

FOOD AND DRUG LAW JOURNAL

*Analyzing the Laws, Regulations, and Policies
Affecting FDA-Regulated Products*

No Longer “If,” But “When”: The Coming Abbreviated Approval Pathway for Follow-on Biologics

*Jeremiah J. Kelly
Michael David*



VOLUME 64 NUMBER 1 2009

No Longer “If,” But “When”: The Coming Abbreviated Approval Pathway for Follow-on Biologics

JEREMIAH J. KELLY, JD, MPP*
MICHAEL DAVID, JD, PHD**

INTRODUCTION

In 1984, Congress enacted the Price, Competition & Patent Term Restoration Act of 1984, commonly referred to as “Hatch-Waxman,” to create abbreviated pathways for the approval of generic drug products.¹ Hatch-Waxman aimed to strike a critical balance in the Food, Drug & Cosmetic Act (FDCA) between incentives for drug innovation and the need for lower drug prices through increased competition. Action by the incoming 111th Congress is needed to strike a similar balance for biologic drug products licensed under the Public Health Service Act (PHSA).

The biological drug industry is growing rapidly, evidenced by the quantity of approved biologic drugs on the market, the size of the biologics market, and the importance of these products to patients.² By 2010, analysts project that sales of biological drug products will exceed \$90 billion.³ Because biological drugs generally cost much more than chemically-derived products, averaging between \$10,000 to \$20,000 or more per patient, per year, they contribute significantly to the escalating prescription drug costs in the United States.⁴ Biological drug products are unaffordable for many patients.⁵

Abbreviated approval of follow-on biological drug products, or follow-on biologics,⁶ is receiving increased attention because patents for many of these products

* Mr. Kelly is an Associate at Whiteford, Taylor & Preston, LLP, Baltimore, MD. He is a member of the Specialty Litigation and Biotechnology Practices. Mr. Kelly is a former legislative analyst at the U.S. Food and Drug Administration (FDA), where he was a member of FDA's working group on follow-on biologics. An earlier draft of this paper satisfied course requirements in Food & Drug Law at the University of Maryland School of Law. Any views expressed herein are solely those of the authors and do not necessarily reflect those of Whiteford, Taylor & Preston, its clients, or FDA.

** Michael David is Counsel at Whiteford, Taylor Preston, LLP, Baltimore, MD. He co-chairs the Biotechnology Practice and is a member of the Technology and Intellectual Property Practice. Mr. David's Ph.D. is in molecular biology.

¹ The Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. 98-417 (1984), 21 U.S.C. §§ 355, 357.

² CONGRESSIONAL RESEARCH SERVICE, REPORT FOR CONGRESS: FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES, RL33901, 2 (2007) [hereinafter CRS Report]; Devine, Joshua et al. *Follow-on Biologics: Competition in the Biopharmaceutical Marketplace*, 46 J. AM. PHARM. ASSOC. 193-201, 195 (2006).

³ Frank, Richard G., *Regulation of Follow-on Biologics*, 357 NEW ENG. J. MED. 841-843 (2007); see also, CRS Report, *supra* note 2, at 1.

⁴ Carole Ben-Maimon, President, Barr Laboratories, Testimony at The Law of Biologic Medicine, Senate Judiciary Committee (Jun. 23, 2004), available at <http://judiciary.senate.gov/hearings/hearing.cfm?id=1239> (last visited Nov. 30, 2008).

⁵ Kathleen Jaeger, President, Generic Pharmaceutical Association (GPhA), Remarks at Windhover FDA/CMS Summit (Dec. 5, 2006), available at: <http://www.gphaonline.org/AM/Template.cfm?Section=Testimony1&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=3060> (last visited Nov. 30, 2008).

⁶ “Follow-on biologics,” or alternatively, “follow-on protein products,” are terms that refer to therapeutic protein and peptide products that are intended to be sufficiently similar to a product already approved under §505 of the FDCA or licensed under §351 of the PHSA and would permit that applicant to rely, for approval, on certain existing scientific knowledge about the safety and effectiveness of the

will expire soon. By 2016, more than \$10 billion in biological drug products will lose patent protection.⁷ Over 340 biological drugs are undergoing clinical study in hopes to successfully treat serious medical conditions, such as cancer, AIDS, and diabetes, as well as auto-immune, blood, digestive, and cardiovascular disorders. Competition by follow-on biologics could provide significant cost savings for patients and the federal government.⁸ Price competition, however, is contingent upon FDA's ability to review and approve abbreviated applications or follow-on biologics that require less clinical study and permit some degree of reliance on the information derived from FDA approval of the innovator product.

For historical reasons, most biologics⁹ are regulated by FDA under §351 of the PHSa and only a few biologics, such as insulin and human growth hormone, are regulated as drugs¹⁰ under §505 of the FDCA.¹¹ Legal commentators find that FDA could approve all follow-on biologics through §505(b)(2) of the FDCA, as FDA does for follow-on biologics to an innovator approved under §505(b) of the FDCA.¹² FDA, however, asserts that it lacks the statutory authority to approve an abbreviated application for a follow-on biological drug product if its reference product is licensed under §351 of the PHSa.¹³

The debate over a U.S. regulatory system for follow-on biologics began in the early 2000s.¹⁴ In 2004, the European Union enacted the world's first regulatory system for follow-on biologics.¹⁵ Most recently, Canada has established a framework for the review of abbreviated applications for these products.¹⁶ Without an abbreviated approval pathway analogous to the existing generic approval pathways for chemically-synthesized drug products, price competition in the United States depends on the biotechnology industry's willingness to undertake costly, full-scale product applications. This results in *de facto* market exclusivity for the innovator companies

approved protein product. "Follow-on biologics" may be produced through biotechnology (recombinant DNA technology) or derived from natural sources. 69 Fed. Reg. 503,881.

⁷ Gitter, Donna, *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, 558 (2008).

⁸ Willow, Dawn, *The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare*. 6 CHI-KENT J. INTELL. PROP. 32, 36-37 (2006).

⁹ The PHSa defines a biological product as "any virus, therapeutic serum, toxin, antitoxin or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man." PHSa, § 351(i), 42 U.S.C. § 262(i).

¹⁰ The FDCA defines a "drug" as "(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals; (C) articles (other than food) intended to affect the structure and function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." FDCA, §201(g)(1), 21 U.S.C. §321(g)(1)(2004).

¹¹ Many biologics would satisfy the definition of "drug" under the FDCA. See, Korwek, Edward L., *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 FOOD & DRUG L.J. 257, 260 (2007).

¹² Dudzinski, David M., *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., 200-203 (2005).

¹³ Janet Woodcock, Deputy Commissioner, Chief Medical Officer, Testimony before the Committee on Oversight and Government Reform, U.S. House of Representatives (Mar. 25, 2007), available at: <http://www.fda.gov/ola/2007/policy05022007.html> (last visited Nov. 30, 2008).

¹⁴ See, The Law of Biologic Medicine, Hearing before the Senate Judiciary Committee (Jun. 23, 2004), available at: <http://judiciary.senate.gov/hearings/hearing.cfm?id=1239> (last visited Nov. 30, 2008).

¹⁵ European Commission Directive 2003/63/EC, Art. 10 (2004).

¹⁶ MINISTER OF HEALTH: HEALTH PRODUCTS, FOOD AND DRUG BRANCH, DRAFT GUIDANCE FOR SPONSORS: INFORMATION AND SUBMISSION REQUIREMENTS FOR SUBSEQUENT ENTRY BIOLOGICS (SEBs), at ii. [hereinafter, Canadian SEB Guidance] (2008), available at: <http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/consultation/seb-pbu/2008-1-eng.php> (last visited Nov. 30, 2008).

and high costs for consumers. The follow-on biologics debate is further complicated by underlying scientific concerns about the adequacy of technology to evaluate differences between a follow-on biologic and its innovator reference product.

The 110th Congress has introduced four distinct legislative proposals that would authorize FDA to approve an abbreviated application for a follow-on biological drug product. With the incoming 111th Congress, increased Democratic majorities in both houses, and a Democratic President, it is no longer a question of “if,” but “when” FDA will receive authority to review and license abbreviated applications for follow-on biologics. Congress must create an abbreviated approval pathway for follow-on biologics that balances the need for patient safety, incentives for innovation, price competition, and provides regulatory transparency and flexibility.

Section II of this article discusses the adequacy of the current legal framework for abbreviated approval of follow-on biologics. Section III discusses the scientific concerns involved and the emerging technology to address them. Section IV analyzes both foreign and Congressional approaches to an abbreviated pathway for follow-on biologics. Section V of this article discusses six fundamental questions that the 111th Congress must answer related to building this abbreviated approval pathway.

I. THE CURRENT LEGAL FRAMEWORK

The FDCA, §505, provides approval mechanisms for drugs, whereas biological products are licensed under §351 of the PHSA.¹⁷ For drugs reviewed and approved under the FDCA, two abbreviated approval pathways exist. First, manufacturers wishing to bring a generic version of an innovator drug to the market may submit to FDA an abbreviated new drug application (ANDA) under §505(j) of the FDCA. Second, §505(b)(2) permits FDA to approve an NDA based on publicly available literature or on FDA’s earlier finding of safety and efficacy for the innovator product.¹⁸ There is no abbreviated approval pathway for products licensed under §351 of the PHSA.¹⁹

ANDA approval requires an application to show that the generic is therapeutically equivalent to the previously approved drug listed in the FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*.²⁰ Hatch-Waxman created the ANDA to avoid duplicating the innovator’s costly human clinical studies. Instead, §505(j) permits FDA to impute the safety and effectiveness of the innovator product to the generic.

Under § 505(b)(2), an applicant may rely on literature or FDA’s finding of safety and efficacy for FDA approval of a product where the applicant’s product differs

¹⁷ For a complete description of new drug application (NDA) and biologics license application (BLA) approval processes, see FOOD AND DRUG ADMINISTRATION, INNOVATION OR STAGNATION: CHALLENGE AND OPPORTUNITY ON THE CRITICAL PATH TO NEW MEDICAL PRODUCTS, available at: <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html> (last visited Nov. 30, 2008).

¹⁸ *Id.*

¹⁹ Janet Woodcock, Deputy Commissioner, Chief Medical Officer (now, Director, Center for Drug Evaluation and Research (CDER)), FDA, Testimony before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives (May 2, 2007), available at: <http://www.fda.gov/ola/2007/policy05022007.html> (last visited Nov. 30, 2008).

²⁰ Generic drugs are therapeutically equivalent to and substitutable for the innovator product. Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered. Therapeutic equivalents receive an “A” rating in the *Orange Book*. The FDCA, §505(j), requires the ANDA applicant provide information to show that the proposed generic is: (i) pharmaceutically equivalent (has the same active ingredient, dosage form, route of administration, strength, conditions of use); and (ii) is bioequivalent to the listed drug (the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug). 21 U.S.C. §§505(j)(2)(iii)-(v), 505(j)(8)(B).

from the innovator or requires additional clinical study.²¹ A §505(b)(2) application is appropriate even where the applicant has no “right of reference” to the studies supporting its approval and seeks reliance on investigations not conducted by or for the applicant.²² FDA interprets §505(b)(2) to permit reliance, in part, on FDA’s finding of safety and effectiveness for the listed drug.²³

While FDA has the authority to review and approve abbreviated applications under §505(b)(2) for follow-on biological drug products historically regulated as drugs under §505 of the FDCA, FDA asserts that new legislation is required to grant this authority for follow-on products to innovator products licensed under §351 of the PHSA.²⁴

FDA’s interpretation of §505(b)(2) is contested on many grounds. First, innovator biologic manufacturers argue that any §505(b)(2) approval permitting reliance on innovator data constitutes a taking of trade secrets without just compensation in violation of the Fifth Amendment to the Constitution.²⁵ FDA argues that §505(b)(2) applicants, like §505(j) applicants, rely only on FDA’s *determination* of safety and efficacy of an innovator product and not on the innovator’s *data* itself, and points out that the innovator’s data is never publicly disclosed.²⁶ For example, in FDA’s recent §505(b)(2) approval of Omnitrope [somatotropin (rDNA origin)], FDA argues that it did not require use or disclosure of trade secret or commercial confidential information and, therefore, did not violate the takings clause of the Fifth Amendment to the Constitution.²⁷ Most legal commentators agree.²⁸

Legal commentators also make convincing arguments that FDA has the statutory authority to create an abbreviated biologics license application through notice and comment rulemaking or by broadly interpreting the definition of “drug” under the FDCA to include biological drug products, thus making §505(b)(2) a legitimate approval pathway.²⁹ These arguments rely on the deference given by the courts to administrative agencies making reasonable statutory interpretations under the *Chevron* doctrine.³⁰ The availability of the *Chevron* defense, however, is contingent on

²¹ Lester M. Crawford, Commissioner of Food and Drugs, Food and Drug Administration, Testimony at The Law of Biologic Medicine, Senate Judiciary Committee, (Jun. 23, 2004), available at: <http://judiciary.senate.gov/hearings/hearing.cfm?id=1239>.

²² “Right of reference or use” is “the authority to reply upon, and otherwise use, an investigation for the purpose of obtaining approval of an application, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.” 21 C.F.R. §314.3(b).

