for a detailed summary of the bill's provisions.



a) Biosimilarity

Unlike the Amended ALSMA's case-by-case approach to FDA approval, the PPIBM's biosimilarity provisions would have significantly restricted the FDA's ability to approve FOBs by imposing product-class specific guidance requirements and stringent minimum data requirements. First, the PPIBM's guidance rules would have created a significant initial barrier to FOB approval. By granting the FDA authority to prioritize guidance requests and "summarily reject frivolous or unsupported requests,"[105] the PPIBM would have allowed the FDA to reject

[105]Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2(a)(2) (proposed PHSA § 351(k)(4)(B)(i), (ii)) (2007).

all but the most thoroughly supported applications. Even after a lengthy public comment process for establishing product class guidance,[106] the FDA would have had the discretion to deny approval for products for which it deemed product-class specific guidance impossible to issue "given the current state of scientific and technical knowledge."[107] Second, assuming the FDA issued guidance for a particular FOB approval application, the FOB manufacturer would have been required to conduct physical, chemical, and biological assays "*fully characterizing*" the FOB,[108] comparative nonclinical studies demonstrating similarity,[109] and comparative clinical trials to demonstrate the product's safety, purity, and potency.[110] Third, the PPIBM would have required much more stringent minimum supporting data requirements than either of the ALSMAs.[111] Finally, whereas the Amended ALSMA would have allowed extrapolation of conditions of use, the PPIBM would have required FOB applicants to satisfy all data and clinical testing requirements for each requested condition of use.[112]

[106] First, the FDA would have been required to publish a "concept paper setting forth the specific questions to be addressed . . . and invit[ing] comments on the concept paper from an interested persons." H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(4)(C)(i)). The FDA would then have been required to "accept comments on the concept paper for not less than 4 months." H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(4)(C)(ii)). After considering the public comments, the FDA would then publish its "proposed" guidance and "invite comments . . . from any interested persons." H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(4)(C)(iii), (iv)). The FDA would then "accept comments on the proposed guidance for not less than 6 months," and obtain the advice of a "Similar Biological Products Advisory Committee." H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(4)(C)(v), (vi)). Finally the FDA would then have had the option to approve the guidance or determine that it was unable to issue guidance on the specific FOB. H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(4)(C)(vii)).
[107] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(4)(C)(vii)).
[108] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(5)(B)(iii)) (emphasis added).
[109] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(5)(B)(iv)) (emphasis added).
[110] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(5)(B)(v)).
[111] The PPIBM would have required: 1) "consistency and robustness" of the FOB manufacturing process for both the FOB's active ingredient and its final formulation, 2) "stability, compatibility, . . . and biological and physiochemical integrity of the active ingredient," and 3) a post marketing safety plan beyond ordinary pharmacovigilance to monitor the product's clinical safety and "risk-benefit balance." H.R. 1956, § 2(a)(2) (proposed PHSA §§ 351(k)(5)(B)(i), (ii), (iv)).
[112] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(2)(C)(ii)).

b) Interchangeability

Unlike the Amended ALSMA's liberal interchangeability standard, the PPIBM would simply have prohibited the FDA from designating FOBs as interchangeable.[113] This dramatic shift from the Amended ALSMA solidified the PPIBM as the innovator industry's response to the ALSMA.

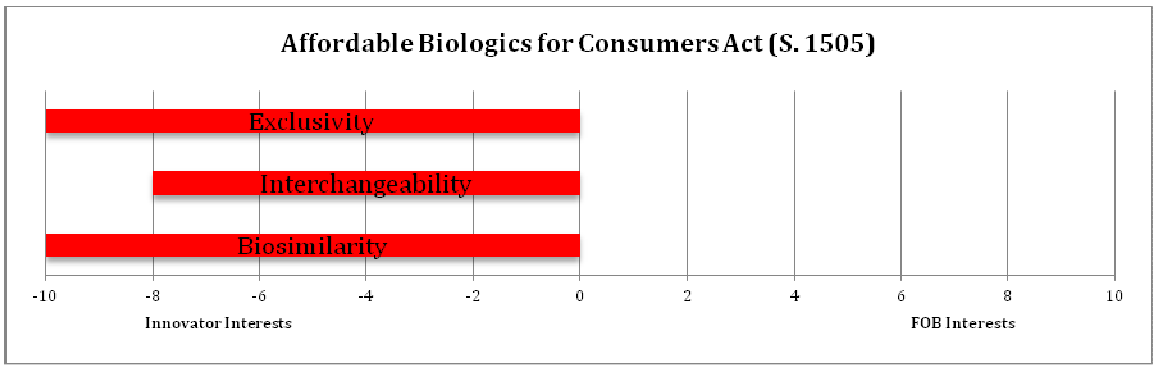
c) Exclusivity

The PPIBM's exclusivity provisions also diverged dramatically from the approach to exclusivity taken under the Amended ALSMA. First, the PPIBM would have provided reference products with twelve and fourteen years of exclusivity against FDA acceptance and approval of FOB applications respectively.[114] Second, the PPIBM would have allowed reference products to gain additional one-year exclusivity periods based on approval of supplements for new reference product indications of use that provided significant clinical benefits compared to existing therapies.[115] This provision would have effectively codified an avenue for anti-competitive evergreening and would have significantly limited generic competition.[116]

3. Affordable Biologics for Consumers Act (S. 1505)

On May 24, 2007, Senator Gregg introduced the Affordable Biologics for Consumers Act (ABCA) into the Senate as S. 1505. The ABCA was very similar to the PPIBM and did not pass the Senate. See Appendix: Table 4 for a detailed summary of the bill's provisions.

[113] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(2)(D)) ("The Secretary shall not designate a similar biological product as therapeutically equivalent to the reference product.").
[114] Section 351(k)(3)(A) of the PHSA would have prevented the FDA from accepting any FOB applications until: 1) the FDA had published final product-class specific guidance applicable to the reference product;, and 2) no less than twelve years had elapsed since the reference product was first approved or licensed. H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(A)(i), (ii)); H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(B)).
[115] H.R. 1956, § 2(a)(2) (proposed PHSA § 351(k)(3)(C)(ii)).
[116] *See supra* Part IV.B.3.



a) Biosimilarity

Even more than the PPIBM, the ABCA's biosimilarity provisions would have significantly restricted the FDA's ability to approve FOBs by imposing product-class specific guidance requirements and more stringent minimum data requirements. The ABCA's would have maintained the PPIBM's data requirements, imposed an additional requirement,[117] and required FOBs to be "as similar to the reference product as may be achieved given the state of scientific knowledge and technology capabilities at the time."[118] Given the inherent complexity of biologic products and the difficulties associated with manufacturing,[119] a provision requiring near perfection could have mandated almost universal rejection by the FDA and perpetuated reference product exclusivity.

b) Interchangeability

Like the PPIBM, the ABCA would have prohibited findings of interchangeability.[120] However, the ABCA would have required the FDA to assess the state of scientific and technical

[117] In addition to the PPIBM's data requirements, the ABCA would have required FOBs to have the same route of administration, dosage form, mechanism of action, and strength as the reference product. S. 1505, 110th Cong. (2007) § 2(a)(2) (proposed PHSA § 351(k)(2)(B)(iii)).
[118] S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(2)(B)(ii)).
[119] *See supra* Part IV.B.1.
[120] S. 1505, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(m)(1)(A)).

knowledge every two years in order to determine whether determinations of interchangeability on a class basis were possible.[121]

c) Exclusivity

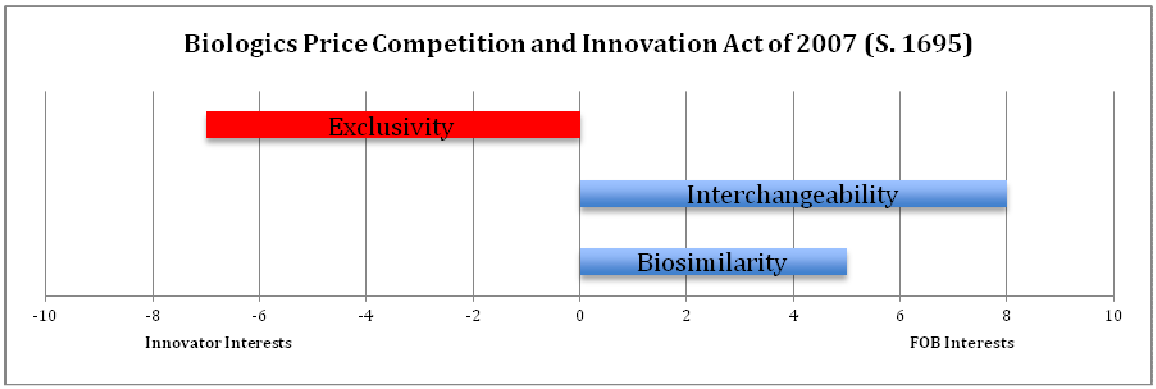
The ABCA's exclusivity provisions would have maintained the PPIBM's twelve-year prohibition on FOB applications and its fourteen-year prohibition on application approval,[122] but it would also have provided the first interchangeable FOB one year of exclusivity.[123] In addition, the bill would have afforded reference products two years of additional exclusivity for new indications that provided any significant clinical benefit, as opposed to a benefit compared to existing therapies.[124]

4. Biologics Price Competition and Innovation Act of 2007 (S. 1695)

On June 26, 2007, Senator Kennedy and the remaining members of the Senate Committee on Health, Education, Labor, and Pensions (HELP) introduced the Biologics Price Competition and Innovation Act of 2007 into the House and Senate as S. 1695. On June 27, 2007, the HELP Committee passed S. 1695 but indicated that work would continue before the bill was formally reported.[125] S. 1695 was formally reported to the Senate on November 19, 2008, and despite introduction of numerous competing bills and amendments, the enacted version of the BPCIA contains language largely identical to S. 1695. See Appendix: Table 5 for a detailed summary of the bill's provisions.

[121] S. 1505, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(m)(1)(B)).
[122] S. 1505, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(7)(A), (B)).
[123] S. 1505, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(9)).
[124] S. 1505, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(7)(C)) (disallowing approval of a submitted application "until at least 16 years have elapsed from the date on which the reference product was approved or licensed").
[125] Carver et al., *supra* note 41, at 763.

Like the PPIBM, S.1695 would have established only one regulatory pathway for approval and licensure of FOBs "biosimilar" to the reference product.[126] Although S. 1695 was generally FOB-friendly, the bill's inclusion of only one regulatory pathway diverged significantly from the Amended ALSMA.



a) Biosimilarity

S. 1695 would have granted the FDA full discretion in determining required studies on a case-by-case basis, and it would have required significant supporting data for biosimilar approval.[127] First, by giving the FDA full discretion to waive any of the bill's required analytical studies,[128] animal studies,[129] or clinical studies required by the bill,[130] S. 1695 would have facilitated FOB approval while ensuring product safety.[131] Second, S. 1695 would have imposed liberal data requirements similar to the Amended ALSMA while also allowing extrapolation for

[126]S. 1695, 110th Cong. § 2(2) (2007) (proposed PHSA § 351(k)). The bill defined a comparable biologic product application as an "abbreviated application for a license of a biological product containing the same, or similar, active ingredient as a biological product for which a license has [already] been approved." H.R. 6257, 109th Cong. § 2(2) (2006) (proposed PHSA § 351(i)(2)).
[127]Movement to a case-by-case approach drew significant criticism from the innovator industry. In a June 26, 2007 letter from then Secretary of Health and Human Services (HHS) Michael Levitt, Levitt argued for a public process for developing product class specific guidance similar to the approach under the PPIBM. Carver et al., *supra* note 41, at 761-62.
[128]S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(2)(A)(i)(I)(aa)).
[129]S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(2)(A)(i)(I)(bb)).
[130]S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(2)(A)(i)(I)(cc)).
[131] In his June 26, 2007 letter, then HHS Secretary Levitt argued that the FDA should not be allowed to waive "critical" data requirements from clinical studies. Carver et al., *supra* note 41, at 762.

conditions of use.[132] Extrapolation was presumably allowed to ensure that once biosimilarity was established, a given FOB would be afforded the same competitive advantages as its reference product.

b) Interchangeability

While based on the Amended ALSMA, S. 1695 would have imposed different requirements for interchangeability on multi-use FOBs versus single-use products.[133] First, for single-use products, S. 1695's interchangeability requirements would have required that an FOB could be expected to produce the same clinical result as the reference product in any given patient.[134] For biologic products administered to an individual more than once, S. 1695 would also have required switching between the FOB and the reference product to pose no greater risk than the reference product's exclusive use.[135] While this additional requirement for multi-use products requires some additional showing, it exists only to ensure that multi-use products are as safe as single-use products.[136] Second, S. 1695 would have given FOBs a significant competitive advantage by allowing automatic substitution of interchangeable FOBs for reference products without the intervention of a health care provider.[137]

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[132] S. 1695 would have required: 1) the FOB's conditions of use were previously approved for the reference product, 2) the route of administration, dosage form, and strength to be the same, 3) all facilities to meet relevant standards, and 4) FOB manufacturers must consent to inspection of their facilities. S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA §§ 351(k)(2)(A)(i)(III)-(V)); *id*. (proposed PHSA § 351(k)(3)(B)). It is important to note also that S. 1695 would not have required any postmarketing studies for approval, whereas the Amended ALSMA and the PPIBM had at least some postmarketing requirement. In his June 26, 2007 letter, then HHS Secretary Levitt criticized these liberal requirements and argued that FOB applicants should be required to establish biosimilarity, including clinical trial data, for each condition of intended use. Carver et al., *supra* note 41, at 762.

[133] *See generally* S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(4)).

[134] S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(4)(A)(ii)).

[135] S. 1695, 110th Cong. § 2(a)(2) (2007) (proposed PHSA § 351(k)(4)(B)).

[136] In his June 26, 2007 letter, then HHS Secretary Levitt argued that biosimilar legislation should not allow for determinations of interchangeability. Carver et al., *supra* note 41, at 762. Levitt would have preferred a "therapeutic equivalence" standard similar to the interchangeability standard under the Hatch-Waxman Act because"[t]echnology is not yet sufficiently advanced to allow this type of comparison for more complex protein products." *Id*. Additionally, Levitt argued that FOB applicants should be required to establish interchangeability for all intended conditions of use. *Id*.

[137] S. 1695, 110th Cong. § 2(b)(3) (2007) (proposed PHSA § 351(i)(3)).

c) Exclusivity

In a departure from previous FOB-friendly bills, S. 1965 would have balanced significantly longer reference product exclusivity periods against its liberal biosimilarity and interchangeability provisions.[138] S. 1695 would have minimally protected FOB interests by providing one year of interchangeable exclusivity and eliminating exclusivity for reference product supplements.[139] Then, by providing reference products with four and twelve years of exclusivity against FOB application submission and approval respectively,[140] S. 1605 would have struck a reference-friendly middle ground between the polarized exclusivity provisions of the Amended ALSMA and the PPIBM.[141] However, significant concerns about the potential for evergreening persisted.[142]

C. 110th Congress, Second Session

1. Pathway for Biosimilars Act (H.R. 5629)

On March 13, 2008, Representative Eshoo introduced the Pathway for Biosimilars Act of 2008 (PBA) into the House as H.R. 5629. The PBA would have combined provisions from the PPIBM and from S. 1695 to primarily protect reference product interests. This bill, however, did not pass the House. See Table 6 for a detailed summary of the bill's provisions.