²³ FDA, RESPONSE TO CITIZEN PETITIONS [hereinafter, FDA Oct. 2003 Response to Citizen Petitions] (Docket Nos. 2001P-0323/CP1 & 5; 2002P-0447/CP1; and 2003P-0408/CP1), 9 (Oct. 14, 2003).

²⁴ Woodcock; Mar. 25, 2007, *supra* note 13; FDA, OMNITROPE [SOMATROPIN (RDNA ORIGIN)] QUESTIONS AND ANSWERS, available at: <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>. (last visited Nov. 30, 2008).

²⁵ See Yoo, John C., *Takings Issues in the Approval of Generic Biologics*. 60 FOOD & DRUG L.J. 34 (2005); Manheim, Bruce et al. *Follow-on Biologics: Ensuring Continued Innovation in the Biotech Industry*, 25 HEALTH AFFAIRS, No. 2, 397 (2006).

²⁶ FDA Oct. 2003 Response to Citizen Petitions, *supra* note 23, at 14.

²⁷ FDA, Response to Citizen Petitions (Pfizer, Genentech, and Biotechnology Industry Organization, Dockets Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355), p. 37-8, n. 70 (May 30, 2006), [hereinafter referred to as May 2006 FDA Response to Citizen Petitions], available at: <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>. (last visited Nov. 30, 2008) (“We also do not find that takings concerns are implicated by reliance on the finding of safety and effectiveness for Genotropin to approve the Omnitrope 505(b)(2) application.”).

²⁸ See Wasson, Andrew, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biological Products*, 2005 DUKE L. & TECH. REV. 4, para. 30 (2005); Yoo. *supra* note 25, at 42; Dudzinski, *supra* note 12, at 220, n. 558; Manheim, *supra* note 25.

²⁹ Dinh, Tam Q., *Potential Pathways for Abbreviated Approval of Generic Biologics Under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77 (2007); Dudzinski, *supra* note 12, at 200-203. (FDA’s approval of Axonex opened the door for the administrative BLA based on Berlex Labs, Inc. v. Food and Drug Administration, 942 F. Supp. 19, 21 (D.D.C. (1996)); Wasson, *supra* note 28 at para. 5.

³⁰ See *Chevron U.S.A. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 104 S.Ct. 2778 (1984).

notice-and-comment rulemaking under the Administrative Procedures Act (APA).³¹ Instead, FDA has made a strategic decision to pursue clear statutory authority in light of strong opposition to its interpretation of §505(b)(2) and the statutory differences between the FDCA and the PHSA. FDA's position places the burden to build an abbreviated approval pathway for follow-on biologics on Congress.

II. THE SCIENTIFIC CHALLENGES TO ABBREVIATED APPROVAL OF FOLLOW-ON BIOLOGICS

A chief argument against abbreviated approval of follow-on biologics is the scientific difficulty in measuring the structural differences, and their effects, between the innovator and the follow-on product. Several factors make this evaluation challenging, including the impact of manufacturing differences between the innovator and follow-on product, the structural characterization of the follow-on product, and immunogenicity concerns.³²

Generally, chemical pharmaceuticals are relatively small molecules, synthesized *in vitro* through well-defined chemical synthesis steps. Therefore, their purification and characterization are relatively straightforward. By contrast, biological drug products are typically produced *in vivo* (in a biological system) and, as a result, are complex and less well understood.³³ The biological product is often a larger molecule. These factors provide opportunities for a follow-on biologic, even where it is designed to be the same as the innovator biological drug product, to differ from the FDA-approved innovator product.³⁴

The manufacturing process of a biological drug product plays a critical role in determining the product's safety, purity and potency. Purification of the biomolecule from the biological system can be difficult.³⁵ The active ingredient in a biological drug product is typically obtained from human or animal blood, or from an eukaryotic cell culture.³⁶ This requires that, during the manufacturing process of a biological drug product, the product is free of pathogenic microorganisms or toxins present, or potentially present, in the biological system from which the biological drug is developed. Methods to purify the biomolecule from harmful agents are available.³⁷ Ongoing purification and testing through each state of the manufacturing process is necessary to eliminate contamination and confirm the molecular parameters (e.g., amino acid sequence, glycosylation patterns,³⁸ mo-

³¹ *Id.* See also 5 U.S.C. §551.

³² See Fed Reg. Vol. 69, No. 157 (Aug. 16, 2004).

³³ David Beir, Testimony at The Law of Biologic Medicine, Senate Judiciary Committee (Jun. 23, 2004), available at: <http://judiciary.senate.gov/hearings/hearing.cfm?id=1239>. (last visited Nov. 30, 2008); Korwek, *supra* note 11, at 257.

³⁴ Sara Radcliff, Biotechnology Industry Organization, Testimony at Public Workshop on the Scientific Considerations Related to Developing Follow-on Protein Products. (Sept. 14, 2004) available at Docket No. 2004N-0355.

³⁵ Beir, *supra* note 33, at 1.

³⁶ The biological drug's active ingredient isolated from cell cultures, eukaryotic or prokaryotic, or from plants, often is genetically engineered, *i.e.* the cell or organism has been engineered with a "foreign" (not normally found in that cell or organism) template for production in the biological system of the biological active ingredient of the biological drug.

³⁷ Radcliff, *supra* note 34, at 3. For example, one approach is to heat-treat the biological sample at some point during purification. That is not always risk-free, as some biomolecules are heat-labile or heat-sensitive. Another approach to inactivate a pathogen might involve the use of a detergent. However, the detergent might affect the desired biomolecule produced in two different biological systems differently. Review of a follow-on biological drug would need to determine whether an appropriate decontamination step was undertaken in the manufacturing process and whether that step affected the structure of the molecule. See Darling, Allan, *A Review: Validation of Biopharmaceutical Purification Processes for Virus Clearance Evaluation*, 21 MOLECULAR BIOLOGY 57 (2002).

³⁸ Glycosylation is a process whereby a carbohydrate molecule is covalently attached inside the organism to a biologic molecule, typically a protein.

lecular heterogeneity, isoform profile, and potency) that determine a product's toxicity, pharmacokinetic profile, pharmacodynamic profile, immunogenicity, and ultimately, its safety and effectiveness.³⁹

Characterizing the differences between a biological drug product and a follow-on product is challenging. Different cell lines or different growing conditions between two products can affect the biomolecule structure in subtle ways. For example, the proportion of the molecule that might have undergone post-synthesis processing,⁴⁰ phosphorylation,⁴¹ or the extent and location of glycosylation might differ. Theoretically, small differences could affect the bioactivity of the biological drug as well as its immunogenic properties.⁴² This requires a competent analysis of the structural similarity of the follow-on biological drug product to the approved biological drug product. Opponents of an abbreviated approval of follow-on biologics argue validly that it is more difficult to achieve identical structure and bioactivity between a follow-on biologic and innovator biologic than between two chemical compounds and that, indeed, this may be impossible with current technology.⁴³

Technology for characterizing differences in purity and structure between an innovator biologic and a follow-on is improving.⁴⁴ Separation methods, used serially, can be part of the characterization of the molecule and succeed at purifying the biologic's active ingredient prior to its further evaluation.⁴⁵ Analytical techniques include filtration, separation by density in various centrifugation approaches, chromatography (multiple affinity columns, layers, and gels, separating on principles including size, electronic charge, relative affinity to column materials are used, each applicable to particular situations), gel electrophoresis, denaturing two-dimensional gel electrophoresis, high performance liquid chromatography (HPLC), reverse phase HPLC, improved protein sequencing, magnetic resonance, and x-ray crystallography.⁴⁶ Significant advancement in these disciplines provide a sound basis for utilizing the fundamental principles and procedures of comparability evaluation for follow-on biologics.⁴⁷

³⁹ Radcliff, *supra* note 34 at 3; *See also*, Gary Walsh, *BIOPHARMACEUTICALS: BIOCHEMISTRY AND BIOTECHNOLOGY* 2nd Ed. (2004); Thillaivinayagalingam, Pranavan & Keshavaraz-Moore, Eli, *Tutorial: Biopharmaceutical Purification Strategies: Bed-height Optimization Can Reduce Cost and Increase Speed of Production*, 27 *GENETIC ENGINEERING & BIOTECHNOLOGY NEWS* 1 (2007).

⁴⁰ There are numerous *in-vivo* post-synthesis processes. These include terminal modifications such as methylation, acetylation, amidation, and other terminus additions. Some molecules are trimmed post-transcription as part of the mechanism of activation of the molecule. *See*, Walsh, C.T., *POST-TRANSLATIONAL MODIFICATIONS OF PROTEINS: EXPANDING NATURE'S INVENTORY*, Roberts and Co. (2007); Schaller, Johann et. al., *HUMAN PLASMA PROTEINS*, Ch. 5, John Wiley and Sons (2008).

⁴¹ Phosphorylation is the addition of a phosphate group to a protein molecule or a small molecule. *Id.*

⁴² Radcliff, *supra* note 34 at 2, n. 5.

⁴³ Generic drugs, approved under §505(j) of the FDCA, must be therapeutically equivalent (same clinical effect and safety profile) and bioequivalent (absence of significant difference in the rate and extent to which the active ingredient or active moiety becomes available when administered as the same dose and under the same conditions) as the reference drug. 21 C.F.R. §320.1(c); 21 U.S.C. §355(j)(8).

⁴⁴ Allen Geoffrey, Ph.D., Chairman, Insmad Inc., Testimony at Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States, hearing before the House Committee on Energy & Commerce (May 2, 2007), *available at*: http://energycommerce.house.gov/cmte_mtgs/110-he-hrg.050207.Allan-testimony.pdf. (last visited Nov. 30, 2008).

⁴⁵ Radcliff, *supra* note 34 at 3.

⁴⁶ Dudzinski, *supra* note 12, at 222-223.

⁴⁷ Ajaz S. Hussain, Testimony at Follow-On Biologics Hearing before the Senate Health, Education, Labor and Pensions (HELP) Committee, (Mar. 8, 2007), *available at*: http://help.senate.gov/Hearings/2007_03_08/2007_03_08.html. (last visited Nov. 30, 2008). *See also*, Allan, *supra* note 37.

An important safety concern for a follow-on biologic is a patient's potentially harmful immunogenic response to the differences between the innovator and follow-on.⁴⁸ However, *in vitro* assays to show antibody responses to the same antigens or the response by blood samples to the molecule are well-developed.⁴⁹

If not completely eliminated, the need for clinical studies may be reduced by the use of the above-mentioned analytical testing methods, as well as *in vitro* and in culture bioassays, comparability studies (pharmacodynamic⁵⁰ or pharmacokinetic), and pre-clinical animal testing.⁵¹ Even under an abbreviated regulatory scheme, FDA will likely require significant newly generated data to review and approve a follow-on biologic.⁵² Study requirements will decline over time as science methodology allows improved characterization, affords predictive tools to evaluate immunogenicity, and as FDA develops its expertise in comparing biological drug products.⁵³ Depending on the complexity of the biologic active ingredient, current scientific understanding would appear to permit a flexible, case-by-case evaluation of the similarity between a follow-on biologic and a reference innovator in an abbreviated product application.⁵⁴

III. ANALYSIS OF FOREIGN REGULATORY & CONGRESSIONAL APPROACHES FOR REVIEW AND APPROVAL OF FOLLOW-ON BIOLOGICS

European and Canadian drug regulators have established abbreviated approval pathways for follow-on biologics. The international progress has placed added pressure on Congress to provide FDA with authority to approve abbreviated applications for follow-on biologics whose reference innovator is licensed under §351 of the PHS. The 110th Congress introduced four legislative proposals to provide FDA with the authority to approve follow-on biologics. The exiting and incoming administrations, as well as key industry groups, are supportive.⁵⁵ These indicators point to a growing

⁴⁸ Immunogenicity is the ability of an antigen to provoke an immune response. Adverse immune responses to a follow-on could generate: 1) a clinical deficiency where the product is intended as replacement for a missing endogenous substance; or 2) hypersensitivity resulting from antibody activity. For example, 150 cases of pure red cell aplasia (PRCA) were identified in Eprex patients due to a manufacturing change. See, Wick, Jeannette Y. et al., *Biogeneric: Potential Benefits and Obstacles*, 21 THE CONSULTANT PHARMACIST 3 (2006); Schellekens, Huub, *Follow-on Biologics: Challenges of the "Next Generation,"* NEPHROLOGY DIALYSIS TRANSPLANTATION, Vol. 20 (Supp.4), p. iv31-36 (2005); Mathieu, Mark, BIOLOGICS DEVELOPMENT: A REGULATORY OVERVIEW, 3d. Ed., 91 (2004).

⁴⁹ See Mathieu, *supra* note 48.

⁵⁰ In a pharmacodynamic study, the effect of the drug on the body and its mechanism of action are studied.

⁵¹ In a pharmacokinetic study, a number of people receive the innovator drug and the follow-on chemical and the amount of drug available in the body at different point is compared. An *in vitro* assay of the activity of the drug in a sample taken from the human study participant (e.g., an antibody's binding ability) is also tested. See, e.g., CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER), FDA, FDA GUIDANCE CONCERNING DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS, [hereinafter 1996 FDA Guidance] (1996), available at: <http://www.fda.gov/cder/guidance/compare.htm>. (last visited Nov. 30, 2008).

⁵² Combe, Christian, et al. *Biosimilar Epoetins: An Analysis of Based on Recently Implemented Agency Guidelines on Comparability of Biopharmaceutical Proteins*. 25 PHARMACOTHERAPY (2005).

⁵³ FDA has the scientific expertise to compare biological drugs products and began describing how a manufacturer could demonstrate comparability as early as 1996. See, 1996 FDA Guidance.

⁵⁴ Gitter, *supra* note 7.

⁵⁵ OFFICE OF MANAGEMENT AND BUDGET, *THE BUDGET OF THE UNITED STATES GOVERNMENT FOR FISCAL YEAR 2009: THE DEPARTMENT OF HEALTH AND HUMAN SERVICES*, at 65, available at: <http://www.whitehouse.gov/omb/budget/fy2009/pdf/budget/hhs.pdf>. (last visited Nov. 30, 2008). The Barack Obama administration will likely follow Democratic legislators, such as Sen. Edward M. Kennedy, Chairman of the Senate HELP Committee and Rep. Henry A. Waxman, Chairman of House Energy & Commerce, both of whom are sponsors of follow-on legislation. Industry interest is discussed below.

consensus that an abbreviated approval pathway for follow-on biologics is necessary and imminent. This section provides an in-depth analysis of the European and Canadian follow-on frameworks and the 110th Congress' proposals.

A. *European Medicines Evaluation Agency (EMA) Guidance on the Regulation of Biosimilars*

In June 2003, the European Commission established a regulatory framework for similar biological medicinal products, or "biosimilars."⁵⁶ The statutory framework modified the EU's medical products statute to permit review of abbreviated applications for biosimilars through a case-by-case approach.⁵⁷ In December 2003, EMA published two guidance documents clarifying the requirements of biosimilar applications. Biosimilar applications require: 1) a showing of pharmaceutical, chemical and bioequivalence; 2) bioavailability data; and 3) clinical data.⁵⁸ Both guidance documents provide regulatory flexibility to require more extensive data for biosimilar applications that seek approval of more complex biomolecule structures.⁵⁹ The EMA framework forbids reference by the EMA to the innovator's file in evaluating a biosimilar application.⁶⁰ The EMA framework extends eight years of innovator exclusivity during which no biosimilar application can be accepted and an additional two years during which no biosimilar application may be approved.⁶¹ In addition to these 10 years of exclusivity, the EMA approach extends an additional year of exclusivity to an innovator if a new therapeutic indication for the product is approved.⁶²

Two EMA guidance documents adopted in February 2006 give direction to industry on how to study comparability of biological drug products and report the resulting comparability data on quality, safety and efficacy.⁶³ For non-clinical and clinical data, the EMA suggests *in vitro* assays and *in vivo* animal studies to evaluate a biosimilar's pharmacodynamic (PD) effect, repeat-dose toxicity, and other safety concerns.⁶⁴ The EMA guidance also suggests that applications include: 1) comparative pharmacokinetic (PK) studies between the reference product and the biosimilar; 2) PD studies with markers selected based on their relevance to demonstrating therapeutic effect; or 3) confirmatory PK/PD in cases where the PD properties of the reference product, the dose/exposure and response/efficacy relationships, are well-characterized and at least one PD marker is a surrogate

⁵⁶ The use of the term "biosimilar" indicates that EMA also does not equate such products with generics. Moran, Nuala, *Sandoz Files Suit Against FDA for Non-Action on Omnitrope*. 16 *BIO WORLD TODAY*, No. 182, 6 (2005).

⁵⁷ European Commissioner Directive, 2003/63/EC, Art. 10 (2004).

⁵⁸ Sponsors are required to conduct clinical trial to evaluate immunogenicity unless immunogenicity concerns can be addressed by less demanding analytical means. EMA GUIDELINE ON COMPARABILITY OF MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL STUDIED [hereinafter EMA Guidance 1], at 5-6 (2006), available at: <http://www.emea.europa.eu/pdfs/human/biosimilar/3277505en.pdf>. (last visited Nov. 30, 2008); See EMA GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: QUALITY ISSUES [hereinafter EMA Guidance 2], at 3 (2006), available at: <http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>. (last visited Nov. 30, 2008).

⁵⁹ EMA Guidance 1, *supra* note 58, at 7.

⁶⁰ *Id.*

⁶¹ Beier, *supra* note 33 at 9.

⁶² EMA Guidance 1, *supra* note 58, at 7.

⁶³ EMA Guidance 2, *supra* note 58.

⁶⁴ EMA Guidance 1, *supra* note 58, at 4.

endpoint for efficacy.⁶⁵ For efficacy, the guidance states that “usually, comparative clinical trials will be necessary to demonstrate clinical comparability between the similar biologic and the reference medicinal product.”⁶⁶ EMEA guidance contemplates a biosimilar applicant’s reliance, to some degree, on innovator product data to reduce the quantity of data required for biosimilar approval.⁶⁷ In April 2006, EMEA approved Sandoz’s application for the “biosimilar” Omnitrope, marking the first follow-on biologic approval under the EMEA’s biosimilar guidance.⁶⁸ EMEA’s case-by-case approach is, in many respects, the model for Canada’s follow-on framework and also serves as guidance to Congress in legislating in this area.

B. Health Canada (HC) Guidance on Regulation of Subsequent Entry Biologics

In January 2008, Health Canada (HC) issued guidance outlining data requirements for a subsequent entry biologic (SEB).⁶⁹ Applicants must demonstrate similarity to the safety, quality and efficacy of a reference innovator product for its approved indications.⁷⁰ The guidance is a legally non-binding first step to be followed by regulations that will establish a comprehensive, legally-binding SEB regulatory framework.⁷¹

The HC guidance describes the type of data typically necessary for SEB approval, including: 1) a complete chemistry and manufacturing data package; 2) a rationale for the choice of the innovator biologic as the comparator and extensive published information on its safety and efficacy; 3) sufficient characterization information to demonstrate both chemical and biological comparability of the SEB to the innovator; 4) sufficient comparative animal toxicity and toxicological data; 5) pharmacodynamic data to demonstrate comparable bioactivity based on parameters or surrogate markers that are clinically relevant and validated; 6) pharmacokinetic data to demonstrate comparable bioavailability of the SEB to the innovator product based on suitable validated pharmacokinetic parameters; 7) data characterizing the immunogenic profile of the SEB in humans and its potential impact on safety and efficacy; and 8) a clinical package which demonstrates the safety and efficacy of the SEB, including comparative studies between the SEB and innovator products and data for the innovator product in the public domain.⁷² The guidance explains that additional SEB data needs will

⁶⁵ *Id.* at 5-6.

⁶⁶ *Id.*

⁶⁷ EMEA Guidance 2, *supra* note 58, at 3. (“The similar biological medicinal product may refer to the non-clinical and clinical data previously generated with the reference product, however, non-clinical and clinical data will normally be required.”)

⁶⁸ SANDOZ Media Release, *Sandoz Receives European Commission Marketing Authorization for Omnitrope*, 1 (Apr. 18, 2006), available at: <http://www.sandoz.com/site/en/index.shtml> (last visited Nov. 30, 2008).

⁶⁹ The term “subsequent entry biologic (SEB)” describes a biologic product that would be similar to and would enter the market subsequent to an approved innovator biologic. The guidance states that SEB is used in lieu of “biogeneric” to distinguish the regulatory process and standards for generic drugs. MINISTER OF HEALTH: HEALTH PRODUCTS, FOOD AND DRUG BRANCH, DRAFT GUIDANCE FOR SPONSORS: INFORMATION AND SUBMISSION REQUIREMENTS FOR SUBSEQUENT ENTRY BIOLOGICS (SEBs) [hereinafter, Canadian SEB Guidance], p. ii, (2008), available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/003-2008-seb-pbu_e.pdf. (last visited Nov. 30, 2008).

⁷⁰ Canadian SEB Guidance, *supra* note 69, at 14.

⁷¹ “Guidance documents are administrative instruments *not having force of law* and, as such, allow for *flexibility* in approach.” Canadian SEB Guidance, *supra* note 69, at 2, 6.

⁷² HEALTH CANADA, FACT SHEET: SUBSEQUENT ENTRY BIOLOGICS IN CANADA, (2008), available at: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/fs-fi_seb-pbu_07-2006_e.html. (last visited Nov. 30, 2008).

be determined case-by-case.⁷³ Where the weight of evidence submitted to support an SEB approval must be clinical trial data, HC's guidance advises against that applicant utilizing the SEB approval pathway.⁷⁴

Under the HC framework, SEB product labeling must be different from the reference biological drug product.⁷⁵ Finally, the guidance explains HC's intention to harmonize its definitions, terminology, and guidance documents with the international regulatory bodies.⁷⁶ The HC guidance does not provide any marketing exclusivity for the innovator or SEB.⁷⁷ In sum, HC's SEB guidance provides a flexible, case-by-case approach to the review and approval of follow-on biologics. This guidance, however, will be followed by regulations with the force and effect of law.

C. *The Access to Life-Saving Medicine Act (H.R. 1038)*

Representative Henry A. Waxman (D-CA), a chief co-sponsor of the original Hatch-Waxman amendments to the FDCA and now Chairman of the House Energy & Commerce Committee,⁷⁸ introduced H.R. 1038, the "Access to Life-Saving Medicine Act," which would amend the PHSA to permit approval of abbreviated biological product applications for products that contain the same or similar active ingredients as a previously-licensed biological reference product.⁷⁹ This bill allows for applications to FDA for products that are comparable to⁸⁰ or interchangeable with⁸¹ the reference product.

H.R. 1038 would not mandate clinical trials. It would require a follow-on applicant to submit for approval: 1) data demonstrating that the product is comparable to or interchangeable with the reference product; 2) data demonstrating that the follow-on and the reference product contain highly similar principal molecular

⁷³ "Factors to be considered in granting indications for an SEB application, while on a case-by-case basis, would depend on the product, the level of reliance on the reference biologic product in the development programme for the product, the demonstrated level of similarity between the SEB and the reference biologic product, and the availability of postmarket information." Canadian SEB Guidance, *supra* note 69, at 6.

⁷⁴ "A final determination of comparability/similarity can be based on a *combination* of analytical testing, biological assays, and non-clinical and clinical data. However, to be considered a SEB, the *weight* of evidence should be provided the analytical and biological characterization. In situations where: 1) the analytical procedures used are not sufficient to discern relevant difference that can impact the safety and efficacy of the product; or 2) the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the SEB and the reference biologic product are likely to be observed; therefore, non-clinical and clinical studies are expected to contribute significantly to a potential determination of comparability/similarity, the regulatory pathway for SEBs *may not be appropriate*." *Id.* at 13.

⁷⁵ *Id.* at 17.

⁷⁶ *Id.*

⁷⁷ While the guidance document does not specify, Canadian law provides eight years of data exclusivity for innovator products in addition to patent protection. Canadian *Food and Drug Regulations*, § s.C.08.004.1 (Oct. 2006); CANADIAN GENERIC PHARMACEUTICAL ASSOCIATION, "Generic Drug Makers Challenge Federal Data Exclusivity Rules," *available at*: http://www.canadiangenerics.ca/en/advocacy/data_exclusivity.asp (last visited Nov. 30, 2008)

⁷⁸ ASSOCIATED PRESS, *Waxman Topples Dingell for Key Panel Chair*, (Nov. 20, 2008), *available at*: <http://www.msnbc.msn.com/id/27820508/> (last visited Nov. 30, 2008).

⁷⁹ H.R. 1038, 110th Cong. (2007); *See also* S. 623, 110th Congress (2007), (Senate companion of H.R. 1038).

⁸⁰ *Id.* §2(a)(4), defining comparability as "the absence of clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product" supported by data from 1) chemical, physical, and biological assay and other non-clinical studies or 2) data from any necessary clinical studies."

⁸¹ *Id.* §2(a)(4), defining interchangeability as "comparable to a reference product" and "expected to produce the same clinical result as the reference product in any given patient."

structural features; 3) data demonstrating that the biological product and the reference product utilize the same mechanism of action for the condition of use prescribed, recommended or suggested in the proposed labeling; 4) information to show that the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product; 5) information to show that the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product; and 6) data showing the facility producing the biological product meets standards to ensure safety, purity, and potency.⁸² Under H.R. 1038, the applicant may also submit any publicly available data regarding FDA's previous determination that the reference product is safe, pure and potent.

H.R. 1038 gives FDA authority to make interchangeability determinations for a comparable product and the reference product based on whether a product can be expected to produce the same clinical result as the reference product in any given patient.⁸³ The bill requires FDA to issue guidance regarding standards and requirements for interchangeability within one year of enactment. H.R. 1038 provides 180 days of market exclusivity to the first marketed product found to be interchangeable with a reference product.⁸⁴ Not only may FDA not approve a second follow-on product in this time period, but the innovator may not market a rebranded form of its reference product directly or indirectly.⁸⁵ This bill provides no innovator exclusivity.

Under H.R. 1038, FDA is prohibited from mandating post-market studies as a condition of approval.⁸⁶ The bill gives FDA the discretion to designate an official name for a comparable biological product.⁸⁷ The bill requires FDA to promulgate regulations for review and approval of comparable biological product applications.⁸⁸ The bill also provides for a process to govern patent infringement claims against an applicant or prospective applicant for a comparable biological product license.