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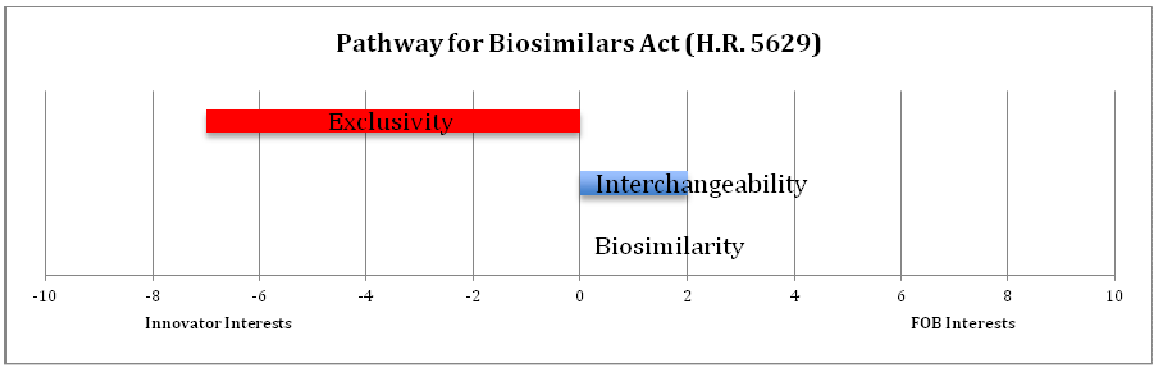
[138] Although S. 1695 attempted to compromise between FOB and innovator industry interests, both sides of the debate continued to argue for changes to the bill. For example, Bio continued to lobby for the fully fourteen-year innovator exclusivity period, while GPhA argued for shorter innovator exclusivity periods. Carver et al., *supra* note 41, at 761. Similarly, in a June 26, 2007 letter from then Secretary of Health and Human Services (HHS) Michael Levitt, Levitt supported a twelve-year innovator exclusivity period, but argued for inclusion of supplemental reference product exclusivity for new indications of use requiring clinical trials. *Id*. at 762.

[139] S. 1695, 110th Cong. § 2(b)(3) (2007) (proposed PHSA § 351(k)(6)(A)). Senator Kennedy clarified that the twelve year innovator exclusivity period was intended to apply "only to products that are analogous to a 'new chemical entity' under the Hatch-Waxman amendments." Carver et al., *supra* note 41, at 763.

[140] S. 1695, 110th Cong. § 2(b)(3) (2007) (proposed PHSA § 351(k)(7)(A), (B)).

[141] Generics industry representatives, however, criticized the twelve-year innovator exclusivity period as "arbitrary and excessive." Carver et al., *supra* note 41, at 764. Predictably, the innovator industry was "pleased" with the twelve-year innovator exclusivity period but continued to argue for a fourteen-year period. *Id.* at 765.

[142] The generics industry raised serious concerns that S. 1695's exclusivity provisions would allow reference product manufacturers to evergreen. *Id*. at 764. This practice would allow reference product sponsors to receive additional twelve-year exclusivity periods for minor changes to their products, effectively "maintaining their monopolies in perpetuity." *Id.* In response, GPhA "pledged to 'work with the negotiators to craft language that addresses this issue." *Id.*; *see supra* Part IV.B.3.



a) Biosimilarity

While nearly identical to S. 1695, the PBA's biosimilarity provisions would have minimally limited the FDA's ability to approve FOBs.[143] First, while the PBA would have allowed FDA waiver of unnecessary study requirements, unlike S. 1695, the PBA would have allowed waiver of an immunogenicity study only after publication of final product class guidance.[144] As discussed in Part B.2, requiring product class guidance would have had the potential to dramatically limit FOB approval.[145] Second, by prohibiting condition of use extrapolation for approved FOBs, the PBA would have dramatically raised the bar for FOB approval.[146]

b) Interchangeability

The PBA's interchangeability requirements, while similar to S. 1695, would have incorporated three changes to significantly limit the FDA's ability to grant FOB interchangeability designations. First, FOB applicants would have had to establish biosimilarity

[143] Most importantly, the PBA would have allowed FOB approval only for conditions of use for which the FOB applicant could establish biosimilarity. *See, e.g.* H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(2)(A)(ii)).
[144] H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(2)(B)(ii)).
[145] *See supra* Notes 105-107 and accompanying text.
[146] H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(2)(A)(i)(III)). It is important to note that in his otherwise innovator-friendly September 2008 letter to Representatives Pallone and Deal of the House Energy and Commerce Committee, then FDA Principal Deputy Commissioner and Chief Scientist Frank Torti withdrew from the FDA's previous hard-line approach on conditions of use. Carver et al., *supra* note 41, at 774. In his letter, Torti stated that the clinical data necessary for a finding of biosimilarity would "depend on a number of factors." *Id.* Before this letter, the FDA had stated its opinion that "biosimilarity should be shown for each condition of use." *Id.*

not only to the reference product, but also to any other products deemed interchangeable with the reference product.[147] Second, the PBA would have required the interchangeable FOB to produce the same clinical result in any given patient for each of the reference product's conditions of use.[148] Third, the FDA would have been unable to label an FOB interchangeable until the FDA issued final product guidance on the feasibility and necessary data for interchangeability designations.[149]

c) Exclusivity

The PBA would have combined provisions from the PPIBM, the ABCA, and S. 1695 to provide significant exclusivity advantages to reference product manufacturers. First, like S. 1695, the PBA would have prohibited the FDA from accepting or approving any FOB applications for four and twelve years, respectively.[150] Second, like the ABCA, the PBA would have allowed for two-year reference product exclusivity extensions for product supplementsconstituting significant improvements compared to marketed products.[151] Third, the

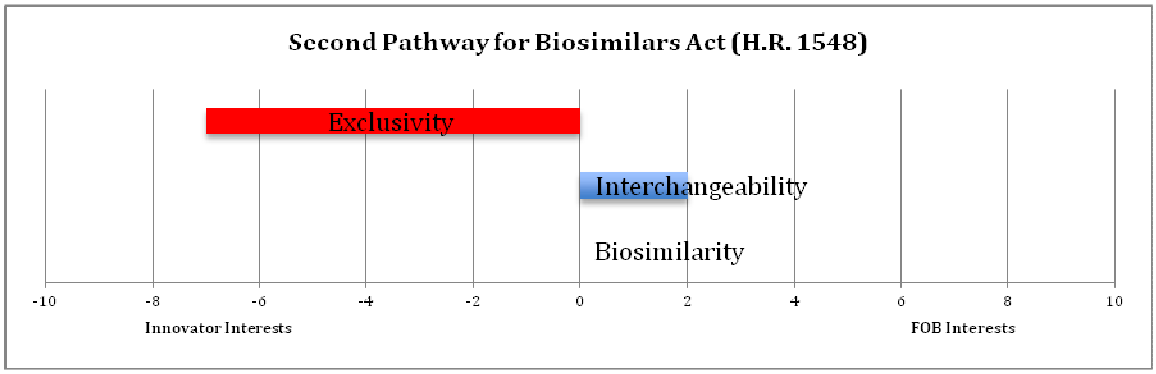
[147]H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(4)(A)(i)(I)).
[148]H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(4)(A)(i)(II)).
[149]H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(4)(B)). In his September 2008 letter to Representatives Pallone and Deal of the House Energy and Commerce Committee, then FDA Principal Deputy Commissioner and Chief Scientist Frank Torti stated that, at this time, legislation should not allow for findings of interchangeability and that patients should only be shifted between different biological products if specifically prescribed by a physician. Carver et al., *supra* note 41, at 773-74. Torti also stated that a finding of interchangeability in the future "would be based on, among other things, a showing of similar relevant structural characteristics . . . , an understanding of the structure-function relationships, and clinical data evaluating the impact of switching patients from one product of the other." *Id*.
[150]H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(7)(A), (B)(ii)). Note also that unlike previously introduced bills, the PBA would have prohibited acceptance of FOB applications until the later of the four-year mark already described or the date of commencement of a guidance issuance proceeding described in paragraph (9) of the PBA. H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(7)(B)(i)); *see generally* H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(9)).
[151]H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(7)(D)). The ABCA would have allowed supplements approved within twelve years of the reference product's first licensure for any new indication that constituted a significant clinical benefit. S. 1505, § 2(a)(2) (proposed PHSA § 351(k)(7)(C)). There was no explicit requirement that the indication provide a benefit relative to the reference product or any other marketed alternatives.

PBA would have granted two years of exclusivity to the first approved FOB to be deemed interchangeable.[152]

D. 111th Congress, First Session

1. Second Pathway for Biosimilars Act (H.R. 1548)

On March 17, 2009, Senator Eshoo introduced the Pathway for Biosimilars Act of 2009 (the Second PBA) into the House as H.R. 1548.[153] The Second PBA was nearly identical to the PBA and would not have differed from the provisions on biosimilarity, interchangeability, or exclusivity already discussed in Part C.1.[154] Like the PBA, this bill did not pass the House. See Table 7 for a detailed summary of the bill's provisions.



2. Promoting Innovation and Access to Life-Saving Medicine Act (H.R. 1427)

On March 11, 2009, Representative Waxman introduced a third version of his biosimilars bill titled the Promoting Innovation and Access to Life-Saving Medicine Act (PILSM) into the House as H.R. 1427. The PILSM embodied many of the underlying themes of the original

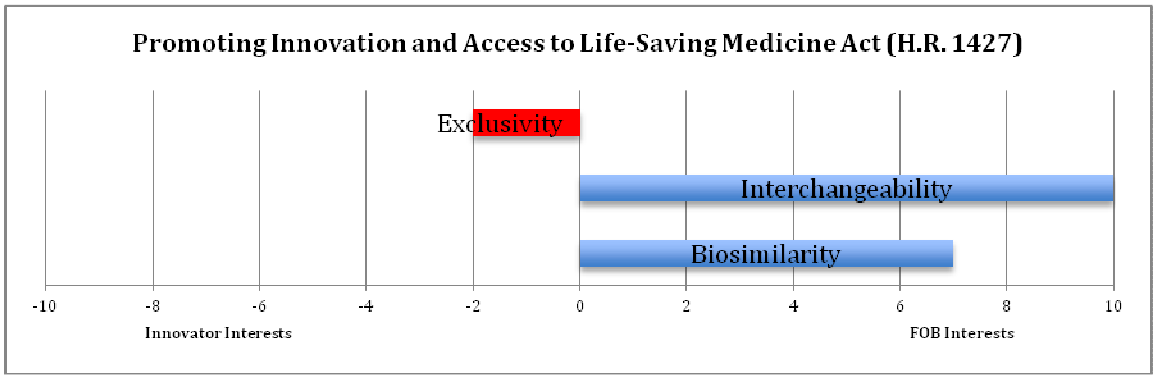
[152] H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(6)). Also note that whereas the one year period of interchangeable exclusivity under both S. 1695 and the PBA may have been measured from the date of first commercial marketing, for products marketed before being deemed interchangeable, the PBA would have begun the two year exclusivity period on the date the FOB was deemed interchangeable. *Id.*

[153] *See generally* H.R. 1548, 111th Cong. (2009).

[154] For purposes of exhaustion, note that the Second PBA would have amended the interchangeability requirements for multi-use products to require no greater risk to patients "in terms of safety, diminished efficacy, and *reduced or enhanced potency*." H.R. 1548, 111th Cong. § 101(a)(2) (2009) (proposed PHSA § 351(k)(4)(A)(ii)). The "reduced or enhanced potency" language was not present in the original PBA. *See* H.R. 5629, 110th Cong. § 101(a)(2) (2008) (proposed PHSA § 351(k)(4)(A)(ii)).

ALSMA, but its substantive provisions on biosimilarity, interchangeability, and exclusivity would have differed significantly. Like previous Waxman bills, the PILSM did not pass the House. See Table 8 for a detailed summary of the bill's provisions.

Like the ALSMA, the PILSM would have established two regulatory pathways for approval and licensure of biosimilar FOBs and for FOB products not deemed biosimilar but that were otherwise safe, pure, and potent for its proposed conditions of use.[155] In so doing, the PILSM would have lowered the bar for FDA approval under an already FOB-friendly provision.



a) Biosimilarity

The PILSM's biosimilarity provisions, while clearly based on the ALSMA,[156] would have given the FDA more discretion to deny approval for certain classes of FOBs and to limit FOB approval to specific conditions of use. First, the PILSM would have removed the provision mandating FDA approval for certain classes of FOBs,[157] thus granting the FDA discretion to reject any FOB applicant regardless of product class. Second, before allowing extrapolation to

[155] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA §§ 351(k)(3), (4)). The bill defined an abbreviated biologic product application as an "abbreviated application for a license of a biological product that relies in part on data or information in an application for another biological product." H.R. 1427, 111th Cong. § 2(a)(2) (2009) (proposed PHSA § 351(i)(2)). This definition would have removed the original ALSMA's language requiring the FOB application to contain "the same, or similar, active ingredient" as a reference product. H.R. 6257, 109th Cong. § 2(2) (2006) (proposed PHSA § 351(i)(2)).

[156] For example, both the ALSMA and the PILSM share the requirements that: 1) the products use the same route of administration, dosage form, and strength, 2) the desired condition of use was previously approved for the reference product, and 3) the product's manufacturing facilities meet applicable standards. In addition, both the ALSMA and the PILSM would have required biosimilarity to have been established using: 1) non-clinical laboratory studies, and 2) any necessary clinical studies.