Finally, H.R. 1038 attempts to remedy the delay in generic drug approval often caused by the submission of citizen petitions. The bill requires that FDA not delay approval of an application because of a citizen petition unless the delay is necessary to protect the public health.⁸⁹

D. *The Patient Protection and Innovative Biologic Medicines Act of 2007 (H.R. 1956)*

H.R. 1956, "The Patient Protection and Innovative Biologic Medicines Act of 2007," chiefly sponsored by Representative Jay Inslee (R-WA), would amend the PHS Act to give FDA the authority to approve "similar biological products" of "biotechnology-derived therapeutic biological product[s]" licensed under §351

⁸² *Id.* §3, §(k)(1).

⁸³ *Id.* §4(B)-(C).

⁸⁴ *Id.* §10(A)(i).

⁸⁵ *Id.* §10(A)-(B). §(B) defines a "rebranded interchangeable product" as "any rebranded interchangeable version of the reference product involved that the holder of the biological license approved under section (a) for that reference product seeks to commence marketing, selling, or distributing, directly or indirectly." This provision was included to stem the tide of authorized generic marketing in the biologics realm. See Section IV(F) below.

⁸⁶ *Id.* §5.

⁸⁷ *Id.* §6.

⁸⁸ *Id.*

⁸⁹ *Id.* §18(A)(i)(I). See also, §18(A)-(B) ("Consideration of a petition shall be separate and apart from the review and approval of the application."). The Food and Drug Administration Amendments Act (FDAAA) of 2007 includes a similar provision. P.L. 110-85, §914, 121 Stat. §953-957.

PHSA.⁹⁰ Under this proposal, FDA can approve follow-on applications where: 1) the applicant demonstrates that the similar biological product conforms with a final product class-specific guidance and the data required by this guidance; 2) the facility in which the similar biological product is made meets standards to assure safety, purity, and potency; and 3) the applicant consents to a facility inspection.⁹¹ Approvals are limited to the reference product's approved indications.

H.R. 1956 prohibits FDA from designating a similar biological product as therapeutically equivalent to the reference product.⁹² The bill would give a reference product 14 years of data exclusivity, which may be extended to 15 years if FDA approves a supplemental application for a new indication during the first 12 years subsequent to approval.⁹³ FDA may not review a follow-on application for 12 years following approval of the reference product.

H.R. 1956 would foreclose any other statutory provision by which FDA may approve a biological product as similar or the same as a reference product.⁹⁴ Before FDA could approve a follow-on product, FDA would be requested to issue product/class-specific guidance detailing the type and quantity of data required for a follow-on application. The bill mandates that any product-class guidance requires certain data elements, including: 1) data demonstrating the consistency and robustness of the manufacturing process for an active ingredient and finished formulation; 2) data regarding the stability, compatibility, and integrity of the active ingredient; 3) data from physical, chemical, and biological assays that fully characterize the similar biological product in comparison with the reference product; 4) data from comparative non-clinical studies demonstrating that the similar biological product and the reference product have similar profiles in terms of pharmacokinetics, pharmacodynamics, toxicity, immunogenicity, and other relevant factors; 5) data from comparative clinical trials of sufficient size and duration to demonstrate that the similar biological product and the reference product have similar profiles in terms of safety, purity, and potency; and 6) a plan for post-marketing safety monitoring, including clinical trials, antibody testing and other immunogenicity testing, patient registries, and other surveillance measures to monitor the safety and risk-benefit balance of the similar biological product.⁹⁵

The bill creates an FDA Similar Biological Products Advisory Committee⁹⁶ and requires FDA designate an official name for any biotechnology-derived therapeutic protein that lacks a unique name adopted by the United States Adopted Names Council (USAN).⁹⁷ The bill also requires FDA to maintain the confidentiality of information submitted in an application under this section for a biological product in the same manner as FDA maintains the confidentiality of drugs approved under section §505 of the FDCA.⁹⁸ H.R. 1956 would deem misbranded any follow-on product labeling lacking: 1) a unique and/or different name from the innovator product; 2) a warning against substitution; and 3) the product's proprietary or proper name.⁹⁹

⁹⁰ The Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. §2(A) (2007).

⁹¹ *Id.* §2, §(k)(2)(B)(i-iii).

⁹² *Id.* §2, §(k)(2)(D). *See also*, §4: FDA must report to Congress every two years on "whether it is feasible, in the current state of scientific and technical knowledge, to make therapeutic equivalence determinations for similar biological products" and "if so, the statutory criteria that should govern such determination."

⁹³ *Id.* §2, §(k)(3)(A-C).

⁹⁴ *Id.* §2, §(k)(3)(D).

⁹⁵ *Id.* §2, §(k)(5).

⁹⁶ *Id.* §2, §(k)(7).

⁹⁷ *Id.* §2, §(k)(1)(A-B).

⁹⁸ *Id.* §2(b).

⁹⁹ *Id.* §3(b).

E. *The Biologics Price Competition and Innovation Act of 2007 (S. 1695)*

S. 1695, the “Biologics Price Competition and Innovation Act of 2007,” introduced by Senator Edward M. Kennedy (D-MA), would amend the PHSA to permit FDA licensure of abbreviated applications for a biological product that is “biosimilar”¹⁰⁰ to or interchangeable¹⁰¹ with a reference product.

An abbreviated application under S. 1695 must include information demonstrating that the biological product is biosimilar to the reference product based on the following data: 1) analytical studies showing high similarity (notwithstanding minor differences in clinically inactive components); 2) animal studies; and 3) clinical studies (including assessment of immunogenicity, pharmacodynamics or pharmacokinetics).¹⁰² An applicant must show that: 1) the biological product and the reference product share the same mechanism of action; 2) the conditions of use in the proposed labeling have been previously approved for the reference product; 3) the route of administration, the dosage form, and the strength of the biological product are the same as the reference product; and 4) the facility where the biological is to be made meets standards to ensure safety, purity, and potency.¹⁰³ This bill includes a provision that gives FDA discretion to require clinical trials.¹⁰⁴ The applicant may submit publicly available information regarding FDA’s previous determination that the reference product is safe, pure, and potent, or any publicly-available information about the reference product itself.¹⁰⁵

FDA may find the biological interchangeable with the reference product if the application is sufficient to show biosimilarity and can be expected to produce the same clinical result as the reference product in any given patient.¹⁰⁶ S. 1695 includes a balancing provision for interchangeability that requires that “the risk in terms of safety or diminished efficacy of alternating or switching between the products is not greater than the risk of using the reference product without switching.”¹⁰⁷

S. 1695 provides 12 years of marketing exclusivity for the reference product¹⁰⁸ and one year of exclusivity for the first interchangeable product.¹⁰⁹ The bill gives FDA discretion to issue guidance documents regarding the process for the submission of applications for a biological product. This guidance can be general or specific; however, the process outlined in the bill requires giving the public an opportunity to comment on a specific guidance.¹¹⁰ This bill includes strong provisions governing

¹⁰⁰ The Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. §2(b), §(k)(2)(I)(BB) (2007). (Defining biosimilarity as “no clinically meaningful difference between the biological product and the reference product in terms of the safety, purity and potency of the product.”).

¹⁰¹ *Id.* §2(b), (interchangeability is where “the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.”).

¹⁰² *Id.* §2(a)(2), §(k)(2)(I)(BB) (2007), The bill explicitly states that the clinical studies are to be “designed to avoid needlessly duplicative or unethical clinical testing.”

¹⁰³ *Id.* §2, §(k)(2)(A)(i)(II-V).

¹⁰⁴ *Id.* §2(k)(2)(A)(i)(ii).

¹⁰⁵ *Id.* §2(k)(2)(A)(iii).

¹⁰⁶ *Id.* §2(k)(4)(A)(i)(ii).

¹⁰⁷ *Id.* §2(k)(4)(B).

¹⁰⁸ *Id.* §2(k)(7).

¹⁰⁹ *Id.* §2(k)(6)(A).

¹¹⁰ *Id.* §2(k)(8). The text of the legislation references the guidance provisions located at 701(h) of the FDCA. *See also, Id.* §(k)(8)(E). While the bill does not require product class-specific guidance, if FDA issues product-class guidance, it must include the criteria FDA will use to determine: 1) if the biologic product is highly similar to the reference product in that class; and 2) whether a biological product meets standards for interchangeability. *See Id.* §(k)(8)(E). FDA may determine “science and experience, as of the date of such guidance, with respect to a product or product class (not including any recombinant protein) does not allow approval of an application for a license as provided under this subsection for such product or product class.” *Id.* §(k)(5)(C).

the information exchange between the applicant and the reference product related to patent infringement actions,¹¹¹ extends the application of risk evaluation and mitigation strategies (enacted under the FDAAA of 2007¹¹² to biological applications submitted under this section, and authorizes FDA to collect user-fees for expedited application review.¹¹³

The bill would require that any follow-on application be submitted under §351 PHSa except where the biological product is part of a class of products where an approved application under §505 FDCA exists at enactment or where an application has been submitted to FDA under §505 within 10 years of enactment.¹¹⁴ The bill restricts approval under §505 of the FDCA where there is another biological product approved under §351 of the PHSa that could be a reference product for the application. Any biologic approved under §505 of the FDCA will be deemed licensed under §351 of the PHSa 10 years after enactment.¹¹⁵

F. *The Pathway for Biosimilars Act (H.R. 5629)*

H.R. 5629, “The Pathway for Biosimilars Act,” introduced by Representative Anna G. Eshoo (D-CA), would create an abbreviated pathway for biosimilars¹¹⁶ under the PHSa.¹¹⁷ Many provisions of H.R. 5629 are identical to S. 1695. These two bills share identical requirements for data sources, an applicant’s approval threshold, discretionary clinical trials,¹¹⁸ risk evaluation and mitigation strategies (REMS),¹¹⁹ innovator and interchangeable marketing exclusivity,¹²⁰ guidance documents,¹²¹ patent dispute resolution,¹²² user fees,¹²³ and a balancing test for interchangeability determinations.¹²⁴

H.R. 5629, however, differs from S. 1695 in important respects. H.R. 5629 requires an applicant to submit an immunogenicity assessment whenever FDA has published a proscribed final guidance document after public comment.¹²⁵ In addition to the baseline exclusivity provided in S. 1695, H.R. 5629 gives the reference license holder two years additional marketing exclusivity if they receive FDA approval of a supplemental application for a “medically significant new indication.” An additional six months exclusivity is offered for an applicant who responds appropriately to a written request for pediatric studies under FDAAA -reauthorized Best Pharmaceuticals for Children Act (BPCA).¹²⁶ Such additional exclusivity could bring an innovator’s total exclusivity period to 12.5 or 14.5 years.

H.R. 5629 includes a unique provision to encourage the issuance of guidance documents, permitting petitions for FDA to issue final guidance on any product

¹¹¹ *Id.* §2(k)(5)(C).

¹¹² FDAAA, P.L. 110-85, §901 *et seq.*, 121 Stat. §926-939.

¹¹³ *Id.* §2(f)(1)(C).

¹¹⁴ *Id.* §2(e).

¹¹⁵ *Id.* §2(e)(4).

¹¹⁶ The Pathway for Biosimilars Act, H.R. 5629, 110th Cong. §101 (2008) (defining “biosimilars” as “demonstrated to be highly similar to a reference licensed product”).

¹¹⁷ *Id.*

¹¹⁸ *Id.*

¹¹⁹ See FDAAA of 2007, P.L. 110-85, §901, *et seq.*, 121 Stat. §926.

¹²⁰ H.R. 5629, *supra*, at §101(k)(6)(7).

¹²¹ *Id.* §(k)(9)(C)(i); See also §701(h), FDCA, 21 U.S.C. §371.

¹²² *Id.* §(l).

¹²³ *Id.* §(2)(f)(4).

¹²⁴ *Id.* §(2)(e).

¹²⁵ *Id.* §101 (k)(2)(B)(ii)(I). FDA must advise that “it is feasible in the current state of scientific knowledge to make determinations on immunogenicity with respect to products in the product class to which the biological product belongs.”

¹²⁶ *Id.* §(k)(8)(i) and (ii), see also FDAAA, Title IV, 121 Stat. 876.

or class where a reference product was licensed more than seven years prior to enactment. If such a petition is made, FDA must issue final guidance with respect to that product class within two years.¹²⁷ In addition, H.R. 5629 requires that the labeling and packaging of a biosimilar product bear a name that uniquely identifies the biological product and distinguishes it from the reference product and any other biological processed licensed under this statute.

G. Comparison of Congressional Approaches for Review and Approval of Follow-on Biologics

TABLE 1: COMPARISON OF LEGISLATIVE PROPOSALS IN THE 110TH CONGRESS

Elements Essential to a Follow-On Approval Pathway	H.R. 1038	H.R. 1956	S. 1695	H.R. 5629
Guidance or Rulemaking	Guidance for reviewers and immunogenicity; rulemaking for remainder.	Guidance.	Guidance.	Guidance.
Scope of Eligible Products	All BLAs may serve as reference product; no product distinctions. FDA may, by guidance, explain that science does not support particular application type.	All BLAs may serve as reference product; no product distinctions. FDA may, by guidance, explain that science does not support particular application type.	All BLAs may serve as reference product; no product distinctions. FDA may, by guidance, explain that science does not support particular application type.	All BLAs may serve as reference product; no product distinctions. FDA may, by guidance, explain that science does not support particular application type.
Interchangeability Determinations	Yes.	Explicitly prohibited.	Yes.	Yes.
Clinical Studies	Discretionary.	Required.	Discretionary.	Discretionary.
Exclusivity for 1 st Interchangeable	180 days.	None.	1 year.	1 year.
Exclusivity for Innovator/Reference Product	None.	15 years.	12 years.	12 years.
Additional Exclusivity	None.	1 year for new clinically significant indication.	None.	2 years for new indication; 6 months for pediatric studies.
505(b)(2) Ratification	No.	No.	No.	No.

¹²⁷ *Id.* §(k)(9)(D).

Elements Essential to a Follow-On Approval Pathway	H.R. 1038	H.R. 1956	S. 1695	H.R. 5629
Uniformity for § 505(b)(2) Approvals	No.	Closes § 505(b)(2) as a follow-on approval pathway.	Permits § 505(b)(2) to function as a follow-on pathway for 10 years, after which all further follow-on applications must come under § 351 PHSA.	Permits § 505(b)(2) to function as a follow-on pathway for 10 years, after which all further follow-on applications must come under § 351 PHSA.
Patent Regime	Yes.	No.	Yes.	Yes.
Risk Evaluation and Mitigation Strategy (REMS)	Postmarketing, but not REMS.	Postmarketing, robust, not REMS.	Yes.	Yes.
Funding	No.	No.	User Fees and Appropriations.	User Fees.
Citizen Petitions	Yes.	No.	No.	No.
Naming	Official Name where necessary.	Official name or USAN.	None.	Unique.
Labeling	No.	Must specify no interchangeable.	None.	REMS.
Similar Biologics Advisory Committee	No.	Yes.	No.	No.

IV. ESSENTIAL COMPONENTS TO AN ABBREVIATED APPROVAL PATHWAY FOR FOLLOW-ON BIOLOGICS

Any legislation in the 111th Congress to give FDA authority to approve follow-on biologics under §351 of the PHSA must determine: 1) if FDA should be granted authority to develop an abbreviated pathway through rulemaking or guidance; 2) if human clinical trials should be mandatory or discretionary; 3) the feasibility of interchangeability¹²⁸ determinations in light of patient safety concerns; 4) the duration of marketing exclusivity, if any, for associated products; 5) which products are eligible for follow-on approval; and 6) the degree to which uniformity is achievable between the FDCA and PHSA. This section analyzes each of these issues and brings administrative law and public policy principles to bear on the choices Congress must make to construct an abbreviated pathway.

A. Rulemaking or Guidance: Determining a Path to the Pathway

Congress must determine whether FDA's forthcoming authority will mature into a regulatory framework by traditional notice and comment rulemaking or by guidance document. There is a debate among academics, Congress, and the judi-

¹²⁸ The degree to which the follow-on product may be substituted for the innovator.

ciary regarding the legitimacy of making administrative policy through guidance documents that circumvent the protections built into the APA.¹²⁹

Administrative regulations and guidance documents are fundamentally different. Rules have several distinct characteristics: 1) they have the force and effect of law; 2) they are grounded in a grant of legislative power by Congress; and 3) they are legally binding on both private parties and the government itself.¹³⁰ Rulemaking is governed by §553 of the APA, which requires three steps: 1) the public must be given notice of the proposed rulemaking;¹³¹ 2) the public must have an opportunity to comment on the proposed rule; and 3) an agency must consider the comments and incorporate in the final rule a “concise general statement” of the rules’ basis and purpose.¹³²

The APA does not define the term “guidance,” however, APA §553(b) exempts from its notice and comment requirements: 1) interpretive rules, 2) general statements of policy, or (iii) rules of agency organization, procedure, or practice.¹³³ A guidance document is typically considered a statement of policy lacking force and effect of law and issued without APA notice-and-comment.¹³⁴ FDA regulations do define guidance as a statement of policy, however, the regulations add a unique development process to the standard guidance.¹³⁵ FDA good guidance regulations outline a “hybrid” guidance process that includes the notice-and-comment feature of APA rulemaking, but results in a document lacking the force and effect of law.¹³⁶

It is critical that Congress be explicit as to whether follow-on legislation calls for guidance, “hybrid” guidance, or rulemaking. Any ambiguity on this point will require the court’s application of the legal effects test articulated in *Cement Kiln*

¹²⁹ Mendelson, Nina A., *Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L. REV. 397, 401 (2007); Stein, Mitchell, 1 ADMINISTRATIVE LAW, §101, 1-5 (2006).

¹³⁰ The APA defines a rule as “the whole or a part of an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency.” 5 U.S.C. §551(4). Rulemaking is “any agency process for formulating, amending, or repealing a rule.” 5 U.S.C. §551 (5). *See also*, Chrysler Corp. v. Brown, 441 U.S. 281, 302 (1979).

¹³¹ APA requires publication in the *Federal Register* reference to the legal authority under which the rule is proposed the terms or a description of the substance of the rule must be published as well. *See, generally*, 5 U.S.C. §553.

¹³² *Id.* The APA creates two procedural models for substantive rulemaking: informal (often called “notice and comment rulemaking”) and formal (often called “on the record”). Cass, Ronald A. et al., ADMINISTRATIVE LAW: CASES AND MATERIALS, 5th Ed., 337 (2006). *See also* Vermont Yankee Nuclear Power Corp. v. Natural Resource Defense Council, Inc. 435 U.S. 519 (1979); Spring Corp. v. FCC, 315 F.3d 369 (D.C. Cir. (2003)); *Doe v. Rumsfeld*, 341 F. Supp. 2d 1 (D.C. Cir. (2004)).

¹³³ 5 U.S.C. §553(b). Legal commentators debate whether guidance documents are interpretive rules or general statements of agency policy. Anthony, Robert A., *Interpretive Rules, Policy Statements, Guidances, Manuals and the Like—Should Federal Agencies Use Them to Bind the Public?*, 41 DUKE L.J. 1311 (1992).

¹³⁴ *General Motors Corp. v. Ruckelshaus*, 742 F.2d 1561, 1565 (D.C. Cir. (1984)); *see also* Anthony, *supra*, (“the agency should be able to treat it [interpretive rules] as binding since the agency is, by definition, merely restating preexisting legal requirements. However, agencies should not treat other agency documents adopted without notice and comment, such as policy statements and *guidance*, as binding since they have not been validly ‘enacted’ into law and would, if treated as binding, create new law.”).

¹³⁵ FDA regulations define a guidance document as “documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency’s interpretation of or policy on a regulatory issue.” 21 CFR §10.115(b).

¹³⁶ These regulations specify that guidance documents “do not establish legally enforceable rights or responsibilities.” 21 CFR §10.115(d). FDA good guidance practices differentiate between a Level 1 (initial interpretation of a statute or regulation, a major change in such an interpretation, or relates to a complex or highly controversial matter) and Level 2 (existing practices or minor changes in interpretation) guidance. Only Level 1 guidance documents are “hybrid” and require notice-and-comment.

Recycling Coalition v. EPA if a *facial* or *as applied* challenge to FDA guidance occurs.¹³⁷ In *Cement Kiln*, the court reviewed whether a Environmental Protection Agency (EPA) guidance was mere guidance without the force or effect of law or a regulation, holding that the court had jurisdiction over a guidance only if it “binds private parties or the agency itself with the ‘force of law.’”¹³⁸ The court held that the guidance at issue in *Cement Kiln* did not impose legally binding requirements and, therefore, was not a regulation.¹³⁹

On its face, the guidance described in proposed legislation likewise fails the legal effects test because it would not have the force and effect of law.¹⁴⁰ Aside from H.R. 1038, which requires both guidance and APA rulemaking, these proposals reflect a “hybrid” guidance approach similar to that specified in FDA’s good guidance regulations.¹⁴¹ For example, H.R. 1956 uses the term guidance, but requires the guidance to be subject to notice and comment and publication in the *Federal Register*.¹⁴² S. 1695 and H.R. 5629 also require notice and comment for any guidance issued. Further, S. 1695 and H.R. 5629’s reference to §701(h) of the FDCA indicates the drafter’s intent that the guidance not have the force and effect of law.¹⁴³

The “hybrid” guidance approach for developing the follow-on pathway is appealing because it will arguably provide FDA with flexibility to adapt to rapidly changing science.¹⁴⁴ In *Cement Kiln*, EPA justified its need for guidance over regulation by arguing that “risk assessors must have the *flexibility* to make adjustments for the specific conditions” present when deciding on permits for facilities that burn hazardous waste as fuel and they “should be free to use the most recent [assessment tools] available rather than be limited to those that may be out-of-date because a regulation has not been revised.”¹⁴⁵

Consensus is growing that a hybrid approach, similar to FDA’s current good guidance practices, balances the need for flexibility, efficiency, and public input. The need for flexibility in reviewing follow-on protein product applications has driven both the Europeans and the Canadians to develop their follow-on pathway by issuing guidance documents. FDA also prefers “a predictable and public product-class

¹³⁷ *Cement Kiln Recycling Coalition v. EPA*, 493 F.3d 207, 227 (D.C. Cir. (2007)) applied a three-factor legal effects test to determine if an agency’s guidance was actually rulemaking. The court considered: 1) the agency’s own characterization of the action; 2) whether the action was published in the *Federal Register* or Code of Federal Regulations; and 3) whether the action has binding effects on private parties or on the agency. The court summarized, “nonetheless, we have held that these criteria merely ‘serve to illuminate the third, for the ultimate focus of the inquiry is whether the agency action partakes of the fundamental characteristic of a regulation, *i.e.*, that it has the force of law.’” *See, also United Technologies Corp. v. EPA*, 821 F.2d 714 (D.C. Cir. (1987)).

¹³⁸ 493 F.3d at 227.

¹³⁹ *Id.*

¹⁴⁰ It is possible that, as applied, FDA’s guidance may run afoul of the legal effects test if the agency characterizes the guidance improperly or applies the guidance in a way that *de facto* legally binds parties. However, if guidance is issued pursuant to FDA good guidance practices, it should “prominently display a statement of the document’s non-binding effect” per 21 CFR §10.115(i)(1)(iv) and not include mandatory language per 21 CFR §10.115(i)(2). Compliance with these provisions would avoid any such challenge.

¹⁴¹ *See*, 21 CFR §10.115

¹⁴² *See*, H.R. 1956, §2(a); §(k)(4).

¹⁴³ *See*, §701(h) FDCA; 21 U.S.C. §371 (H) (guidance documents “shall not confer any rights for or on any person, although they present the views of the Secretary on matters under the jurisdiction of the Food and Drug Administration” and that all documents “indicate the nonbinding nature of the documents.”).

¹⁴⁴ Magill, Elizabeth M., *Agency Choice of Policymaking Form*. 71 U. CHI. L. REV. 1383, 1392 (2004).

¹⁴⁵ 493 F.3d at 227.

guidance process prior to acting on any follow-on applications.”^{146, 147} FDA states that any legislation must ensure that the agency “receives expert and public scientific and technical advice, but should include flexibility for FDA to adjust the process to meet its scientific needs with respect to data requirements and other matters.”¹⁴⁸ The Biotechnology Industry Organization (BIO) argues for a transparent and public process to determine the requirements for approval of a follow-on application and is supporting H.R. 5629.¹⁴⁹ The Generic Pharmaceutical Association (GPhA) has also long-supported the hybrid guidance approach.¹⁵⁰

There are concerns about developing an abbreviated approval pathway by guidance or a “hybrid” process. A flexible guidance process could create a moving target for follow-on applicants without legal recourse to challenge the propriety of any change in FDA position. Indeed, one motivation to proceed by hybrid guidance instead of rulemaking is to evade judicial review because a guidance is non-binding.¹⁵¹ Otherwise, there is little practical difference between “hybrid” guidance and rulemaking. It may be imprudent to issue regulations that will change with rapidly evolving science; however, requiring notice and comment for each change in guidance appears to jettison the efficient characteristics of a typical guidance document, which requires no such process.

Considering the need for flexibility in light of ever-improving scientific expertise, a “hybrid” guidance approach, providing for rulemaking-type notice and comment but without the force and effect of law, will provide a first step by which to develop an abbreviated approval pathway for follow-on biologics. However, like H.R. 1038 and the Canadian SEB framework, Congress must require regulations to be issued within five years through notice and comment rulemaking pursuant to the APA in order to provide the industry with a predictable application process and standards.¹⁵² Further, such regulations would bind the applicant and FDA to fixed positions to avoid a “moving target” scenario where an applicant detrimentally relies on an FDA position that is later changed. Any legislation that requires FDA to act by guidance should be clear about whether it is asking for rulemaking with the force and effect of law or guidance developed through a “hybrid” process similar to FDA’s good guidance practices. FDA, in issuing “hybrid” guidance, must also follow its good guidance practices, properly characterize its non-binding nature and apply it accordingly.¹⁵³

¹⁴⁶ Letter from Michael O. Leavitt, Secretary of HHS, to Senator Edward M. Kennedy, Chairman, Senate HELP Committee (June 26, 2007), [hereinafter June 2007 HHS Letter] *available at*: http://www.thepinksheet.com/nr/FDC/SupportingDocs/pink/2007/070702_Leavitt_biogenerics_letter.pdf. (last visited Nov. 30, 2008). This document officially reflects HHS’s views and may not accurately reflect FDA opinions omitted or augmented by HHS. This notwithstanding, one can infer that FDA’s views are largely represented by this document.