[157] *See supra* note 93 for discussion of the FOB classes deemed comparable as a matter of law under the ALSMA.

additional conditions of use, the PILSM would have required an FOB applicant to provide "information demonstrating that such reliance is scientifically appropriate."[158] It is important to remember that while the PILSM was one of the most FOB-friendly pieces of potential legislation in the BPCIA's legislative history, it also signaled a movement towards compromise with innovator interests.

b) Interchangeability

Like more recent bills, the PILSM would have established different interchangeability requirements for single and multi-use products. First, all biosimilar single-use products would have been found interchangeable,[159] but approval of multi-use products would have required that switching between the FOB and reference product would not increase the risk of adverse effects or diminished effectiveness compared to using the reference product alone.[160] Second, the PILSM did not include any requirement, such as was present in S. 1695, that interchangeable biologics be automatically substitutable for reference products without input from a physician,[161]

c) Exclusivity

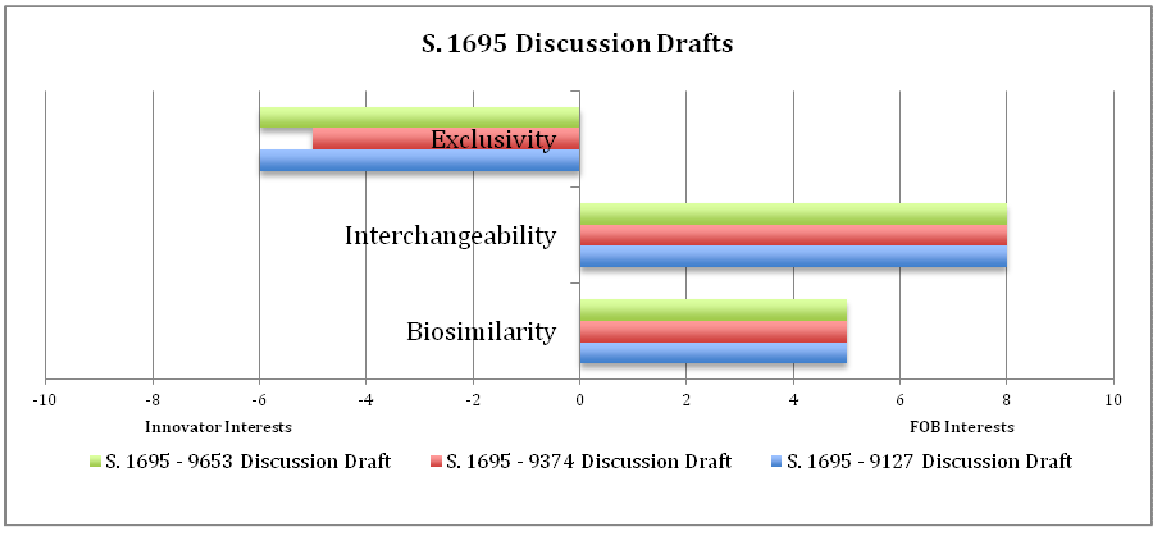
By providing for innovator exclusivity, although limited, and only minimal interchangeable exclusivity, the PILSM's exclusivity provisions moved dramatically towards innovator interests as compared to Representative Waxman's previous two bills. First, the PILSM would have taken a novel approach to reference product exclusivity by creating two tiers of reference product exclusivity based on several conditions.[162] Under the bill, products that did not rely on clinical studies from any previously approved products would have received five year

[158] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(3)(C)).
[159] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(2)(A)).
[160] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(2)(B)).
[161] *See* S. 1695, 110th Cong. § 2(b)(3) (2007) (proposed PHSA § 351(i)(3)).
[162] *See* H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(10)).

of exclusivity,[163] and significantly beneficial improvement products that relied on clinical studies from previously approved products would only have received three years.[164]Second, the PILSM would have allowed a reference product exclusivity period to be extended by six months (three months in certain cases)[165] if the supplement was a significant therapeutic advance and relied on a new clinical study.[166] Third, the PILSM would have provided the first FOB deemed interchangeable with 180 days of exclusivity.[167]

3. Biologics Price Competition and Innovation Act (S. 1695) Discussion Drafts

In March and June 2009, Senator Kennedy and the HELP Committee considered several amendments to S. 1695's exclusivity provisions: the 9127, 9374, and 9653 Discussion Drafts. Subsequently proposed legislation reflected only the provisions introduced in the 9374 and 9653 drafts, and therefore, this section will discuss only those drafts. For detailed descriptions of all three discussion drafts' provisions see Appendix: Table 9-Table 11.



[163] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA §§ 351(k)(10)(A)(i), (k)(10)(B)).
[164] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(10)(A)(ii), (k)(10(C)).
[165] Only one six-month exclusivity extension would have been allowed and it could have been reduced by three months if drug or drug manufacturer's sales exceeded one billion dollars.
[166] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(10)(D)). H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(10)(D)(ii)).
[167] H.R. 1427, 111th Cong. § 3(a)(2) (2009) (proposed PHSA § 351(k)(11)(A)(i)).

a) S. 1695 (9374 Discussion Draft)

The 9374 Discussion Draft (9374) would have contained the same four and twelve-year innovator exclusivity periods as S. 1695,[168] but the bill would have used an amended first licensure provision to prevent reference product sponsors from unduly extending their exclusivity periods. 9374 would have explicitly disallowed exclusivity periods for supplements to reference product applications and any subsequent applications for certain reference product changes.[169]

b) S. 1695 (9653 DiscussionDraft)

The 9653 Discussion Draft (9653) would have established a tiered exclusivity approach based on the PILSM to address concerns over potential evergreening under the statute.[170] First, 9653 would have prohibited the FDA from accepting FOB applications for four years after first licensure of the reference product.[171] Second, novel products and those products based on already approved biologic products would have received nine and two years of exclusivity respectively.[172] Third, like the PILSM, 9653 would have provided for up to two supplemental exclusivity periods for reference product supplements that satisfied several criteria.[173] Finally, 9653 would also have provided for limited interchangeable exclusivity identical to that under S. 1695.[174]

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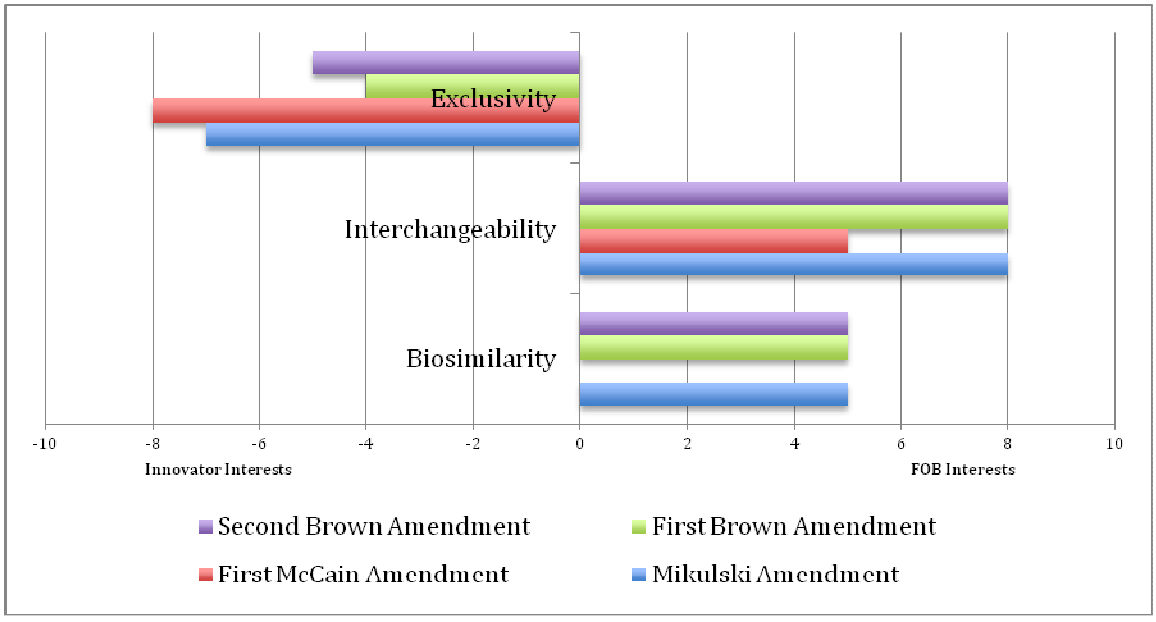
[168] Carver *et al.*, *supra* note 41, at 785-86. In response to the 9374 Discussion Draft, the FTC issued a report on the state of biosimilars competition and on its views of data exclusivity under proposed legislation. *See infra* Part Competition in the Biologics Sector After Enactment of the BPCIA.
[169] Carver *et al.*, *supra* note 41, at 786.
[170] *Id*. at 791-92.
[171] *Id*.
[172] *Id. at 793.*
[173] *Id*.
[174] *See supra* Part Exclusivity.

4. Competing Amendments and Passage of the BPCIA

By July 2009, language on both biosimilarity and interchangeability had for the most part stabilized, but Senate discussion continued on exclusivity and the perceived threat of evergreening.[175] Although several senators introduced competing amendments between July and September 2009, exclusivity provisions remained largely innovator-friendly. On July 13, 2009 the HELP Committee rejected competing proposals and approved the Hatch/Enzi/Hagan Amendment to S. 1695.[176] On September 9, 2009, the HELP Committee reported its consolidated health care reform bill as the Patient Protection and Affordable Care Act (PPACA),[177] and the bill ultimately passed the Senate on December 24, 2009.[178] For a detailed discussion of these competing Senate amendments, see Appendix: Table 12-Table 17.

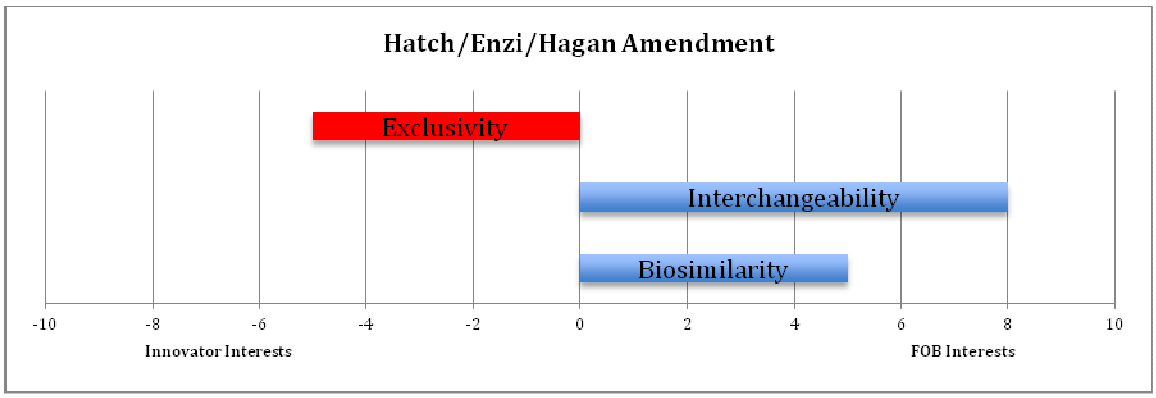


[175] Note, however, that the First McCain Amendment did make some substantive changes to the provisions on both biosimilarity and interchangeability. *See infra* Appendix: Table 13.
[176] Carver *et al.*, *supra* note 41, at 792.
[177] *Id.*
[178] *Id.*; *see generally* H.R. 3590, 111th Cong., Title VII, Subtitle A (as passed by Senate Dec. 24, 2009).

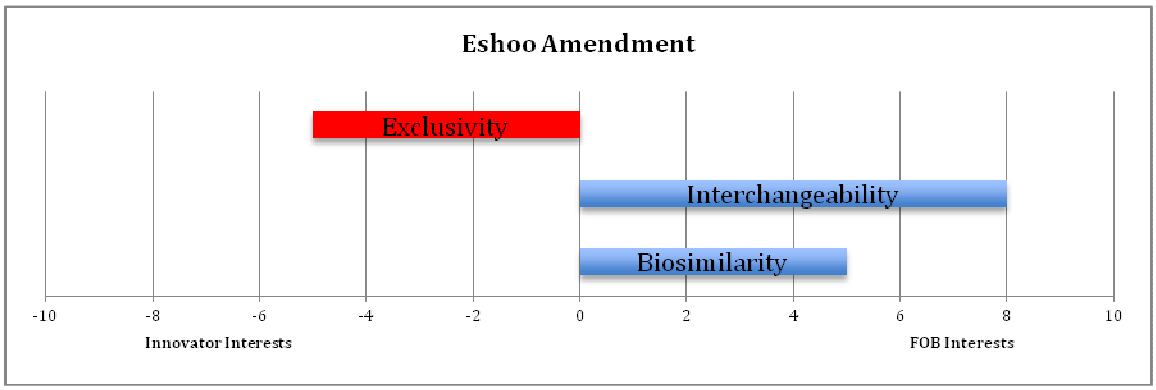
Unlike the competing Senate amendments, the HELP Committee approved the Hatch/Enzi/Hagan Amendment and in so doing maintained most of the S. 1695 provisions.[179] Most importantly, the Hatch/Enzi/Hagan Amendment contained the following features present in S. 1695: 1) FDA discretion to waive unnecessary analytical, animal, or clinical studies, 2) requiring FOB approval for all reference product conditions of use sharing the same mechanism of action, 3) separate interchangeability requirements for single-use and multi-use biologic products, 4) four and twelve-year innovator exclusivity against FOB application and application approval respectively, and 5) one-year interchangeable exclusivity.[180]

However, the Hatch/Enzi/Hagan Amendment also implemented limitations on innovator exclusivity discussed in the 9374 Discussion Draft. To prevent evergreening, the Hatch/Enzi/Hagan Amendment explicitly excluded from the four and twelve-year exclusivity periods certain supplements and product changes,[181] and although some concessions to FOB interests on biosimilarity and interchangeability were made, the amendment was largely considered a significant victory for reference product interests.[182]

[179] The HELP Committee accepted the Hatch/Enzi/Hagan Amendment on July 13, 2009 by a vote of 16-7. Carver *et al.*, *supra* note 41, at 795-96.
[180] *Id*.
[181] Carver *et al.*, *supra* note 41, at 786. For the language defining those products ineligible for exclusivity, see *supra* Part S. 1695 (9374 Discussion Draft).
[182] For example, Representative Waxman stated that "the war was not over," and that there were "a lot of opportunities to revisit these issues." Carver *et al.*, *supra* note 41, at 803. GPhA wrote to President Obama requesting that he ask Congress to put off passage of the biosimilars bill as it then stood, stating that the bill was "little more than camouflaged protection of the unacceptable and unsustainable status quo." *Id*.



On July 14, 2009, Representative Eshoo introduced into the House an amendment based largely on the Hatch/Enzi/Hagan Amendment under discussion in the Senate.[183] For purposes of biosimilarity, interchangeability, and exclusivity, the Eshoo Amendment was identical to the Hatch/Enzi/Hagan Amendment, and on July 31, the House adopted the Eshoo Amendment.[184] Subsequently, on October 29, 2009 the House released its consolidated health care reform bill containing the Eshoo Amendment,[185] and the bill passed the House on November 7, 2009.[186]



In December 2009, several Senators introduced amendments to the Hatch/Enzi/Hagan Amendment already passed in the Senate. However, these amendments had little effect on the biosimilars bill, and when the Senate passed the Patient Protection and Affordable Care Act

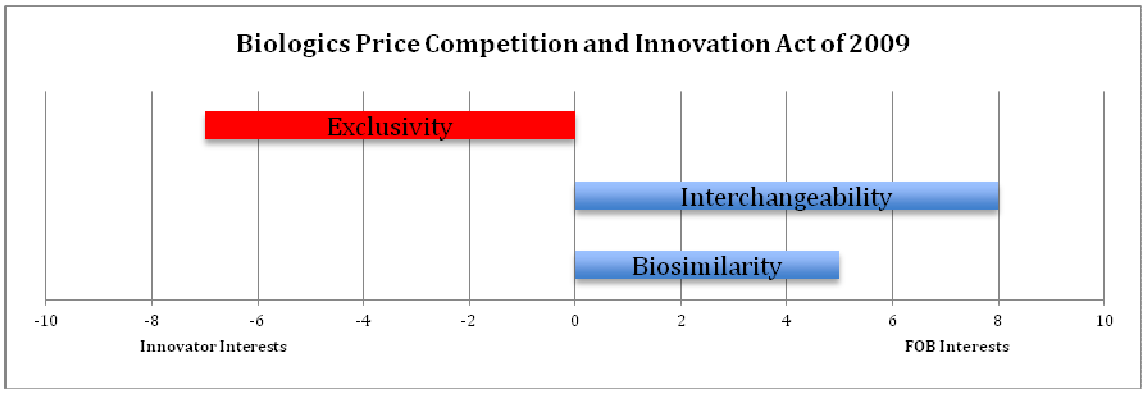
[183] *Id*. at 802.
[184] *Id*. at 803.
[185] *Id*. at 804 n.1194.
[186] *See generally* H.R. 3962, 111th Cong. §§ 2575-77 (as passed by the House, Nov. 7, 2009). It is important to note that several Representatives made floor statements intimating that clinical studies would be necessary to support a finding of interchangeability for a FOB. Carver *et al.*, *supra* note 41, at 804 n.1194.