¹⁴⁷ *Id.* at 3.

¹⁴⁸ *Id.*

¹⁴⁹ BIO. PRINCIPLES ON FOLLOW-ON BIOLOGICS: WHITE PAPER, 2, *available at*: <http://bio.org/health-care/followonbkg/Principles.asp> (last visited Nov. 30, 2008).

¹⁵⁰ GPhA Submission to FDA Docket No. 2004N-0355. (Mar. 16, 2008), *available at*: <http://www.gphaonline.org/AM/Template.cfm?Section=Testimony1&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=1875> (last visited Nov. 30, 2008).

¹⁵¹ *See, Cement Kiln, supra* note 137, at 226.

¹⁵² *See Hussain, supra* note 47, at 8 (“It will be through this notice-and-comment rule-making, as well as the development of guidance, to which the experienced innovator industry and others will be able to contribute ...”).

¹⁵³ FDA is accustomed to issuing scientifically sophisticated guidance documents at a rate twice that of rulemaking. *See Mendelson, Nina A., Regulatory Beneficiaries and Informal Agency Policymaking*, 92 CORNELL L. REV. 397, (2007); Seigue, Erica & Smith, John J., *Perception and Process at the Food and Drug Administration: Obligations and Trade-Offs in Rules and Guidances*, 60 FOOD & DRUG L.J. 17, 25 (2005).

B. *Clinical Trial Data Requirements*

Another point of contention that the 111th Congress must resolve is whether to mandate clinical trials. FDA advocates for the flexibility to raise or lower the level of needed trials depending on the characteristics of the follow-on product.¹⁵⁴ FDA anticipates that clinical studies to address immunogenicity will be necessary.¹⁵⁵ FDA also prefers that this be a mandatory requirement.¹⁵⁶ However, statutory flexibility, in theory, permits FDA to require clinical trials to evaluate immunogenicity.

Assuming FDA is provided with the flexibility it desires to increase or decrease clinical study requirements, it is important to consider how abbreviated the initial follow-on application might be. As mentioned, reduced costs are associated with elimination of expensive clinical trials. To understand what data will likely be needed for the safety and efficacy of a follow-on biological drug product, one can look to FDA's approvals of follow-on biological drug products under §505(b)(2) of the FDCA, including Hylenex (hyaluronidase recombinant human), Hydase (hyaluronidase), Fortical (calcitonin salmon recombinant) Nasal Spray, Amphadase (hyaluronidase), GlucaGen (glucagon recombinant for injection), and Omnitrope (somatotropin [rDNA origin]).¹⁵⁷ In the case of Omnitrope, several characteristics enabled one rhGH product to be adequately compared to another, reducing the need for costly clinical study.¹⁵⁸ These characteristics included: 1) hGH is well-characterized and non-glycosylated;¹⁵⁹ 2) known primary structure of hGH and existing physicochemical tests for the determination of an hGH product's secondary and tertiary structures;¹⁶⁰ 3) availability of clinically relevant bioassays and qualified biomarkers for hGH; 4) hGH has a long and well-documented history of clinical use as a replacement for endogenous growth hormone deficiency; and 5) hGH's mechanism of drug action is known and its human toxicity profile well understood.¹⁶¹

FDA's approval of Omnitrope was based on new clinical trial data specific to Omnitrope, but less than the data required for approval under section §505(b)(1). The Omnitrope application also relied on the approval of Genotropin (a previously approved version of rDNA-derived somatotropin) for the same indications. The approval was based on: 1) physicochemical testing that established, among other things, that the structure of the active ingredient in Omnitrope is highly similar to the structure of the active ingredient in Genotropin; 2) new non-clinical pharmacology and toxicology data specific to Omnitrope; 3) clinical experience and a wealth of published literature concerning the clinical effects (safety and effectiveness) of human growth hormone; 4) pharmacokinetic, pharmacodynamic,

¹⁵⁴ June 2007 HHS Letter, *supra* note 146, at 4.

¹⁵⁵ *Id.*

¹⁵⁶ *Id.*

¹⁵⁷ Janet Woodcock, Deputy Commissioner, Chief Medical Officer, FDA, Testimony before the Committee on Oversight and Government Reform, U.S. House of Representatives (Mar. 26, 2007) available at: <http://www.fda.gov/oc/2007/protein32607.html> (last visited Nov. 30, 2008).

¹⁵⁸ See Dudzinski, David M. & Kesselheim, Aaron S., *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 NEW ENG. J. MED. 843-849 (2008).

¹⁵⁹ Sugar molecules are not added to the protein, which would increase the complexity of a protein and make it more difficult to compare the structures from one version of the protein to another using standard tools, such as mass spectrometry. See Dudzinski, *supra* note 12, at 225.

¹⁶⁰ How the protein folds upon itself.

¹⁶¹ May 2006 FDA Response to Citizen Petitions at 4.

and comparative bioavailability data that established, among other things, that Omnitrope and Genotropin are highly similar based on pharmacokinetic parameters and pharmacodynamic responses; 5) clinical efficacy and safety data from controlled trials comparing Omnitrope to Genotropin and from long-term trials with Omnitrope in pediatric patients; and 6) FDA's conclusions that Genotropin is safe and effective for the indications for which approval was sought in the Omnitrope application and that Omnitrope is highly similar to Genotropin.¹⁶²

The Omnitrope example demonstrates that a follow-on applicant's clinical study requirements will depend on FDA's expertise and experience with the drug class, and on the scientific capability to demonstrate a high degree of similarity between a particular follow-on and its reference product. Any reduction in clinical trial data depends on a number of factors:

the robustness of the manufacturing process, the degree to which structural similarity could be assessed, the extent to which mechanism of action was understood, the existence of valid, mechanistically related pharmacodynamic assays, comparative pharmacokinetics assays, comparative immunogenicity, the amount of clinical data available, and the extent of the experience with the original product or products.¹⁶³

It is expected that the initial follow-on biologic applications under the proposed PHSa abbreviated pathway will require data submissions similar to that submitted for FDA approval of biological drugs under §505(b)(2) of the FDCA.

It is best to provide FDA with flexibility to require a wide range of data to support a follow-on application. FDA approval of follow-on biological drug products is and will continue to be a science-driven, case-by-case approach.¹⁶⁴ Only H.R. 1956 would mandate clinical trials to be a part of the data package submitted for approval under the abbreviated follow-on pathway. The other legislative proposals would give FDA the discretion to increase or decrease the amount of clinical trial data needed. For example, S. 1695 includes a provision that explicitly states that the clinical studies are to be "designed to avoid needlessly duplicative or unethical clinical testing"¹⁶⁵ and H.R. 5629 gives FDA discretion to waive the need for clinical trials provided the application contains sufficient data to demonstrate biosimilarity without them.¹⁶⁶ This is the approach taken by the EMEA and HC frameworks, which provide flexibility regarding the amount of clinical trial data necessary. In this area, the policy justification for avoiding duplicative clinical study is strong. Patients need not be subjected to clinical study if the information derived from the study is unnecessary or duplicative. Immunogenicity and other potential safety concerns, while significant, should be addressed on a case-by-case basis by FDA. For a statute to mandate clinical trials in all cases would subject patients to unnecessary study and undermine the science-based, case-by-case approach FDA advocates and applies in the context of §505(b)(2) approvals.¹⁶⁷

¹⁶² Woodcock, Mar. 26, 2007, Testimony, *supra*.

¹⁶³ Woodcock, Janet, et. al. *The FDA's Assessment of Follow-on Protein Products: A Historical Perspective*. 6 NATURE REVIEWS DRUG DISCOVERY 437, 438 (2007).

¹⁶⁴ *Id.* at 438.

¹⁶⁵ S. 1695 *supra* note 100 at §2(a)(2), §(k)(2)(I)(BB) (2007).

¹⁶⁶ H.R. 5629 *supra* note 116 at §101.

¹⁶⁷ Woodcock, et. al, *supra* note 163 at 2.

C. *Interchangeability*

No other issue in the debate over follow-on biologics better illustrates the magnitude of the legal and policy decisions to be made than the issue of interchangeability. The question whether to provide FDA the ability to make interchangeability determinations for follow-on biologics, as it does for generic drugs under §505 of the FDCA, will likely be answered in the 111th Congress. Interchangeability can be defined in two ways: 1) therapeutic equivalents that could be substituted at the pharmacy level without the intervention of a doctor; or 2) similar products that are not substitutable at the pharmacy level but, under a doctor's supervision, could be used to treat the same condition in the same patient.

Generic drugs approved under §505(j) of the FDCA are therapeutically equivalent¹⁶⁸ to the reference product and can be interchangeable with it, or substitutable for it, without any additional concern for patient safety beyond what accompany an innovator. State law permits such products to be substituted for the reference product by a pharmacist, which can result in substantial cost savings for the patient. As mentioned in Section II of this article, it is unlikely that a manufacturer of a follow-on product could demonstrate that it is identical to an already approved product due to the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in consistently manufacturing a product.¹⁶⁹

FDA states that interchangeability determinations may be possible in the future, but expresses concern over the potential safety risks for pharmacies or patients to substitute products determined to be similar or comparable, but not interchangeable.¹⁷⁰ This could, due to the immunogenicity of the product, result in serious injury or death.¹⁷¹ Because of this danger, FDA believes "that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient's physician."¹⁷² FDA is not satisfied that interchangeability is achievable for follow-on biologics. For example, FDA's approval of Omnitrope was based on evidence demonstrating Omnitrope was "sufficiently similar," but not equivalent to Genotropin.¹⁷³ FDA specifically declined to refer to Omnitrope as a "generic" biologic because Omnitrope is not "A" rated as therapeutically equivalent to (and therefore substitutable for) any of the other approved human growth hormone products.¹⁷⁴

H.R. 1038 allows an applicant to request that FDA make a determination as to the interchangeability of a comparable product and the reference product based on whether a product can be expected to produce the same clinical result as the reference product in any given patient.¹⁷⁵ H.R. 1956 explicitly prohibits FDA from designating a similar biological product as therapeutically equivalent to the

¹⁶⁸ Therapeutic equivalents can be expected to have the same clinical effect and safety profile when administered to patients under the conditions of use in the FDA-approved labeling.

¹⁶⁹ June 2007 HHS Letter, *supra* note 146, at 5.

¹⁷⁰ *Id.*

¹⁷¹ *Id.*

¹⁷² *Id.*

¹⁷³ May 2006 FDA Response to Citizen Petitions, *supra* note 27 at 42.

¹⁷⁴ Sandoz did not seek an "A" therapeutic rating for Omnitrope. FDA designated Omnitrope with a "B" rating in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations the *Orange Book*. *Id.* at 4. See also FDA: Omnitrope (somatropin [rDNA origin]) Questions and Answers, *available at*: <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>. (Jun. 14, 2006).

¹⁷⁵ H.R. 1038, *supra* note 79 §4(B) and (C).

reference product.¹⁷⁶ This bill requires FDA to report to Congress every two years on “whether it is feasible, in the current state of scientific and technical knowledge, to make therapeutic equivalence determinations for similar biological products” and “if so, the statutory criteria that should govern such determination.”¹⁷⁷ This is similar to the European approach.¹⁷⁸

Under S. 1695 and H.R. 5629, the applicant may choose to submit information to demonstrate that the biological product is interchangeable with the reference product.¹⁷⁹ The Secretary may find the biological interchangeable with the reference product if the application is sufficient to show biosimilarity and can be expected to produce the same clinical result as the reference product in any given patient.¹⁸⁰ Also, the bill includes a balancing test for interchangeability that requires that “the risk in terms of safety or diminished efficacy of alternating or switching between the products is not greater than the risk of using the reference product without switching.”¹⁸¹

With three out of the four legislative proposals providing for FDA discretion to make interchangeability determinations, it appears that the statutory authority to do so is inevitable. The bills, despite a lessened patient safety standard for interchangeable follow-on products compared to generic products, are giving FDA wide discretion to make or reject interchangeability determinations. If FDA is not satisfied with the data enough to make such a determination, there is nothing in these proposals that would require FDA to do so if such a bill were to pass Congress.

The anticipated patient savings from abbreviated approval of follow-on biologics depends on the substitution of the reference product with the follow-on product.¹⁸² Without substitution, there is no direct competition in the marketplace to lower price. The GPhA has endorsed an approach to permit FDA to make interchangeability determinations. Consumer cost savings from this approach is estimated to be \$25 billion in the first nine years of enactment and \$5.9 billion for the federal government over the same time.¹⁸³ According to a study by the Pharmaceutical Care Management Association, biogenerics would save the Medicare Part B program alone \$14 billion over 10 years.¹⁸⁴ Additional savings also would accrue to Medicare Part D and other government healthcare programs, such as Medicaid and the Department of Veterans Affairs.¹⁸⁵ However, economists counter this expectation by arguing that the market for follow-on biologic will be slow to develop because of consumer and safety concerns over interchangeability.¹⁸⁶ Any legislation enacting an abbreviated approval pathway should require FDA to report to Congress frequently on the state of its scientific capability to make interchangeability determinations.

¹⁷⁶ H.R. 1956, *supra* note 90 §2, §(K)(2)(D).

¹⁷⁷ *Id.* §4.

¹⁷⁸ Hussain, *supra* note 47, at 5.

¹⁷⁹ S. 1695, *supra* note 100; H.R. 5629, *supra* note 90 §(k)(2)(B).

¹⁸⁰ *Id.* §(k)(4)(A)(i)(ii).

¹⁸¹ *Id.* §(k)(4)(B).

¹⁸² Gitter, *supra* note 7.

¹⁸³ CONGRESSIONAL BUDGET OFFICE, COST ESTIMATE FOR S.1696: BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2007 (2008), available at: <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf> (last visited Nov. 30, 2008).

¹⁸⁴ GPhA, Press Release (Fed. 14, 2007), available at: http://www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=3202 (last visited Nov. 30, 2008).

¹⁸⁵ CBO S.1696 Estimate, *supra* note 183.

¹⁸⁶ Grabowski, Henry et al., *The Market for Follow-on Biologics: How Will It Evolve?*, 25 HEALTH AFFAIRS 1291, 1293 (2006).

While science is presently insufficient to ensure that such products may be safely substituted, FDA should be given discretion to make interchangeability determinations. Without discretion, FDA is precluded from making such determinations at the earliest point at which scientific development makes it possible. Legislation must be enacted with the foresight to permit these decisions when FDA is able to do so. Follow-ons, which need only be similar to an innovator, will likely have a lower safety standard than true §505(j) generics and greater immunologic characteristics. These products should be approved with a labeling statement that the follow-on is or is not substitutable with the reference product, be subject to rigorous post-market safety analysis, and be studied postmarket if necessary.

D. Promoting Innovation With Exclusivity

Another essential element to consider in creating an abbreviated approval pathway for follow-on biologics is the type and length of any exclusivity period necessary to drive innovation. The 1984 Hatch-Waxman amendments drove innovation by offering patent term restoration for products that, while under FDA review, lost some of their patent life. Hatch-Waxman also increased competition by offering 180-day marketing exclusivity to the first generic applicant who challenged an innovator's patent. Innovation and competition considerations drive the debate over follow-on exclusivity.

It is important to distinguish between the types of exclusivity being considered. First, exclusivity under the FDCA and in the legislative proposals discussed above can be exclusivity for the innovator product, referred to as "new product exclusivity" or "data exclusivity,"¹⁸⁷ or it can be exclusivity for the follow-on product. There are also "add-on" types of exclusivity that build on basic exclusivity periods, such as additional exclusivity for approval of a new indication or pediatric exclusivity where the product is studied in a pediatric population.

Innovators argue for a 14-year data exclusivity period, asserting that patent protection is weaker for biologics and the "similarity" approval threshold will precipitate follow-ons working around existing patent protection.¹⁸⁸ The innovators assert that because the biological products are large molecules produced by living cells, the patent claims are often narrow and easy to design around.¹⁸⁹ Narrower patent claims result in a follow-on applicant eluding the innovator's patent protection.¹⁹⁰ Innovators argue that a follow-on biologic, designed to be "sufficiently similar" to the innovator biologic to rely to some degree on the safety and efficacy of the innovator product, may be different enough from the innovator to avoid a patent infringement claim and, thus, make it to market in advance of innovator patent expiration, which undermines incentives to invest in innovation.¹⁹¹

¹⁸⁷ Data exclusivity is the time period after approval of the innovator's product during which FDA may not approve a follow-on biologic product relying to any degree on the safety and efficacy of the innovator product. See, BIO, Press Release entitled *Setting the Record Straight: Generic Drug Industry Lobby "Flat Out Wrong" About BIO Position on Follow-On Biologics*. (Apr. 2008), available at: http://www.bio.org/news/pressreleases/newsitem.asp?id=2008_0401_02 (last visited Nov. 30, 2008).

¹⁸⁸ BIO: A Follow-on Biologics Regime Without Strong Data Exclusivity Will Stifle the Development of New Medicines [hereinafter BIO, Regime], available at: http://www.bio.org/healthcare/followonbkg/FOBMarket_exclusivity_20070926.pdf. (last visited Nov. 30, 2008).

¹⁸⁹ *Id.*, at 1. Manheim, *supra* note 25, at 398.

¹⁹⁰ BIO, Regime, *supra* note 188 at 1.

¹⁹¹ *Id.*

The Department of Health and Human Services supports a substantial period of innovator exclusivity, independent from patent protection, in order to ensure continued innovation.¹⁹² HHS does not propose a specific period, but has approved of the 12-year exclusivity period in S. 1625 and H.R. 5629.¹⁹³ H.R. 1956 would provide 14 years of new product exclusivity. This new product exclusivity would bar FDA from accepting a follow-on application for that period.

GPhA supports H.R. 1038, which provides no exclusivity to the innovator.¹⁹⁴ GPhA argues that such a period is arbitrary, excessive, and would unjustifiably delay access to affordable follow-on biologics by delaying competition.¹⁹⁵ GPhA argues that exclusivity periods should not be used to stretch patents into indefinite product monopolies.¹⁹⁶ The exclusivity period, if too long, will burden patients by delaying competition and follow-on innovation.

A 12 to 14 year period of innovator exclusivity is not arbitrary; studies have shown that the point at which an innovator biological drug becomes profitable (the “break-even” point) is between 12.9 and 16.2 years.¹⁹⁷ The innovator company must have sufficient confidence that it will be able to market its product without competition until this point to recoup its investment. The average time for marketing a drug with patent protection is 11.5 years, with an additional three months for FDA approval after patent expiration.¹⁹⁸ BIO asserts that, in most of the follow-on proposals, innovator exclusivity would run concurrent with the patent term for the product and act as a backstop should the follow-on applicant be able to circumvent the innovator’s patent.¹⁹⁹ It is reasonable that innovator biologics should require greater exclusivity than the 12 years afforded chemical innovators because innovator biologics of the higher costs and increased capital risks for biological drug innovators compared to chemical-based drug innovators.²⁰⁰ A 12-year innovator exclusivity period satisfies this need for promoting innovation to a growing industry and will ultimately be the mechanism by which follow-on price competition is achieved. A 12-year exclusivity period of non-patent exclusivity will not effectively change the status quo if it runs concurrent with the patent term. Such a period would create

¹⁹² June 2007 HHS Letter, *supra* note 146, at 2.

¹⁹³ *Id.*

¹⁹⁴ GPhA Statement on Sens. Kennedy-Enzi-Clinton-Hatch Biogenerics Legislation, [hereinafter GPhA Biogenerics], (2008) available at: http://www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/HTMLDisplay.cfm&ContentID=3560 (last visited Nov. 30, 2008). See also, GPhA, Statement on Repts. Eshoo-Barton Biologics Bill, (Mar. 14, 2008), available at: http://www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/HTMLDisplay.cfm&ContentID=4296 (last visited Nov. 30, 2008).

¹⁹⁵ *Id.*

¹⁹⁶ GPhA, Position Paper on Biogenerics (2008), available at: http://www.gphaonline.org/AM/Template.cfm?Section=Federal_Affairs&TEMPLATE=/CM/HTMLDisplay.cfm&CONTENTID=1948 (last visited Nov. 30, 2008).

¹⁹⁷ Grabowski, Henry and Kyle, Margaret, *Generic Competition and Market Exclusivity Periods in Pharmaceuticals*, MANAGERIAL AND DECISION ECONOMICS, (forthcoming), as cited in BIO, Regime, *supra* note 188, at 4.

¹⁹⁸ CONGRESSIONAL BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY, (July 1998), available at: <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf> (last visited Nov. 30, 2008).

¹⁹⁹ BIO, Regime, *supra* note 188 at 4.

²⁰⁰ Production costs of a biologic are 20-100 times the cost of production for a chemical drug. Also, success rate in Phase III trials for biologics is 54—58 percent versus 65—75 percent for chemical drugs. BIO, Regime, *supra* at 6. See also; Kuhlik, Bruce N., *The Assault on Pharmaceutical Intellectual Property*, 71 U. CHI. L. REV. 93 (2004); Manheim, *supra* note 25, at 401 (arguing that 12 years exclusivity is the minimum).

protection for the innovator against a follow-on company receiving FDA approval and, simultaneously, avoid patent infringement.

This position is supported by public policy considerations. First, without an innovator product, there can be no follow-on to provide price competition against. Without an innovator approval to serve as the reference product, there will be no incentive for a follow-on sponsor to innovate as well. Complete opposition to an exclusivity period does not comport with sound policy; the debate should center on the duration of exclusivity and not whether to provide it at all.

The FDCA provides additional innovator exclusivity in certain circumstances, such as receiving approval for additional new indication or studying the drug product in a pediatric population. Under §505 FDCA, an approved product receives additional exclusivity where that product is approved for a new indication. Under the Best Pharmaceuticals for Children Act (BPCA), a six-month pediatric exclusivity attaches after a patent term expires.²⁰¹ Only two of the legislative proposals attempt to mirror these provisions of the FDCA. H.R. 1956 would provide one additional year of marketing exclusivity if the sponsor receives approval for an additional indication. H.R. 5629 would provide two years for a sponsor who receives approval for an additional indication for their product. H.R. 5629 is the only bill that proposes six months of pediatric exclusivity. FDA suggests additional exclusivity be granted if the sponsor, during the exclusivity period, submits and FDA approves a supplement for a new indication for which new clinical trials were required (other than bioavailability) as is the case for other drugs.²⁰² BIO agrees, but GPhA does not.²⁰³ Both types of add-on exclusivity should be required elements of any follow-on regulatory scheme because it is a necessary incentive to encourage study of a product to maximize its utility, but also because the provisions should be applied uniformly across all pharmaceutical product classes.

In terms of exclusivity for a follow-on product, the 110th Congress' proposals make a break from the §505(j) ANDA provisions. Unlike §505(j), the proposed follow-on exclusivity is not tied to patent challenges.²⁰⁴ Rather, the proposed legislation offers follow-on exclusivity as an incentive to companies who can demonstrate interchangeability with the innovator product. H.R. 1038 provides 180 days marketing exclusivity for the first applicant found interchangeable to the reference biologic drug product.²⁰⁵ S. 1695 and H.R. 5629 provide one year exclusivity under the same condition.²⁰⁶ As mentioned above, the likelihood of competition creating consumer cost-savings depends greatly on the ability of a follow-on product to be interchangeable, either at the physician or pharmacy level, or both, with the innovator product. Overcoming the many scientific challenges in demonstrating interchangeability will require substantial investment and effort on behalf of the follow-on product sponsor. Exclusivity for the follow-on applicant is essential to encourage the development of interchangeable follow-on products.

²⁰¹ CBER's, FDA, FREQUENTLY ASKED QUESTIONS FOR NEW DRUG PRODUCT EXCLUSIVITY, *available at*: <http://www.fda.gov/cder/about/smallbiz/exclusivity.htm> (last visited Nov. 30, 2008).

²⁰² June 2007 HHS Letter, *supra* note 146, at 2.

²⁰³ BIO, Regime, *supra* note 188 at 4.

²⁰⁴ §505(j)(2)(A)(vii) requires an ANDA applicant to submit a patent certification to the reference holder stating: (I) that such patent information has not been filed; or (II) that such patent has expired; or (III) the date on which the patent will expire; or (IV) that such patent is invalid or will not be infringed by the manufacturer, use, or sale of the new drug for which the application is submitted. The first generic drug company to successfully challenge an innovator's patent under paragraph IV is awarded with 180-days marketing exclusivity against any subsequently approved generic for the same referenced innovator.

²⁰⁵ H.R. 1038, *supra* note 79 at §3(a)(K)(10).

²⁰⁶ S. 1695 note 100, *supra*, at §2(a)(k)(6), H.R. 5629 *supra* note 116 §101(a)(k)(6).

E. *Scope of Products Eligible for Abbreviated Approval*

There is also a debate among regulators and legal scholars over which products should be eligible for consideration under an abbreviated approval pathway for follow-on biologics. Despite the wide spectrum of protein-based therapeutics, there can be logical delineations made between those products that would lend themselves to follow-on approval and those that would not. Commentators recommend that FDA consider drawing a line between a “biologic biologic” and “biologic drug.”²⁰⁷ Under this rationale, “biologic biologics”—i.e., traditional biologics such as vaccines, toxins, antitoxins, viral and pathogen particles and blood products—would be excluded from follow-on consideration.²⁰⁸ “Biological drugs” that would be eligible for abbreviated approval include those products falling into the constraints of synthetic origin and reproducible structure such as nucleic acids, proteins and monoclonal antibodies.²⁰⁹

FDA supports exclusion for certain types of products from an abbreviated approval pathway, such as vaccines or blood products.²¹⁰ While exclusion from abbreviated review and approval may be appropriate now, regulatory classification by statute should leave open the door to re-evaluation, considering that the science of characterization is rapidly improving. FDA favors periodic reports to Congress advising on the state of the science and whether science supports expanding the scope of the legislation or a moratorium for these “biologic biologics” that could expire or be re-authorized.²¹¹

Both of these avenues to split types of biologics into classes appear to be arbitrary. For example, monoclonal antibodies are not nearly as easy to structurally characterize as a nucleic acid or a short protein. Likewise, FDA’s exclusion of vaccines as a potential follow-on biologic is also too broad. Vaccines are many things, ranging from small peptides to complex microorganisms. It appears that any legislative need to differentiate between categories of products eligible for this pathway can be achieved if FDA is given sufficient flexibility to determine, by guidance or regulation, which products the Agency deems appropriate for abbreviated review.