(PPACA or H.R. 3590) on December 24, 2009, the provisions were identical to those under the Senate healthcare bill consolidating S. 1695 and the Hatch/Enzi/Hagan Amendment.[187]For detailed descriptions of these proposed amendments, see Appendix: Table 18-Table 20.

VI. Biologics Price Competition and Innovation Act of 2009

On March 21, 2010 the House passed the PPACA, and on March 23, 2010 President Obama signed the Act into law.[188] The specific PPACA provisions implementing an abbreviated approval pathway for biologics are referred to as the Biologics Price Competition and Innovation Act of 2009 (BPCIA).[189] See Appendix: Table 21 for a detailed description of the BPCIA's provisions.

Like S. 1695 and the Hatch/Enzi/Hagan Amendment, the BPCIA established only one regulatory pathway for approval and licensure of FOBs.[190] The BPCIA allows the FDA to approve biologic products only if they are determined to be "biosimilar."[191]



A. Biosimilarity

The BPCIA's biosimilarity provisions are largely identical to S. 1695 as amended by the Hatch/Enzi/Hagan Amendment. The BPCIA grants the FDA discretion in determining required

[187] *Id.* at 805.
[188] *Id.* at 806.
[189] *See generally* 42 U.S.C. § 262 (2010).
[190] *See generally* 42 U.S.C. § 262(k) (2010).
[191] 42 U.S.C. § 262(k)(2)(A)(i)(II).

studies on a case-by-case basis,[192] but it also requires significant supporting data for biosimilar approval.

The BPCIA allows the FDA to approve biological products deemed "biosimilar" to a reference product based on specific types of testing designed to establish specific aspects of biosimilarity,[193] but the Act also explicitly grants the FDA discretion to waive any unnecessary testing requirements.[194] First, the BPCIA requires "analytical studies" demonstrating the FOB is "highly similar . . . notwithstanding minor differences in clinically inactive components."[195] The BPCIA's language suggest it requires the FOB as a whole to be "highly similar" to the reference product, whereas some previous bills focused primarily on comparing the products' active ingredients.[196] Second, the BPCIA explicitly requires "animal studies (including the assessment of toxicity)."[197] Third, the BPCIA requires "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use."[198] This type of hierarchical testing regimen maintains the FDA's authority to set data requirements on a case-by-case basis while still requiring significant supporting data as necessary.

The BPCIA's additional approval requirements are identical to those of S. 1695. The BPCIA requires an application for follow-on approval to contain information demonstrating that: 1) "the biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the

[192] 42 U.S.C. § 262(k)(2)(A)(ii) (requiring analytical, animal, and clinical studies but reserving to the FDA the discretion to waive any "unnecessary" studies).
[193] 42 U.S.C. § 262(k)(2)(A)(i)(I).
[194] 42 U.S.C. § 262(k)(2)(A)(ii).
[195] 42 U.S.C. § 262(k)(2)(A)(i)(I)(aa).
[196] *See, e.g.,* H.R. 1038, 110th Cong. § 3(a)(2) (2007) (proposed PHSA § 351(k)(1)(B)) (requiring data demonstrating "highly similar principal molecular structural features"); H.R. 1956, 110th Cong. § 2(a)(2) (proposed PHSA § 351(k)(5)(B)(ii)) (requiring data demonstrating "stability" and "integrity of the active ingredient").
[197] 42 U.S.C. § 262(k)(2)(A)(i)(I)(bb) (2010).
[198] 42 U.S.C. § 262(k)(2)(A)(i)(I)(cc) (2010).

proposed labeling;"[199] 2) the "condition of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product;"[200] 3) "the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product;"[201] and 4) "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;"[202] and 5) that the FOB manufacturer "consents to the inspection of the facility that is the subject of the application."[203] Finally, the BPCIA allows extrapolation of FOB conditions of use based on a finding of biosimilarity.[204]

B. Interchangeability

Again, the BPCIA's interchangeability requirements are nearly identical to those under S. 1695. The BPCIA imposes different requirements for interchangeability on multi-use FOBs versus single-use products.[205] For single-use products, the BPCIA requires an FOB to be biosimilar and "expected to produce the same clinical result as the reference product in any given patient."[206] For biologic products that would be administered to an individual more than once, the BPCIA requires switching between the FOB and the reference product to pose no greater risk than the reference product's exclusive use.[207] Further, the BPCIA's definition of interchangeability explicitly indicates that an approved interchangeable FOB "may be substituted

[199] 42 U.S.C. § 262(k)(2)(A)(i)(II) (2010).
[200] 42 U.S.C. § 262(k)(2)(A)(i)(III) (2010).
[201] 42 U.S.C. § 262(k)(2)(A)(i)(IV) (2010).
[202] 42 U.S.C. § 262(k)(2)(A)(i)(V) (2010).
[203] 42 U.S.C. § 262(a)(2)(C)(ii) (2010).
[204] In his June 26, 2007 letter, then HHS Secretary Levitt argued that FOB applicants should be required to establish biosimilarity, including clinical trial data, for each condition of intended use. Carver *et al.*, *supra* note 41, at 762.
[205] *See generally* 42 U.S.C. § 262(k)(4) (2010).
[206] 42 U.S.C. § 262(k)(4)(A) (2010).
[207] 42 U.S.C. § 262(k)(4)(B) (2010).

for the reference product without the intervention of the health care provider who prescribed the reference product."[208]

C. Exclusivity

Like the S. 1695 – 9374 Discussion Draft, the BPCIA provides significant innovator exclusivity and very limited exclusivity for the first interchangeable FOB. First, the BPCIA prohibits the FDA from accepting FOB applications for four years after the reference product's date of first licensure.[209]Second, the BPCIA prevents the FDA from approving FOB applications for twelve years from the reference product's first licensure.[210] Third, the BPCIA uses the 9374 first licensure provision to prevent reference product sponsors from unduly extending their exclusivity periods. The BPCIA explicitly excludes from the four and twelve-year exclusivity periods: 1) supplements to reference product applications,[211] 2) any "subsequent application filed by the same sponsor or manufacturer of the biological product" 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,"[212] or b) "a modification to the structure of the biological product that does not result in a change in safety, purity, or potency."[213]

The BPCIA also minimally addresses FOB interests by providing some interchangeable exclusivity. Like 9374, the BPCIA provides exclusivity for the first interchangeable FOB until the earlier of one year after the first marketing of the interchangeable FOB or another date

[208]42 US.C. § 262(i)(3) (2010).
[209]42 U.S.C. § 262(k)(7)(B) (2010).
[210]42 U.S.C § 262(k)(7)(A) (2010).
[211] 42 U.S.C. § 262(k)(7)(C)(i) (2010).
[212] 42 U.S.C. § 262(k)(7)(C)(ii)(I) (2010).
[213] 42 U.S.C. § 262(k)(7)(C)(ii)(II) (2010).

determined by the status of any pending patent infringement litigation involving the interchangeable product.[214]

VII. Promulgation of FDA Regulations on Biosimilars

In enacting the BPCIA, Congress attempted to balance reference product sponsors' interest in protecting their investments in innovation and consumers' and FOB manufacturers' interest in bringing less expensive competing biological products to market. The disparity of legislator, interest group, scientist, and consumer interests is evident in the BPCIA's long and complex legislative history.[215] See Figure 1 below for a graphical representation of how biosimilarity, interchangeability, and exclusivity provisions introduced throughout the BPCIA's legislative history conformed to either FOB or innovator interests. It is clear that the Act as enacted represents a meaningful compromise between FOB and innovator interests,[216] but individual provisions within the BPCIA often cater to specific interest groups. While biosimilarity and interchangeability provisions under the BPCIA are largely FOB-friendly, the Act's limited regulatory pathway and ample innovator exclusivity provisions provide strong protection for reference product interests. See Figure 2 below for a comparison of the BPCIA against the extent to which FOB and innovator interests were represented on average over the act's legislative history.

[214] 42 U.S.C. § 262(k)(6) (2010).
[215] Carver *et al.*, *supra* note 41, at 816.
[216] *Id*. at 817.

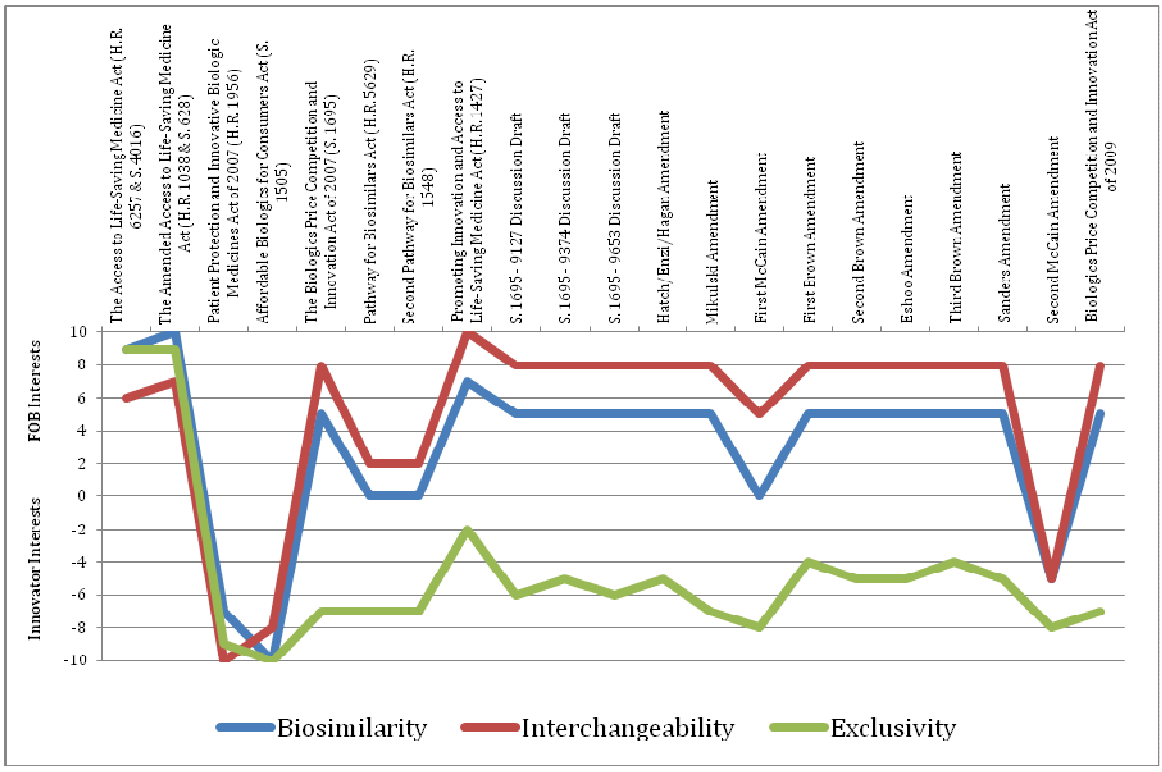


Figure 1: Evolution of BPCIA Provisions vs. FOB/Innovator Interests

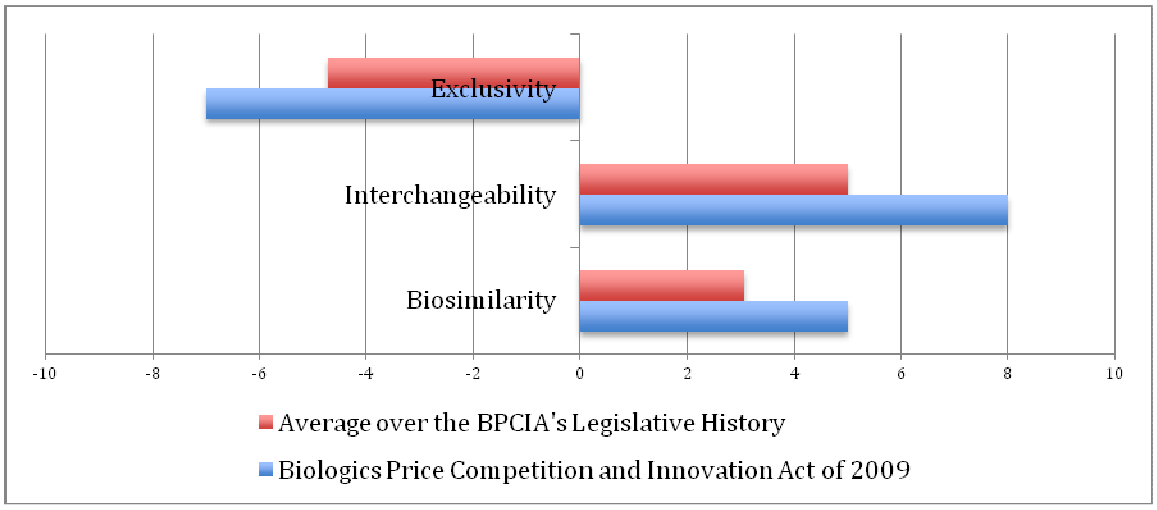


Figure 2: FOB and Innovator Interests as Represented by the BPCIA in Comparison to the Act's Legislative Historical Average

It is also important to note, however, that although debate around introduced bills and amendments was contentious, the various bills and amendments actually passed in the House and Senate were relatively consistent. See Figure 3 below for a graphical representation of

stakeholder interests represented by S. 1695 and its subsequent iterations. While biosimilarity and interchangeability standards protected FOB interests and were largely settled by introduction of S. 1695, some disagreement on exclusivity continued throughout the BPCIA's legislative history. In the end, however, the BPCIA's exclusivity provisions were designed to provide strong reference product protection. In promulgating its regulations under the BPCIA, it is imperative for the FDA to remain faithful to Congress' intent to balance competing interests.

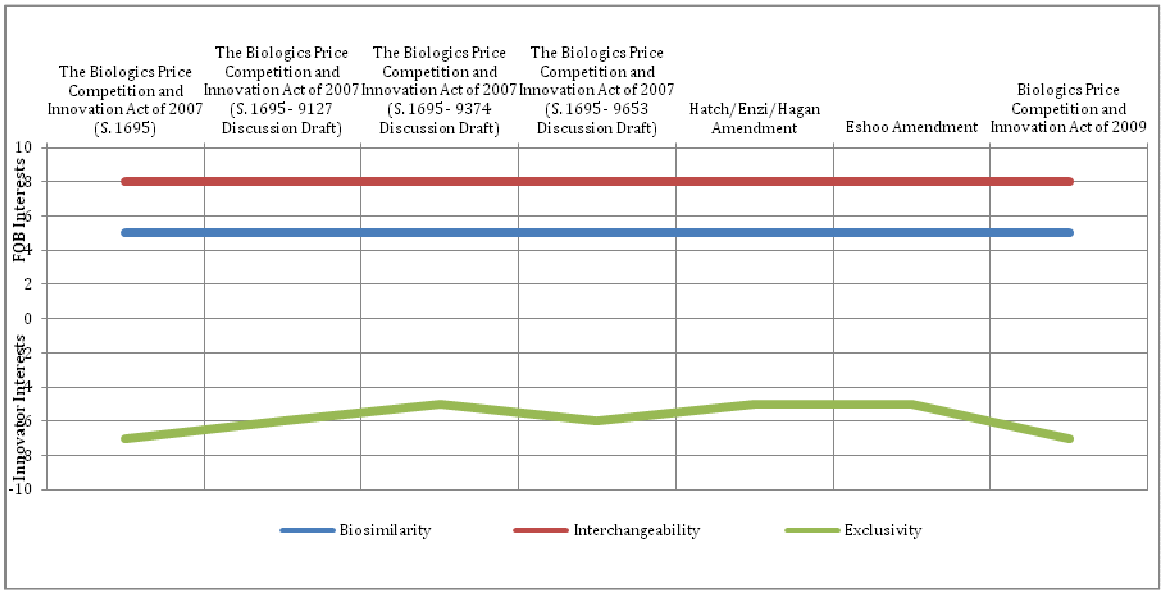


Figure 3: Evolution of Adopted Bills/Amendments vs. FOB/Innovator Interests

A. Legislative Intent Evinced by the BPCIA's Legislative History

By establishing only one regulatory pathway for truly biosimilar products(as opposed to non-similar products) under the BPCIA, Congress intended to limit the types of biologic products approvable under an abbreviated pathway. In 2006, 2007, and 2009, Representative Waxman introduced three biosimilars bills, all of which would have established two pathways for approving not only biosimilar biologic products, but also products that differed from

reference products in some way.[217]However, all three times Congress rejected the approach and chose only to allow approval of truly biosimilar products under the BPCIA.[218] In so doing, Congress demonstrated its intent to limit biologic products approvable under an abbreviated pathway to true biosimilars. The Congressional intent evinced through the evolution of the biosimilarity, interchangeability, and exclusivity provisions, however, is more complex.

1. Biosimilarity

Comparison of the biosimilarity provisions throughout the BPCIA's legislative history indicates a consistent legislative intent to stimulate biologics competition through broad FOB approval by: 1) providing the FDA with discretion to waive unnecessary testing requirements, 2) establishing less stringent data requirements, and 3) requiring approval for broad product conditions of use.

Respectively, the Amended ALSMA and the ABCA represented the most FOB-friendly and innovator-friendly legislative positions on biosimilarity. On testing requirements, the Amended ALSMA would have allowed the FDA to determine the analytical requirements for each FOB applicant on a case-by-case basis and would have mandated approval for certain classes of biologics.[219] By reserving full discretion to the FDA in determining testing requirements for FOBs and compelling approval of other products, the Amended ALSMA demonstrated its drafters' desire to require minimal analytical and clinical data, if any, for FOB approval. This less stringent requirement would have allowed more FOBs to gain approval and to enter the market quickly as reference product competitors. The ABCA, by contrast, would have significantly restricted the FDA's ability to approve FOBs by imposing product-class

[217]*See generally* Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. (2009); Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007); Access to Life-Saving Medicine Act, H.R. 6257, 109th Cong. (2006).
[218]*See supra* Part VI.
[219]*See supra* Part V.B.1.a).

specific guidance requirements and stringent testing requirements.[220] The ABCA would have mandated: 1) physical, chemical, and biological assays fully characterizing the FOB, 2) comparative nonclinical studies, and 3) comparative clinical trials.[221] With these two relatively extreme options in mind, Congress passed S. 1695, and ultimately the BPIA, requiring analytical, animal, and at least one clinical study, but granting the FDA the discretion to waive any unnecessary testing requirements.[222]The BPCIA's testing provisions are much more similar to the Amended ALSMA than the ABCA, which indicate Congress' intent to broaden the number of FOBs approvable under an abbreviated pathway. Further, although the distinction between the Amended ALSMA and the BPCIA is fine, it is an important difference to recognize. By choosing to first require a clinical study but concurrently give the FDA the option to waive the clinical study requirement, Congress evinced its intent to ensure proper testing for FOB approval, but also to minimize testing and drive down FOB approval costs.

In terms of other required data, the Amended ALSMA would have required FOB applicants to provide data demonstrating: 1) the products used the same mechanism of action but only to the extent the mechanism of action was known for the reference product; 2) the FOB's condition or conditions of use had previously been approved for the reference product; 3) the products had the same route of administration, dosage form, and strength; and 4) all FOB facilities met relevant standards.[223] In addition, the applicant would have had the option of providing any additional publicly available information regarding the reference product, which would have provided FOB applicants with significant flexibility in supplementing their

[220]*See supra* Part V.B.3.a).
[221]*See supra* Part V.B.3.a).
[222]*See supra* Part V.B.4.a).
[223]*See supra* Part V.B.1.a).

applications with external information.[224] Finally, the Amended ALSMA would not have required a post-marketing safety plan and would have explicitly forbid the FDA from requiring any additional post-marketing studies as a "condition of approval."[225] By contrast, the ABCA would have required data showing: 1) a post-marketing safety plan, 2) consistency and robustness of the manufacturing process, 3) stability, compatibility, and biological and physiochemical integrity of the active ingredient, and 4) that the products were "as similar to the reference product as may be achieved given the state of scientific knowledge and technology capabilities at the time."[226]While it would have placed requirements on manufacturing, chemical similarity, and the like, the ABCA's language would have imposed stringent standards across the board. Further, given the inherent complexity of biologic products and the difficulties associated with manufacturing,[227] a provision requiring FOB applicants to come as close to perfection as possible given the state of the art would have had the potential to mandate almost universal rejection by the FDA. This provision would have set the bar for biosimilarity extremely high and obviously would have helped to perpetuate reference product monopolies. However, despite the ABCA's radically different provisions, Congress passed S. 1695 and the BPCIA with requirements nearly identical to those under the Amended ALSMA.[228] In enacting S. 1695's biosimilarity language, Congress again demonstrated its intent to facilitate FOB approval by minimizing required data. Further, by allowing FOB manufacturers to submit public information in support of their applications, Congress provided FOBs with the flexibility to avoid the costs of personally generating supporting data thereby reducing overall approval costs.

[224] *See supra* Part V.B.1.a).
[225] *See supra* Part V.B.1.a).
[226] *See supra* Part V.B.3.a).
[227] *See supra* Part IV.B.1.
[228] S. 1695 added a requirement that all manufacturers must consent to an inspection of the facilities, but also eliminated any mention of post-marketing studies. *See supra* Part V.B.4.a).

In terms of approved conditions of use, again the Amended ALSMA and the ABCA represent opposite ends of the interest spectrum in the BPCIA's legislative history. For FOBs with an unknown mechanism of action, the Amended ALSMA would only have required the FDA to approve the FOB for the specific conditions of use for which its application established comparability.[229] However, for FOBs with a known mechanism of action, the Amended ALSMA would have required the FDA to approve the FOB for "*all* conditions of use of the reference product,"[230] not just the condition of use for which the application established comparability. By contrast, the ABCA would only have allowed approval for conditions of use for which biosimilarity was specifically established.[231] By passing S. 1695 and eventually the BPCIA, Congress chose an even more FOB-friendly approach to conditions of use than the Amended ALSMA. Under the BPCIA, the FDA is required to approve FOBs for all conditions of use for which the products have the same mechanism of action.[232] This broad approval mechanism indicates Congress' further intent to facilitate broad FOB approval, thereby stimulating competition with reference products in all conditions of use based on significantly less supporting data.

Finally, it is important to note that S. 1695, with its FOB-friendly testing, data, and conditions of use requirements, was only the fifth bill introduced in the BPCIA's legislative history. S. 1695's approach to biosimilarity was reproduced identically in the BPCIA despite the introduction of fifteen major competing bills and amendments subsequent to S. 1695's introduction. This consistency throughout the legislative process is perhaps the strongest

[229] *See supra* Part V.B.1.a).
[230] *See supra* Part V.B.1.a).
[231] *See supra* Part V.B.2.a).
[232] *See supra* Part V.B.4.a); Appendix: Table 5.

indicator of Congress' intent to facilitate broad FOB approval based on relatively minimal data requirements, so long as applicants establish product safety.

2. Interchangeability

Development of interchangeability provisions throughout the BPCIA's legislative history indicates Congress' strong intent to increase FOB market share by: 1) allowing interchangeability designations, 2) requiring only reasonable showings of interchangeability, and 3) allowing automatic pharmacy substitution for interchangeable FOBs.

It is important to note that unlike biosimilarity standards that differed from bill to bill only in terms of requirement stringency, several bills proposed during the BPCIA's legislative history would have strictly forbidden any determinations of FOB interchangeability.[233]However, by allowing interchangeability designations under the BPCIA, Congress made a commitment to providing further competitive advantages for certain successful FOB market entrants. In addition, by allowing interchangeability, Congress created an inherently pro-FOB floor for comparison of interchangeability provisions introduced throughout the BPCIA's legislative history. Among possible provisions allowing interchangeability, the Amended ALSMA and the PBA most strongly represented FOB and innovator interests respectively. The Amended ALSMA would have required all approved FOB products to be deemed interchangeable so long as the FOB could be expected to produce the same clinical results in any given patient.[234] This, coupled with the previously discussed Amended ALSMA's more relaxed biosimilarity standard, would have forced the FDA to find significantly more FOBs interchangeable with their corresponding reference products. By contrast, the PBA would have imposed a product class guidance based approach with different requirements for interchangeability on multi-use FOBs

[233] *See, e.g.*, discussion of PPIBM *supra* Part V.B.2.b).
[234]*See supra* Part V.B.1.b).

versus single-use products. Under the PBA, FOB applicants would have had to establish: 1) biosimilarity not only to the reference product, but also to any other products deemed interchangeable with the reference product, and 2) interchangeability for each specific condition of use.[235] Further, the FDA would have been unable to label an FOB interchangeable until the FDA issued final product guidelines stating that an interchangeability determination was even possible and identifying the data supporting an interchangeability determination.[236] The addition of guidance requirements to the PBA's interchangeability provisions would have significantly limited the FDA's ability to find FOBs interchangeable and quite possibly would have forestalled any such designations as impossible. S. 1695 and the BPCIA's interchangeability provisions take a FOB-friendly approach by largely tracking the Amended ALSMA; however, the BPCIA goes beyond the Amended ALSMA by requiring multi-use FOBs to pose no additional risk compared to exclusive use of the reference product. While this requirement for multi-use products does require some additional showing by FOB applicants beyond biosimilarity, it seems present only to ensure that multi-use products are as safe and reliable as single-use products. Therefore, the BPCIA's liberal interchangeability requirements reflect Congress' intent to grant interchangeability designations to FOBs. The BPCIA's adoption of S. 1695's liberal interchangeability standard indicates Congress' intent to broadly provide FOBs with competitive advantages similar to those afforded reference products limited only when necessary to ensure product safety.

Further, S. 1695 and the BPCIA define interchangeability to allow automatic substitution for the reference product without consultation or intervention of a given patient's physician.[237] S. 1695 was the first piece of potential legislation to allow automatic substitution, and although

[235] *See supra* Part V.C.1.b).
[236] *See supra* Part V.C.1.b).
[237] See *supra* Part V.B.4.b).

subsequent amendments were introduced to prohibit automatic substitution,[238] its ultimate inclusion in the BPCIA indicates Congress' intent to maximize FOB market share without significant additional cost.

Finally, like the BPCIA's biosimilarity standard, the BPCIA's interchangeability provisions are identical to S. 1695. Congress considered fifteen bills and amendments after introduction of S. 1695, none of which would have prohibited interchangeability and only two of which would have limited interchangeability.[239] Congress' adherence to perhaps the most FOB-friendly interchangeability provision introduced during the BPCIA's legislative history is strong evidence of the legislature's intent to facilitate interchangeability designations and maximize FOB competition.

3. Exclusivity

The evolution of the BPCIA's exclusivity provisions, while complex, indicates Congress' dedication to protecting reference product interests by: 1) establishing significant innovator exclusivity periods while 2) restricting reference products to one period of exclusivity to prevent evergreening.

The ALSMA and the PPIBM represented the most FOB-friendly and innovator-friendly legislative positions on exclusivity. The ALSMA would have established up to 180 days of exclusivity, depending on the status of any pending patent infringement litigation, for the first interchangeable FOB, but it would have allowed no reference product exclusivity.[240] By disallowing any exclusivity for innovator products, the ALSMA would have forced reference

[238] For example, both the First and Second McCain Amendments would have prohibited automatic substitution of interchangeable FOBs. *See infra* Appendix: Table 13 and Table 20.
[239] As discussed, the PBA and the Second PBA would have required the FDA to issue product class specific guidance advising that interchangeability was possible for each FOB class. *See supra* Parts V.C.1.b) and V.D.1.
[240] *See supra* Part V.A.1.c).

products to rely strictly on a product's patent term for marketing protection.[241] Eliminating innovator exclusivity would have allowed FOB applicants to submit applications for licensure to the FDA, conduct necessary testing, gain FDA approval, and begin marketing their FOBs the day a reference product's patent term expired.In stark contrast, the PPIBM would have provided ample innovator exclusivity and supplemental exclusivity without any provision for interchangeable FOB exclusivity. First, the bill would have prohibited FOB application acceptance or approval for twelve and fourteen years respectively.[242]Second, the PPIBM would have allowed reference products to gain additional one-year exclusivity periods based on approval of reference product supplements that provided a significant clinical benefit in comparison with existing therapies.[243]It is important to note the real possibility that this provision would have provided a statutory avenue for anti-competitive evergreening. Third, the PPIMB would have provided no period of interchangeable FOB exclusivity.[244]

While the BPCIA provides for limited interchangeable exclusivity, the Act's extensive innovator exclusivity period and explicit prohibition of supplemental reference product exclusivity, evidences Congress' primary intent to provide reference products with a significant but finite monopoly independent from patent protection. The BPCIA's exclusivity provisions, identical to the S. 1695 – 9374 Discussion Draft, provide reference products with twelve and fourteen years of exclusivity against FOB application acceptance and approval respectively.[245] However, the BPCIA also explicitly excludes reference product supplements or applications for

[241] As discussed, FDA approval of a given biologic product takes between ten and fifteen years, and reference product sponsors may only have five to ten years of market exclusivity under the remainder of the patent term. *See supra* Part IV.B.2.
[242]*See supra* Part V.B.2.c).
[243]*See supra* Part V.B.2.c).
[244]*See supra* Part V.B.2.c).
[245]*See supra* Part VI.C.

changes to the reference product from the four and twelve-year exclusivity periods.[246] Under Subsection (k)(7)(c), only: 1) changes resulting in a new indication, dosing schedule, dosage form, delivery system, delivery device, or strength, or 2) structural changes are eligible for additional exclusivity periods.[247] This Subsection was adopted to explicitly combat evergreening through incremental improvements to reference products.[248]In so doing, Congress evinces its intent to protect reference product sponsors' significant front-end investment in innovation while safeguarding against anti-competitive evergreening.

Throughout the legislative history, members of Congress introduced dramatically different exclusivity provisions for consideration. Innovator exclusivity ranged from zero to fourteen years.[249] Innovator exclusivity could have applied only to application approval (as opposed to application submission), or it could have applied differently based on a reference product's novelty compared to that of other reference products.[250]However, despite the numerous and varied competing proposals, Congress enacted exclusivity provisions almost identical to S. 1695 as a part of the BPCIA. This evinces a strong and continuous commitment to lengthy reference product exclusivity and preventing undue exclusivity extensions through evergreening or supplemental exclusivity periods.

B. Competition in the Biologics Sector After Enactment of the BPCIA

Despite Congressional enactment of the BPCIA, the inherent costs and complexities associated with producing follow-on biologics has the potential to severely constrain the ability

[246] *See supra* Parts IV.B.3, VI.C
[247] *See supra* Part VI.C.
[248] *See supra* Parts V.D.3.a), V.D.4, VI.C.
[249] For example, the ALSMA would not have provided for any reference product exclusivity. *See supra* Part V.A.1.c). By contrast, the PPIBM would have prohibited application acceptance and application approval for twelve and fourteen years respectively. *See supra* Part V.B.2.c).
[250] For example, the ABCA would have created a tiered approach to innovator exclusivity that would have granted different exclusivity periods based on how similar a product was to a previously approved biologic product. *See supra* Part V.B.3.c).

of follow-on products to enter the biologics market or acquire significant market share therein.[251]In a published report,[252] the FTC predicts that because of the significant costs associated with their development, follow-on biologic entry is likely to occur only in markets of more than $250 million, even under the BPCIA's accelerated approval pathway for follow-on biologics.[253] Given such high entry costs, the FTC believes only large companies with significant resources are likely to produce follow-on products,[254] and only two to three FOBs could be expected to enter the market for a given reference product.[255] In contrast, nine generic pharmaceutical products generally enter the market for a given traditional brand name drug.[256]

According to the FTC report, the limited entry of competing FOBs in conjunction with the significant costs incurred by companies in the manufacture of both brand name and follow-on biologics make significant price reductions for biologic products under the BPCIA unlikely. Although brand name manufacturers will most likely respond to FOB competition by offering price discounts to maintain their market share, even after follow-on entry, competition is likely to resemble brand-to-brand competition as opposed to the brand-to-generic competition seen for traditional pharmaceuticals after the Hatch-Waxman Act.[257] Multiple studies predict that no more than three FOBs will ultimately enter the market, and that the resulting price drops will be

[251]FED. TRADE COMM'N, *supra* note 59, at iv.
[252] It is important to note that the FTC Report on FOB competition was issued in response to introduction of S. 1695 into the Senate. However, because the BPCIA as enacted is nearly identical to S. 1695, the FTC's predictions still carry weight.
[253]FED. TRADE COMM'N, *supra* note 59, at v.
[254] *Id.* at iii-iv.
[255] One study estimated that the average number of follow-on biologic entrants per brand name drug would be two, whereas traditional pharmaceuticals see, on average, nine generic manufacturers enter the market. Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 440 (2007). The FTC estimates that only two or three follow-on manufacturers are likely even to attempt market entry for a given reference biologic. FED. TRADE COMM'N, *supra* note 59, at v.
[256]Grabowski et al., *supra* note 255, at 440.
[257]FED. TRADE COMM'N, *supra* note 59, at v, 23.

limited to between ten and thirty percent.[258] As a consequence, brand name manufacturers are likely to retain seventy to ninety percent of their market share.[259] The BPCI as enacted will allow brand name biologic manufacturers to preserve a significant market share and continue to command high price premiums, even after entry of competing follow-on biologics.[260] Therefore, the benefits of an abbreviated FDA approval process for FOBs will not be realized unless the FDA promulgates regulations that more fully effectuate Congress' intent in enacting the BPCIA.

C. Recommendations on How FDA Regulations Can More Effectively Implement Congress' Intent

Because the biologics market is likely to remain hostile to FOB market entry even after the BPCIA's enactment, it is imperative that the FDA promulgates regulations designed to facilitate strong FOB competition while maintaining incentives for brand name manufacturers to produce innovative biologic products.

1. Biosimilarity

To increase competition in the biologics sector through introduction of biosimilar FOBs as Congress intended, the FDA must promulgate regulations that: 1) require a progressive hierarchical approach to FOB testing and 2) require FOB approval for all reference product conditions of use for which the two products share the same mechanism of action.

A three step progressive hierarchical FOB testing regimen will ensure the safety, purity, and potency of FOB products while requiring costly and time consuming testing only to the extent required. In determining whether to waive either animal or clinical testing, the FDA must consider factors such as ethical concerns regarding unnecessary testing on animals and humans

[258] John A. Vernon et al., *Exploration of Potential Economics of Follow-On Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55, 68 (2010). One study conducted by Alexis Ahlstrom et al. predicted a decrease in drug costs of between ten and thirty percent. Adelman & Holman, *supra* note 23, at 582. A second study estimated that biologic prices would remain at eighty-two percent of the branded price. Grabowski et al., *supra* note 255.
[259] FED. TRADE COMM'N, *supra* note 59, at v; Adelman & Holman, *supra* note 23, at 584.
[260] FED. TRADE COMM'N, *supra* note 59, at v.; Adelman & Holman, *supra* note 23, at 583.

and the availability of pertinent public or reference product data from animal or human clinical testing. [261] First, the FDA must require all FOB manufacturers to conduct extensive analytical assays to compare physical and chemical product attributes like primary and higher order structure, post-translational modification, product variance, and impurities.[262] Second, if physical and chemical characterization were sufficient to show the presence of no new impurities in the FOB as compared to the reference product, then the FDA should consider waiving animal studies.[263] However, in all other circumstances the FDA should require animal studies after completion of all physical and chemical assays to verify comparability.[264] Third, the FDA should consider waiving clinical study requirements if comparability has been established through physical and chemical testing and if animal testing revealed no issues regarding biosimilarity.[265] To be clear, however, the need for animal and clinical studies should be determined by the FDA on a case-by-case basis only after fully reviewing the results of the previous level of testing and always with a priority on product safety.

In cases where the FDA does find a need for clinical studies, the FDA should implement a similar progressive approach to allowing extrapolation of clinical data from one indication to other indications that rely on the same mechanism of action.[266] For the first condition of use, the

[261] *Biologics Price Competition and Innovation Act of 2009: Hearing Before the Food and Drug Administration* 256-58 (Nov. 2, 2010) [hereinafter *FDA Hearing on BPCIA Part 1*] (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer).
[262] *Biologics Price Competition and Innovation Act of 2009: Hearing Before the Food and Drug Administration* 332 (Nov. 3, 2010) [hereinafter *FDA Hearing on BPCIA Part 2*] (statement of Rasmus Rojkjaer from Generic Pharmaceutical Association (GPhA)); *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 256-58 (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer).
[263] *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 275-77 (statement of Satish Tripathi from Biomedical Consulting International).
[264] *Id.*; *FDA Hearing on BPCIA Part* 2*, supra* note 262, at 332 (statement of RasmusRojkjaer from Generic Pharmaceutical Association (GPhA)).
[265] *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 275-77 (statement of Satish Tripathi from Biomedical Consulting International).
[266] *Id.* at 259 (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer) ("Typically, if the mechanism of action is well understood

FDA should require FOB manufacturers to develop products that conform to the variability range allowed the reference product. Similarly, FOB manufacturer should be required to conduct clinical testing to prove safety and efficacy only to the extent the FDA requires the reference product sponsor to establish safety and efficacy when making changes to the reference product's manufacturing process.[267] For biologic products with well-defined mechanisms of action, a single clinical study may be sufficient for approval for all conditions of use sharing that mechanism of action.[268] However, for products with less defined mechanisms of action, the FDA should require additional clinical studies increasing incrementally in size and robustness as necessary to establish safety and efficacy before approving an FOB across conditions of use.[269]

Critics of a progressive hierarchical approach to biosimilarity determinations have repeatedly argued that, because analytical techniques have limited predictive value in terms of clinical concerns, the FDA should require both comparative non-clinical and clinical studies for all FOB applicants.[270]For example, Jay Siegel from Johnson & Johnson argues that biosimilars should be required to be as similar "as is reasonably achievable" based on non-clinical and

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for a particular compound, extrapolation of indications can be scientifically justified. Even when originator products go through major manufacturing process changes, the new product, in most cases, is allowed on the market by justifying extrapolation of safety and efficacy-based data on a nonclinical comparability exercise only.")

[267] *Id.* at 246-48 (statement of Rivka Kreitman, Head of Innovative Research and Development Global Group Teva); *FDA Hearing on BPCIA Part 2*, *supra* note 2612, at 333 (statement of Rasmus Rojkjaer from Generic Pharmaceutical Association (GPhA)).

[268] *FDA Hearing on BPCIA Part 1*, *supra* note 261 (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer).

[269] *Id.* at 246-48 (statement of Rivka Kreitman, Head of Innovative Research and Development Global Group Teva); *FDA Hearing on BPCIA Part 2*, *supra* note 2612, at 332-33 (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer). Interestingly, Owen Fields, a regulatory strategist from Pfizer, supports extrapolation for conditions of use so long as each FOB is considered on a case-by-case basis and the products' mechanism of action is sufficiently characterized. *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 231 (statement of Owen Fields, Regulatory Strategist for Pfizer).

[270] _*See, e.g., FDA Hearing on BPCIA Part 2*, *supra* note 2, at *id.* at 340-41 (2010) (statement of Sara Radcliffe, Executive Vice President for Health at the Biotechnology Industry Organization (BIO)) (stating that "comparative non-clinical and clinical studies should also be performed"); *FDA Hearing on BPCIA Part 1*, *supra* note 261, at *Id.* at 16-17 (statement of Marcia Boyle, President and Founder of the Immune Deficiency Foundation (IDF)) ("Given the very nature of biologic products, FDA should not waive the requirement for clinical studies."); *Id*. at 24-25 (statement of Janet Wyatt from the Arthritis Foundation) (arguing that "clinical evidence of the efficacy of biosimilars is absolutely essential for ensuring patient and provider confidence and biosimilar projects").

clinical testing.[271]These arguments, however, ignore Congress' intent to facilitate broad and inexpensive FOB approval and instead urge the FDA to implement a heightened biosimilarity standard. As discussed, the PPIBM would have strictly required clinical testing of all FOBs,[272] but Congress chose to reserve FDA discretion to waive unnecessary testing under the BPCIA. Further, Congress considered and rejected the ABCA's heightened biosimilarity standard requiring FOBs to be as similar to reference products as is reasonably achievable.[273]In addition, some critics argue that approval for several conditions of use based on a shared mechanism of action should never be granted without clinical testing specific to each condition of use.[274] Congress could have prohibited extrapolation in approving product conditions of use by passing one of several proposed bills and amendments advocating precisely such an approach,[275] but Congress chose repeatedly to reject such proposals.

Further, arguments for required clinical testing altogether miss the point of a progressive hierarchical testing regime. The testing regime proposed here would allow waiver of animal or clinical testing only when truly unnecessary. While many experts in the field argue that complete characterization is possible using physical and chemical techniques for certain biologic products,[276] in cases where proper characterization is not possible, the FDA retains full authority to require any and all animal and clinical testing it deems necessary. In summary, a flexible, hierarchical testing approach allows the FDA, FOB manufacturers, and consumers to realize all

[271] *FDA Hearing on BPCIA Part 2*, *supra* note 261, at 13*Id.* at 17 (2010) (statement of Jay Siegel, Johnson & Johnson).
[272] *See supra* Part V.B.2.a).
[273] *See supra* Part V.B.3.a).
[274] *FDA Hearing on BPCIA Part 2*, *supra* note 261262, at 17 (statement of Jay Siegel, Johnson & Johnson) (asserting that in terms of FOB approval, "the same mechanism of action is necessary but not sufficient").
[275] For example, the PPIBM and the PBA would both have limited FOB approval to specific conditions of use for which comparability was established.
[276] *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 256-58 57 (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer) (stating that "the scientific tools do exist to characterize both biosimilar and reference products proteins").

of the benefits of an abbreviated pathway by eliminating costly testing when unnecessary, while simultaneously ensuring consumer safety.

2. Interchangeability

To increase FOB market share through interchangeability designations as Congress intended under the BPCIA, the FDA must promulgate regulations that: 1) require a case-by-case determination of necessary clinical trials, 2) require only clinical tests reflective of the product's actual pattern of use, and 3) allow automatic pharmacy substitution for interchangeable FOBs.

A case-by-case determination of required clinical trials based on a product's actual use profile would establish an interchangeable FOB's safety and efficacy while minimizing costly and unnecessary clinical testing. First, to minimize patient exposure to trials, interchangeability should be established in specifically desired populations by a small clinical study, and the number of patients should be determined on a case-by-case basis. [277] In addition, clinical trials should be designed to reflect the reference product's actual use profile.[278] For example, for products administered only once, clinical studies should require only that a single administration of the FOB produce the same clinical result in patients as would a single administration of the reference product. Both the reference product and the FOB, however, should not be administered to the same patient. For products to be administered more than once, clinical studies should require that switching between the FOB and reference products have no greater risk to the patient than exclusive, repeated use of the reference product. Such clinical trials, however, must be limited to the number of switches and administrations expected during actual product use. Second, to prevent an unnecessarily heightened standard for FOBs as compared to reference products, requirements for interchangeability (i.e. clinical results, purity, and safety)

[277] *Id.* at 277 (statement of Satish Tripathi from Biomedical Consulting International).
[278] *Id.* at 259-60 (2010) (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer).

should be identical to those required for original FDA approval of the reference product.[279]Third, because automatic substitution is critical to expanding FOB market share,[280] FOBs should be automatically substituted for the reference product without patient or physician consultation; however, substitution should only be allowed after interchangeability has been established through the appropriate clinical studies.

Some critics argue that the current state of scientific understanding does not allow for determinations of interchangeability at all.[281] Other groups representing reference product manufacturer interests acknowledge that determinations of interchangeability may be possible. However, these groups argue for an "appropriately high standard"[282] requiring: 1) "no divergence in safety or efficacy profiles" for single-use or multi-use products in "any relevant patient population," and 2) clinical trials for each indication of use.[283] Again, however, critics' arguments are contrary to legislative intent. Congress could have passed one of several bills proposed during the BPCIA's legislative history strictly forbidding determinations of FOB interchangeability.[284]However, by allowing interchangeability designations under the BPCIA, Congress made a commitment to providing further competitive advantages for certain successful FOB market entrants. Further, critics arguing for a prohibitively stringent interchangeability standard misunderstand the case-by-case approach to clinical testing. Congress did not intend

[279] *Id.* at 259-60260 (2010) (statement of Sumant Ramachandra, Senior Vice President for Research and Development Regulatory Medical Affairs and Hospira's Chief Scientific Officer) ("Requirements for approval, including an interchangeability determination, should be based on the safety and efficacy profile of the reference drug.").
[280] *See supra*, Part IV.B.4.
[281] *See, e.g.*, *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 201-04202-04 (statement of Gregory Schimizzi representing the Coalition of State Rheumatology Organizations) ("Anything short of barring interchangeability at this time would be detrimental to patient safety and would erode physician confidence in prescribing these medications.").
[282] *Hearing on BPCIA Part 2*, *supra* note 261, at *Id.* at 342-43 (2010) (statement of Sara Radcliffe, Executive Vice President for Health at the Biotechnology Industry Organization (BIO)).
[283] *Id.* (statement of Sara Radcliffe, Executive Vice President for Health at the Biotechnology Industry Organization (BIO)).
[284] For example, see the PPIBM. *See supra* Part V.B.2.b).

for the FDA to elevate interchangeability requirements to an unattainable level.[285] Separate requirements for single and multi-use biologics were designed simply to ensure patient safety, not to aggressively prevent FOB products from being labeled as interchangeable. A case-by-case determination of required clinical studies based on the standards imposed for reference products grants the FDA the necessary discretion to ensure patient safety while minimizing costs to FOB manufacturers. Without such discretion, the FDA would be unable to implement Congress' intent to increase FOB market share and decrease the prohibitive monopoly prices reference product sponsors currently charge.[286]

Critics also argue that automatic substitution of interchangeable FOBs should not be allowed because such decisions require very careful consideration of the associated risks by both the patient and the physician.[287] Again, critics of automatic substitution have not considered the legislative intent evinced by the BPCIA. Although bills and amendments were introduced to prohibit automatic substitution,[288]the BPCIA explicitly mandates automatic substitution of interchangeable biologics without consultation or intervention of a given patient's physician.[289]In so doing, Congress recognized that automatic substitution is essential to FOB success.[290]Further, because a case-by-case determination of safety for each interchangeable FOB will ensure the safety of such products, there is little risk in automatic substitution. Congress intended for interchangeable FOBs to gain market share through automatic substitution, and the approach introduced here provides a framework for ensuring Congress' intent is effectuated safely.

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[285] *FDA Hearing on BPCIA Part 2*, *supra* note 261261, at 334-35 (statement of RasmusRojkjaer from Generic Pharmaceutical Association (GPhA)).
[286] *Id.* (statement of Rasmus Rojkjaer from Generic Pharmaceutical Association (GPhA)).
[287] *FDA Hearing on BPCIA Part 1*, *supra* note 261,*Id.* at 35 (statement of Janet Wyatt from the Arthritis Foundation).
[288] For example, both the First and Second McCain Amendments would have prohibited automatic substitution of interchangeable FOBs. *See infra* Appendix: Table 13Table 13 and Table 20Table 20.
[289] *See supra* Part V.B.4.b).
[290] *See supra* Part IV.B.4.

3. Exclusivity

To protect reference product exclusivity while preventing anticompetitive evergreening as Congress intended, the FDA must promulgate regulations that: 1) ensure supplements and changes under Subsection (k)(7)(c) are protected by the remaining period of exclusivity granted to the reference product and 2) require a significant change to a reference product in terms of safety, purity, or potency to obtain an additional 12-year exclusivity period.

Broadening a reference product's existing 12-year exclusivity period to incorporate supplements and changes to that reference product for the remainder the product's exclusivity period would effectuate Congress' intent to provide innovative products with robust exclusivity protection.[291] Subsection (k)(7)(c) was intended to define a group of biologic products based on a reference product and very similar to a reference product, which the BPCIA does not consider sufficiently innovative apart from the original reference product. The supplements and changes described in Subsection (k)(7)(c) are inherently dependent on the reference product to which they correspond. Therefore, to provide reference product manufacturers with strong protection, the FDA should apply the remainder of the reference product's original 12-year exclusivity period to these similar products as well.

In addition, the FDA should promulgate regulations that require a significant change in safety, purity, or potency as a result of a structural change before granting an application filed by a reference product sponsor, manufacturer, or affiliated party an additional 12-year exclusivity period.[292]Because even minor structural changes often presuppose a change in safety or potency,[293]allowing reference product sponsors to gain additional 12-year exclusivity periods

[291] *FDA Hearing on BPCIA Part 2*, *supra* note 261261, at 346-48 (statement of Sara Radcliffe, Executive Vice President for Health, at the Biotechnology Industry Organization (BIO)).
[292] *Id.* (statement of Sara Radcliffe, Executive Vice President for Health at the Biotechnology Industry Organization (BIO)).
[293] *Id.* at 278-80 (2010) (statement of Bernard Rhee and Robert Bakin, Technology & Business Law Advisors).

after making such changes would legitimize and incentivize the anti-competitive evergreening strategy.[294] While incremental improvements to reference products may produce valuable products, such products do little to reduce the costs of biologics to patients.[295]Extending exclusivity periods to incrementally altered products would create a near absolute bar to FOB development regardless of a reference product's patent status and regardless of the need for less expensive biologic products.[296] Allowing reference product sponsors to monopolize product sectors in this way would be contrary to the statute's plain meaning and to Congress' intent to create a strong FOB industry. The FDA should, therefore, grant independent 12-year exclusivity periods only to products that exhibit a marked change in safety, purity, or potency.

Some argue that the FDA should interpret the BPCIA as providing additional 12-year exclusivity periods to important product improvements or beneficial alternatives, no matter how insignificant the change to the reference product.[297]Proponents of this interpretation argue that additional data exclusivity periods are necessary to incentivize continuing innovation. However, granting exclusivity to products only marginally different from an existing reference product would most likely only incentivize lower-risk innovation by continuously and incrementally altering existing products rather than investing in higher risk research into truly innovative products for unmet clinical needs.[298]Throughout the BPCIA's legislative history, the underlying goal behind biosimilars legislation has been to increase competition and decrease the cost of biologics products to consumers. Subsection (7)(k)(c) was adopted in the Hatch/Enzi/Hagan Amendment and ultimately in the BPCIA to explicitly combat evergreening through incremental

[294] *See supra* Part IV.B.3.
[295] *FDA Hearing on BPCIA Part 1*, *supra* note 261, at 116-21 (statement of Sara Crager, American Medical Students Association, Universities Allied for Essential Medicines).
[296] *Id.* at 295-96 (2010) (statement of Michael Behan, Chief Counsel and Legislative Director for U.S. Senator Bernie Sanders).
[297] *See, e.g.*, *id.*at 222-23 (2010) (statement of Jim Shehan, Novo Nordisk).
[298] *Id.* at 116-21 (2010) (statement of Sara Crager, American Medical Students Association, Universities Allied for Essential Medicines).

improvements to reference products.[299] By granting exclusivity to minor reference product supplements and structural changes only to the extent of the existing 12-year reference product exclusivity period, the FDA would effectuate Congress' intended balance: stimulating truly innovative research while creating a robust competitive market for FOBs.

VIII. Conclusion

In the wake of the BPCIA, three things are clear. First, the high cost of developing and obtaining FDA approval for biologic products prevent many patients from obtaining the new and potentially life-saving biologic treatments they require. Second, by enacting the BPCIA, Congress intended to balance reference product sponsors' interest in protecting their investments and consumers' and FOB manufacturers' interest in bringing less expensive competing biological products to market. Third, the BPCIA alone is not enough to increase FOB competition and spark significant price reductions for biologic products. What remains unclear, however, is how the FDA will address the biologics industry's problems and competing interests.

Because the biologics market is likely to remain hostile to FOB market entry even after the BPCIA's enactment, it is imperative that the FDA promulgates regulations designed to facilitate strong FOB competition while maintaining incentives for brand name manufacturers to produce innovative biologic products. The FDA can facilitate FOB approval by requiring a progressive hierarchical approach to FOB testing and allowing extrapolation for multiple conditions of use utilizing the same mechanism of action. The FDA can then increase FOB market share by reasonably limiting interchangeability requirements and allowing automatic pharmacy substitution. Finally, the FDA can continue to reward brand name innovation while limiting product evergreening by incorporating reference product supplements and improvements into a product's original exclusivity period while reserving additional exclusivity

[299] *See supra* Parts V.D.3.a), V.D.4, and VI.C.

periods to truly innovative products only. By implementing these recommendations, the FDA can pave a clear path to increased competition and broader patient access to biologic products.

IX. Appendix: Proposed Legislation in the BPCIA's Legislative History

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY A. PHSA § 351(k)(1) - comparable biological products B. PHSA § 351(k)(2) – different biological products 1. Allows approval if the product is safe, pure, and potent relative to the reference product for a specific condition of use **TESTING REQUIREMENTS** A. FDA discretion in determining required data 1. Non-clinical laboratory studies 2. Any necessary clinical studies for one or more appropriate conditions of use B. Mandated FDA approval for specifically identified products **OTHER REQUIREMENTS** A. Data demonstrating that products utilize the same mechanism of action for the conditions of use, but only to the extent such mechanisms are known for the reference product B. Condition of use was previously approved for the reference product C. Same route of administration, dosage form, and strength D. All facilities must meet relevant standards E. Option to provide additional information F. Optional postmarketing safety study **CONDITIONS OF USE** A. Known Mechanism of Action – must approve for all conditions of use regardless of comparability B. Unknown Mechanism of Action – must only approve for conditions of use supported by comparability	**REQUIREMENTS** A. Active ingredient(s) had principal molecular structural features comparable to those of the reference product, and B. Expected to produce the same clinical result as the reference product 1. In any given patient 2. In the condition or conditions of use for which both products were labeled	**INNOVATOR EXCLUSIVITY –** None **INTERCHANGEABLE EXCLUSIVITY –** the shorter of: A. 180 days after first commercial marketing of the first interchangeable product, or B. Various other dates dependent on the pendency and outcome of patent litigation **SUPPLEMENT EXCLUSIVITY –** none

Table 1: The Access to Life-Saving Medicine Act (H.R. 6257 & S. 4016)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY A. PHSA § 351(k)(1) - comparable biological products B. PHSA § 351(k)(2) – different biological products 1. Allows approval if the product is safe, pure, and potent relative to the reference product for a specific condition of use **TESTING REQUIREMENTS** - ALSMA **OTHER REQUIREMENTS**- ALSMA **CONDITIONS OF USE** - ALSMA	**REQUIREMENTS** A. Comparable to the reference product; and B. Expected to produce the same clinical result in a given patient	**INNOVATOR EXCLUSIVITY –** None **INTERCHANGEABLE EXCLUSIVITY** – ALSMA **SUPPLEMENT EXCLUSIVITY –** none

Table 2: The Amended Access to Life-Savings Medicine Act (H.R. 1038 & S. 623)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY A. PHSA § 351(k) - biological products satisfying class guidance **TESTING REQUIREMENTS** A. Physical, chemical, and biological assays fully characterizing the product compared to the reference B. Comparative nonclinical studies on pharmacodynamics, toxicity, immunogenicity, etc. C. Comparative clinical trials **OTHER REQUIREMENTS** A. All facilities must meet relevant standards B. Manufacturers must consent to inspection of facilities C. Must conform to applicable product-class guidance to ensure safety, purity, and potency D. Consistency and robustness of the manufacturing process for active ingredient and final formulation E. Stability, compatibility, and biological and physiochemical integrity of active ingredient F. Postmarketing safety plan	**REQUIREMENTS** – no interchangeability	**INNOVATOR EXCLUSIVITY** A. Application submission – 12 years B. Application approval – 14 years **INTERCHANGEABLE EXCLUSIVITY –** none **SUPPLEMENT EXCLUSIVITY –** 1 year if: A. FDA approved a supplement for a new indication of use, and B. The new indication was a significant clinical benefit in comparison with existing therapies.

CONDITIONS OF USE A. Must only approve for conditions of use for which comparability is established		

Table 3: Patient Protection and Innovative Biologic Medicines Act of 2007 (H.R. 1956)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY - PPIBM **TESTING REQUIREMENTS** - PPIBM **OTHER REQUIREMENTS** – PPIBM plus: A. Same route of administration, dosage form, mechanism of action, and strength B. Must be as similar as may be achieved given the state of scientific knowledge and technology at the time **CONDITIONS OF USE** - PPIBM	**REQUIREMENTS** A. No interchangeability B. However, would have required the FDA to assess every two years whether interchangeability designations were technically possible	**INNOVATOR EXCLUSIVITY** - PPIBM **INTERCHANGEABLE EXCLUSIVITY –** 1 year **SUPPLEMENT EXCLUSIVITY –** 2 years if: A. FDA approved a supplement for a new indication of use within 12 years of first licensure, and B. The new indication was a significant clinical benefit

Table 4: Affordable Biologics for Consumers Act (S. 1505)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY A. PHSA § 351(k) – biosimilar biological products **TESTING REQUIREMENTS – "biosimilarity"** (can be waived at FDA discretion): A. Analytical studies demonstrating high similarity notwithstanding minor differences in clinically inactive components B. Animal studies C. A clinical study or studies (including immunogenicity, and	**REQUIREMENTS** A. Single Use Products – Could be expected to produce the same clinical result as the reference product in any given patient B. Multi-Use Products - Risk to patients in terms of safety or diminished	**INNOVATOR EXCLUSIVITY** A. Application Submission – 4 years B. Application Approval – 12 years **INTERCHANGEABLE EXCLUSIVITY**

pharmacokinetics or pharmacodynamics) sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use **OTHER REQUIREMENTS** A. Same mechanism of action but only to the extent the mechanism or mechanisms of action are known B. Condition of use was previously approved for the reference product C. Route of administration, dosage form, and strength are the same D. All facilities must meet relevant standards E. Manufacturers must consent to inspection of facilities F. Option to provide additional information **CONDITIONS OF USE** A. Must approve for all conditions of use for which the products use the same mechanism of action	efficacy from switching between the two products was no greater than the risk from exclusive use of the reference product. C. Allowed automatic pharmacy substitution	A. 1 year from first commercial marketing of interchangeable, or B. Date dependent on initiation, status, and outcome of patent litigation **SUPPLEMENT EXCLUSIVITY –** none

Table 5: Biologics Price Competition and Innovation Act of 2007 (S. 1695)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING REQUIREMENTS** – S. 1695 A. Exception – immunogenicity study can only be waived if the FDA has published a final guidance: 1. Advising that it is feasible in current state of scientific knowledge to make determinations on immunogenicity for the product class, and 2. Explaining the data required to support such a determination **OTHER REQUIREMENTS** – S. 1695 **CONDITIONS OF USE** A. Must only approve for conditions of use for which comparability is established	**REQUIREMENTS** – S. 1695 except: A. FDA must publish a final guidance: 1. Advising that it is feasible in current state of scientific knowledge to make determinations on interchangeability for the product class, and 2. Explaining the data required to support such a determination	**INNOVATOR EXCLUSIVITY** A. Application Submission – the later of: 1. Commencement of guidance issuance proceeding, or 2. 4 years after reference product licensure B. Application Approval – 12 years **INTERCHANGEABLE EXCLUSIVITY –** 2 years after the later of:

		A. First commercial marketing of interchangeable, or B. Date the product is deemed interchangeable. **SUPPLEMENT EXCLUSIVITY –** 2 years if: A. FDA approved a supplement for a new indication of use with 8 years of first licensure, and B. The new indication was a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of disease

Table 6: Pathway for Biosimilars Act (H.R. 5629)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING REQUIREMENTS** - PBA **OTHER REQUIREMENTS**– S. 1695 **CONDITIONS OF USE** - PBA	**REQUIREMENTS** - PBA	**INNOVATOR EXCLUSIVITY** - PBA **INTERCHANGEABLE EXCLUSIVITY –**PBA **SUPPLEMENT EXCLUSIVITY –**PBA

Table 7: Second Pathway for Biosimilars Act (H.R. 1548)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY

REGULATORY PATHWAY

A. PHSA § 351(k)(1) - biosimilar biological products
B. PHSA § 351(k)(2) – different biological products
    1. Allows approval if the product is safe, pure, and potent for a specific condition of use

TESTING REQUIREMENTS

A. Absence of clinically meaningful differences in terms of safety, purity, and potency if treatment were initiated with FOB based on:
    1. Non-clinical laboratory studies including chemical, physical, and biological assays
    2. Any necessary clinical studies sufficient to confirm safety, purity, and potency

OTHER REQUIREMENTS

A. Utilize the same mechanism of action for the condition of use, but only to the extent such mechanisms are known for the reference product or can reasonably be determined
B. Condition of use was previously approved for the reference product
C. Same route of administration, dosage form, and strength
D. All facilities must meet relevant standards

CONDITIONS OF USE

A. Must only approve for conditions of use for which biosimilarity is established
    1. Exception - extrapolation of biosimilarity to other conditions of use may be allowed if applicant can provide information showing the such reliance is scientifically appropriate

REQUIREMENTS – with respect to a given condition of use:

A. Single-Use Products - biosimilarity
B. Multi-Use Products
    1. Biosimilarity
    2. Risk to patients in terms of clinically significant change in immunogenicity or diminished effectiveness

INNOVATOR EXCLUSIVITY

A. Application Approval - 5 years if:
    1. No major substance of the product, nor any highly similar major substance, have been licensed, and
    2. The reference product application did not rely on any clinical safety, purity, or potency study in another application.
    3. Exception –specifically identified product classes are not eligible.
B. Application Approval - 3 years if:
    1. Supplement contains a major substance, or any highly similar major substance, that has been approved, and
    2. Application contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or sponsored by the applicant, and
    3. Supplement is a significant therapeutic advance.

INTERCHANGEABLE EXCLUSIVITY –ALSMA

SUPPLEMENT EXCLUSIVITY

A. 6 months if:
    1. FDA approved the supplement no later than 1 year before innovator exclusivity expiration, and
    2. Supplement contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or sponsored by the applicant, and
    3. Supplement is a significant therapeutic advance.
B. However, any extension will be reduced by 3

		months if combined annual sales exceed $1,000,000 for: 1. All products containing the major substance, and 2. All products owned or marketed by the applicant or affiliates.

Table 8: Promoting Innovation and Access to Life-Saving Medicine Act (H.R. 1548)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING REQUIREMENTS** – S. 1695 **OTHER REQUIREMENTS** – S. 1695 **CONDITIONS OF USE** – S. 1695	**REQUIREMENTS** – S. 1695	**INNOVATOR EXCLUSIVITY** A. Original Biological Product - 12 Years B. Supplement to Existing Biological Product – until expiration of reference product exclusivity. Includes: 1. Reference product supplement 2. Application submitted by sponsor or manufacturer of previously licensed product that proposes one or more changes **INTERCHANGEABLE EXCLUSIVITY** – S. 1695 **SUPPLEMENT EXCLUSIVITY** – none

Table 9: Biologics Price Competition and Innovation Act (S. 1695 - 9127 Discussion Draft)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING REQUIREMENTS** – S. 1695 **OTHER**	**REQUIREMENTS** – S. 1695	**INNOVATOR EXCLUSIVITY** A. Application Submission – 4 years B. Application Approval – 12 years C. EXCLUSIONS 1. Any supplement to a reference product 2. Any subsequent application filed by the same sponsor or manufacturer of the biological product for either: a. A change (not including a modification to the structure of the biological

REQUIREMENTS – S. 1695 **CONDITIONS OF USE** – S. 1695		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 **INTERCHANGEABLE EXCLUSIVITY** – S. 1695 **SUPPLEMENT EXCLUSIVITY** – none

Table 10: Biologics Price Competition and Innovation Act (S. 1695 - 9374 Discussion Draft)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING REQUIREMENTS** – S. 1695 **OTHER REQUIREMENTS** – S. 1695 **CONDITIONS OF USE** – S. 1695	**REQUIREMENTS** – S. 1695	**INNOVATOR EXCLUSIVITY** A. Application Submission – 4 years B. Application Approval - 9 years if: 1. No major substance of the product, nor any highly similar major substance, have been licensed, and 2. The reference product application did not rely on any clinical safety, purity, or potency study in another application. 3. Exception –specifically identified product classes are not eligible. C. Application Approval - 2 years if: 1. Supplement contains a major substance, or any highly similar major substance, that has been approved, and 2. Application contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or sponsored by the applicant, and 3. Supplement is a significant therapeutic advance. **INTERCHANGEABLE EXCLUSIVITY** – S. 1695 **SUPPLEMENT EXCLUSIVITY** A. 2 years if: 1. FDA approved the supplement no later than 1 year before innovator exclusivity expiration, and 2. Supplement contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or

		sponsored by the applicant, and 3. Supplement is a significant therapeutic advance. B. 2 additional years if: 1. FDA approved the second supplement no later than 1 year before first supplement exclusivity expiration, and 2. Second supplement contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or sponsored by the applicant, and 3. Second supplement is a significant therapeutic advance.

Table 11: Biologics Price Competition and Innovation Act (S. 1695 - 9653 Discussion Draft)

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING REQUIREMENTS** – S. 1695 **OTHER REQUIREMENTS** – S. 1695 **CONDITIONS OF USE** – S. 1695	**REQUIREMENTS** – S. 1695	**INNOVATOR EXCLUSIVITY –** 10 years **INTERCHANGEABLE EXCLUSIVITY** – none **SUPPLEMENT EXCLUSIVITY** A. 1 year if: 1. FDA approved the supplement within 8 years of reference product first licensure, and 2. Supplement for new therapeutic indication(s) comprising a new biological products that meaningfully differ from a previously-licensed biological product in molecular structure, starting materials, or manufacturing process, and 3. Significant clinical benefit in comparison with existing therapies, constituting a major contribution to patient care. B. Limited to one extension per reference product

Table 12: Mikulski Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – S. 1695 **TESTING**	**REQUIREMENTS** – no automatic pharmacy substitution with respect to an individual unless such	**INNOVATOR EXCLUSIVITY** A. Application Submission – 4 years B. Application Approval - 10 years

REQUIREMENTS – required one or more clinical studies to establish safety, purity, and potency **OTHER REQUIREMENTS** – S. 1695 **CONDITIONS OF USE** – S. 1695	interchange is prescribed by a physician for such individual	**INTERCHANGEABLE EXCLUSIVITY** – none **SUPPLEMENT EXCLUSIVITY -** 2 years if there was a significant advancement with respect to the reference product

Table 13: First McCain Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – 9653 **TESTING REQUIREMENTS** – 9653 **OTHER REQUIREMENTS** – 9653 **CONDITIONS OF USE** – 9653	**REQUIREMENTS** – 9653	**INNOVATOR EXCLUSIVITY** A. Application Approval - 7 years if: 1. No major substance of the product, nor any highly similar major substance, have been licensed, and 2. The reference product application did not rely on any clinical safety, purity, or potency study in another application. 3. Exception –specifically identified product classes are not eligible. B. Application Approval - 3 years if: 1. Supplement contains a major substance, or any highly similar major substance, that has been approved, and 2. Application contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or sponsored by the applicant, and 3. Supplement is a significant therapeutic advance. **INTERCHANGEABLE EXCLUSIVITY –** 9653 **SUPPLEMENT EXCLUSIVITY** - 9653

Table 14: First Brown Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – 9653 **TESTING REQUIREMENTS** – 9653 **OTHER REQUIREMENTS** – 9653 **CONDITIONS OF USE** – 9653	**REQUIREMENTS** – 9653	**INNOVATOR EXCLUSIVITY** A. Application Approval - 9 years if: 4. No major substance of the product, nor any highly similar major substance, have been licensed, and 5. The reference product application did not rely on any clinical safety, purity, or potency study in another application. 6. Exception –specifically identified product classes are not eligible. B. Application Approval - 3 years if: 4. Supplement contains a major substance, or any highly similar major substance, that has been approved, and 5. Application contains reports of new clinical investigations (other than pharmacokinetic or pharmacodynamic) essential to its approval and conducted or sponsored by the applicant, and 6. Supplement is a significant therapeutic advance. **INTERCHANGEABLE EXCLUSIVITY –** 9653 **SUPPLEMENT EXCLUSIVITY** - PILSM

Table 15: Second Brown Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – 9374 **TESTING REQUIREMENTS** – 9374 **OTHER REQUIREMENTS** – 9374 **CONDITIONS OF**	**REQUIREMENTS** – 9374	**INNOVATOR EXCLUSIVITY** - 9374 **INTERCHANGEABLE EXCLUSIVITY** – 9374 **SUPPLEMENT EXCLUSIVITY** - 9374

USE – 9374		

Table 16: Hatch/Enzi/Hagan Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – Hatch/Enzi/Hagan Amendment **TESTING REQUIREMENTS** – Hatch/Enzi/Hagan Amendment **OTHER REQUIREMENTS** – Hatch/Enzi/Hagan Amendment **CONDITIONS OF USE** – Hatch/Enzi/Hagan Amendment	**REQUIREMENTS** – Hatch/Enzi/Hagan Amendment	**INNOVATOR EXCLUSIVITY** - Hatch/Enzi/Hagan Amendment **INTERCHANGEABLE EXCLUSIVITY** – Hatch/Enzi/Hagan Amendment **SUPPLEMENT EXCLUSIVITY** - Hatch/Enzi/Hagan Amendment

Table 17: Eshoo Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – Eshoo Amendment **TESTING REQUIREMENTS** – Eshoo Amendment	**REQUIREMENTS** – Eshoo Amendment	**INNOVATOR EXCLUSIVITY** – expires on the earlier of: A. 12 years after first licensure, or B. Date on which gross sales from reference product equaled $3.5 billion **INTERCHANGEABLE EXCLUSIVITY** – Eshoo Amendment **SUPPLEMENT EXCLUSIVITY** - Eshoo Amendment

OTHER REQUIREMENTS – Eshoo Amendment **CONDITIONS OF USE** – Eshoo Amendment		

Table 18: Third Brown Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – Eshoo Amendment **TESTING REQUIREMENTS** – would have established cost sharing arrangements under which FOB applicants could have gained access to reference product clinical data for a fee payable to reference product sponsors (but set by the FDA) **OTHER REQUIREMENTS** – Eshoo Amendment **CONDITIONS OF USE** – Eshoo	**REQUIREMENTS** – Eshoo Amendment	**INNOVATOR EXCLUSIVITY** – expires on the earlier of: A. 12 years after first licensure, or B. Date on which gross sales from reference product equaled $3.5 billion **INTERCHANGEABLE EXCLUSIVITY** – Eshoo Amendment **SUPPLEMENT EXCLUSIVITY** - Eshoo Amendment

Amendment		

Table 19: Sanders Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY – Eshoo Amendment **TESTING REQUIREMENTS** A. Analytical Studies – could only be waived after public notice and comment B. Animal Studies – could only be waived after public notice and comment C. Clinical Studies – could not be waived **OTHER REQUIREMENTS** – Eshoo Amendment **CONDITIONS OF USE** – Eshoo Amendment	**REQUIREMENTS** A. Required "therapeutic equivalence" as opposed to "interchangeable" B. No automatic pharmacy substitution with respect to an individual unless such interchange is prescribed by a physician for such individual	**INNOVATOR EXCLUSIVITY** A. Application Submission – 4 years B. Application Approval - 10 years **INTERCHANGEABLE EXCLUSIVITY** – Eshoo Amendment **SUPPLEMENT EXCLUSIVITY -** 2 years if A. Supplement was a change (not including modification of structure) resulting in a new indication, and B. Significant therapeutic advancement (including a modification resulting in a new dosage form, new dosing regimen, or new rout of administration).

Table 20: Second McCain Amendment

BIOSIMILARITY	INTERCHANGEABILITY	EXCLUSIVITY
REGULATORY PATHWAY A. PHSA § 351(k) – biosimilar biological products **TESTING REQUIREMENTS** A. Analytical studies demonstrating high similarity notwithstanding minor differences in clinically inactive components B. Animal studies C. A clinical study or studies (including immunogenicity, and pharmacokinetics or pharmacodynamics) sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use **OTHER REQUIREMENTS** A. Same mechanism of action but only to the extent the mechanism or mechanisms of action are known B. Condition of use was previously approved for the reference product C. Route of administration, dosage form, and strength are the same D. All facilities must meet relevant standards E. Manufacturers must consent to inspection of facilities F. Option to provide additional information **CONDITIONS OF USE** A. Must approve for all conditions of use for which the products use the same mechanism of action	**REQUIREMENTS** A. Single Use Products – Could be expected to produce the same clinical result as the reference product in any given patient B. Multi-Use Products - Risk to patients in terms of safety or diminished efficacy from switching between the two products was no greater than the risk from exclusive use of the reference product. C. Allows automatic pharmacy substitution	**INNOVATOR EXCLUSIVITY** A. Application Submission - 4 years B. Application Approval - 12 years C. EXCLUSIONS 1. Any supplement to a reference product 2. Any subsequent application filed by the same sponsor or manufacturer of the biological product 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 **INTERCHANGEABLE EXCLUSIVITY** A. 1 year from first commercial marketing of interchangeable, or B. Date dependent on initiation, status, and outcome of patent litigation **SUPPLEMENT EXCLUSIVITY –** none

Table 21: Biologics Price Competition and Innovation Act of 2009