It would be prudent for Congress to avoid rigid classification. The distinct feature of the legislative function is that it sets a *general principle* to be applied prospectively.²¹² Statutes should not be wholly lacking in describing the specific means by which the general principal ought to be achieved; in fact, this is one of the chief shortcomings of modern legislation.²¹³ However, especially where “frequent adjustment or detailed expert knowledge of the field is necessary, a legislative delegation within general policy standards is valid.”²¹⁴ Determining the scope of an abbreviated approval pathway for follow-on biologics does require expertise and wide discretion given to FDA. Otherwise, mandatory statutory provisions concerning product

²⁰⁷ Dudzinski, *supra* note 12, at 186.

²⁰⁸ *Id.*

²⁰⁹ *Id.* at 187.

²¹⁰ June 2007 HHS Letter, *supra* note 146, at 3. (that “science does not exist to adequately protect patient safety and ensure product efficacy through an abbreviated follow-on pathway for all biologics, and questions exist whether some products, such as vaccines or bloods products, would ever lend themselves to such a pathway.”).

²¹¹ *Id.* at 2.

²¹² Singer, Norman J., 1 STATUTES AND STATUTORY CONSTRUCTION. Sixth Ed., 10 (2002).

²¹³ *Id.*

²¹⁴ *Id.* at 212.

eligibility would bind FDA into the future when scientific development renders such classifications obsolete.

S. 1695, H.R. 5629,²¹⁵ and H.R. 1956²¹⁶ give FDA the discretion to, by guidance, limit the scope of the abbreviated approval pathway. For instance, S.1695 would give FDA the authority to declare the “science and experience, as of the date of such guidance, with respect to a product or product class (not including any recombinant protein) does not allow approval of an application for a license as provided under this subsection for such product or product class.”²¹⁷ Such an approach allows scientific expertise to drive inclusion or exclusion for consideration under the pathway. This approach would allow FDA to issue a subsequent guidance to reverse a position with regard to a product class, should the science warrant such a reversal.

Uniquely among the follow-on bills, H.R. 1038 undermines administrative law principles by stripping FDA of its flexibility over what type of product may be appropriate for an abbreviated pathway. H.R. 1038 lists five product classes for which FDA “shall find the following types of products to contain highly similar molecular structural features.”²¹⁸ This language is taken directly from the Orphan Drug Act, which provides a definition of “sameness” for a macromolecule.²¹⁹ The “similarity” that FDA must impute under the Orphan Drug Act was not designed to pre-determine FDA’s comparability analysis between a follow-on and an innovator biologics’ safety and efficacy. Rather, this standard was to provide marketing exclusivity to a similar molecule for a company developing an orphan drug.²²⁰ In the follow-on biologics context, this section would mandate not only eligibility but similarity without any discretion given to FDA to evaluate known or unknown differences between products. This is a prime example of the importance to give wide discretion to the scientific agency with expertise the Congress lacks. The S. 1695 guidance approach would give FDA maximum flexibility to determine the inclusion or exclusion from an abbreviated approval pathway.

²¹⁵ S. 1695, *supra* note 100 §(k)(8), H.R. 5629, *supra* note 116 §(9)(C)(1).

²¹⁶ H.R. 1956, *supra* note 70 §2, A(4)(C)(vii).

²¹⁷ S. 1695, *supra* note 100 §(k)(8)(E).

²¹⁸ “(i) Two protein biological products with differences in structure solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence; (ii) Two polysaccharide biological products with similar saccharine repeating units, even if the number of units differ and even if there are differences in post-polymerization modifications; (iii) Two glycosylated protein products with differences in structure between them solely due to post-translational events, infidelity of translation or transcription, or minor differences in amino acid sequence, and if they had similar saccharine repeating units, even if the number of units differ and even if there were differences in post-polymerization modifications; (iv) Two polynucleotide biological products with identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars); (v) Closely related, complex partly definable biological products with similar therapeutic intent, such as two live viral products for the same indication. Two biological products not enumerated in the foregoing clauses may be demonstrated to contain highly similar principal molecular structural features based upon such data and other information characterizing the two products as the Secretary deems necessary.” H.R. 1038 *supra* note 79 at §(k)(1)(B).

²¹⁹ A drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug. 21 C.F.R. §316.3(b)13(ii).

²²⁰ 21 C.F.R. §316.3(b)13(ii) (1991); Jay P., Johnson & Johnson, Testimony at Follow-on Biologics, before the Senate HELP Committee (Mar. 8, 2008), *available at*: http://help.senate.gov/Hearings/2007_03_08/2007_03_08.html. (last visited: Nov. 30, 2008).

F. Uniformity between PHSA & FDCA

It is arguable whether or not both the PHSA and the FDCA, which overlap in many areas, need to be preserved as they relate to abbreviated applications or if all abbreviated applications should fall under one uniform statute.²²¹ Legal commentators cite both the advantages of particularized provisions related to the products regulated under the distinct statutes, but also disadvantages and confusion resulting from a dual regulatory system lacking strong scientific or legal justification for the duality.²²²

This analysis argues for uniformity in key areas between the existing abbreviated pathways under §505 FDCA [§505(j) ANDA and §505(b)(2)] and the proposed follow-on pathway under §351 PHSA. While the FDCA and the PHSA contain provisions of joint applicability²²³ that may act alone to apply certain provisions of the FDCA discussed below to an abbreviated approval pathway under §351 PHSA (e.g., prescription drug user fees and REMS), Congress should explicitly authorize the application of these provisions to the new abbreviated approval pathway for follow-on biologics. Any argument that current joint applicability provisions alone are sufficient to create uniformity for abbreviated applications leaves unresolved existing problems facing such applications under §505 of the FDCA. This section argues for reform and uniformity for abbreviated applications in the following areas: post-marketing safety and evaluation, patent dispute resolution, statutory ratification of FDA's interpretation of §505(b)(2) authority and practice, determining whether or not FDA may continue to approve follow-on products through §505(b)(2), providing for user-fees for application review, and eliminating barriers to competition such as blocking petitions and authorized generics.

Post-market Safety & Evaluation. Follow-on biologics will have risks that may only become apparent in the post-marketing period. The dangers of immunogenicity, described in Sections III and V(B) above, alone warrant close post-marketing monitoring and analysis.²²⁴ Some industry innovator commentators express concern

²²¹ It is interesting that the legislative proposals in the 110th Congress focus completely on adding to §351 PHSA. Doing so would avoid the need to graft an abbreviated approval pathway into an already complicated regulatory scheme under the FDCA. This notwithstanding, equal if not greater regulatory dilemmas may arise over time as two separate statutes evolve, but with the same basic function to permit the review and approval of abbreviated applications. Congress authorizing a pathway developed by guidance instead of rulemaking presents the likelihood that FDA regulations will not be promulgated to harmonize the two statutes. In sum, both Congress (by amending §351 of the PHSA) and FDA (by pushing for a guidance process) may not achieve the uniformity that many expect. While commentators make administrative law arguments that FDA could achieve uniformity alone, no author has argued for a *Congressional* approach to open the FDCA's abbreviated approval pathways to biologics licensed under §351 PHSA.

²²² Dudzinski, *supra* note 12, at 180. ("... one may ask if two overlapping and redundant statutes need to be preserved. Notwithstanding that the task to parse and clean-up the statutes in question would be momentous, the PHSA serves a useful function in filling in 'gaps' left in the FDCA, and vice versa ... Yet within this vague statutory framework there is room for many special amendments and particularized adjudications that do not comport with scientific considerations or legal justifications ...").

²²³ 42 U.S.C. 262(j) ("The Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such act [21 U.S.C. 355]."). See also, Dudzinski, *supra* note 12, at 180 ("the overlap of the PHSA and the FDCA is solidified statutorily with language of joint applicability in both subject to provisos that neither can be construed to affect, modify, repeal, or supersede provisions of the other.").

²²⁴ Schellekens, Huub, *Follow-on Biologics: Challenges of the "Next Generation."* 20 NEPHROLOGY DIALYSIS TRANSPLANTATION, iv34 (2005).

that H.R. 1038 does not mention post-market surveillance and limits FDA's ability to require post-market clinical trials.²²⁵ FDA worries about patient safety in light of what appears to be the lower safety standard for follow-ons and the potential for unintended interchangeability.²²⁶ Post-market safety surveillance and FDA's ability to mandate post-market clinical studies should be an essential component of any abbreviated approval pathway. This approach is consistent with FDA's authority under the FDCA and also the PHSa. Furthermore, innovative methods that authorize FDA to utilize data post-market data obtained by other governmental entities, such as Medicare claims related to biologics used by Medicare beneficiaries.²²⁷

The names of follow-on products also present the potential for patient confusion and false expectations that the products will perform like the innovator. There is debate over whether follow-ons should be uniquely named by an independent naming authority, such as the USAN.²²⁸ The traceability and accountability needed for adequate pharmacovigilance will depend largely on how products will be named.²²⁹ Congress must balance the need to limit patient confusion regarding these names and the need to trace a product to a patient. H.R. 1038, H.R. 1956, and H.R. 5629 require that follow-on biologics receive a different name than the innovator reference product.

In addition, FDAAA²³⁰ included an overhaul of FDA's risk management and post-market surveillance program to require, under §909, that FDA determine for each product if a risk evaluation and mitigation strategy (REMS) is necessary. REMS are designed to manage a known or potential serious risk associated with a drug or biological product.²³¹ A REMS will be required if FDA finds that a REMS is necessary to ensure that the benefits of the drug or biological product outweigh the risks of the product, and FDA notifies the sponsor.²³² A REMS can include a Medication Guide, Patient Package Insert, a communication plan, elements to assure safe use, an implementation system, and must include a timetable for re-assessment of the REMS. REMS should be uniformly applied to all products licensed or approved by FDA and will be an essential component to the safety of a follow-on biologic, regardless of its approval under §351 of the PHSa or §505(b)(2) of the FDCA. In proposing a REMS in the product application, FDA should require that post-market safety evaluation be evaluated at pre-determined intervals for, at minimum, three years after approval.

Patent Dispute Resolution. The Hatch-Waxman Amendments linked granting approval to a generic applicant to resolution of patent disputes between the generic applicant and the innovator. Hatch-Waxman provides 180-day marketing exclusivity to the first generic applicant successfully challenging an innovator's patent²³³ and a

²²⁵ *Id.* at 16. *See also*, David Schenkein, Vice President, Clinical Hematology/Oncology, Genentech, Inc., Testimony at Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States (May 2, 2007), available at: <http://energycommerce.house.gov/cmte/mgtgs/110-he-hrg.050207.Biosimilar.shtml>.

²²⁶ June 2007 HHS Letter, *supra* note 146, at 5.

²²⁷ DiMartino, Lisa D. et al., *Using Medicare Administrative Data to Conduct Postmarketing Surveillance of Follow-on Biologics: Issues and Opportunities*, 63 FOOD & DRUG L.J. 891 (2008).

²²⁸ 12 FDA WEEK 16, 7-8 (Apr. 21, 2006).

²²⁹ *Id.*

²³⁰ P.L. 110-85, § 901, *et. seq.*, 121 Stat. §926.

²³¹ FDA, Questions and Answers on the *Federal Register* Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (Mar. 2008) available at: http://www.fda.gov/cder/regulatory/FDAAA/FR_QA.htm. (last visited Nov. 30, 2008).

²³² *Id.*

²³³ *Id.*

30-month stay provision that precludes FDA approval of a generic drug once the patent owner receives a paragraph IV certification notice that the generic applicant believes the patent is invalid or will not be infringed).²³⁴

Most of the proposals in the 110th Congress disconnect the 180-day exclusivity period from patent certification. They leave unclear if or how FDA's 30-month automatic stay of approval in case of patent dispute might impact a follow-on biologics application. H.R. 1038 and S. 1695 provide for a patent dispute resolution process between the innovator and prospective follow-on that involves FDA before or during a patent dispute. H.R. 5629 precludes FDA approval of a follow-on biologic application until any patent infringement is complete. Disconnecting the patent resolution and FDA approval processes will give certainty to the innovator, the follow-on applicant, and patients. The resolution of the patent dispute can account for the relative losses to innovator drug owner and generic applicant, and the 180-day market exclusivity, where appropriate, can be preserved and granted upon resolution of the patent dispute.

Any legislation in the 111th Congress will have an opportunity to determine whether or not the follow-on pathway should include a patent dispute mechanism similar to Hatch-Waxman. The 111th Congress should also consider the merits of disconnecting patent disputes from generic drug review under §505(j) of the FDCA. The opportunity exists to reconsider the resolution of patent disputes in a manner that leaves FDA less involved. Litigation over patents will occur, but should not be linked to the regulatory approval process in a manner that places burden on FDA.²³⁵ Uniformity of the approval process and patent resolution in the two drug regulatory systems is desirable.

Ratification of FDA's 505(b)(2) Interpretation. As mentioned above, Fifth Amendment takings arguments persist over FDA's interpretation of its authority under §505(b)(2). The legal distinction between FDA's reliance on the innovators' application data versus FDA's reliance on its own finding of safety and efficacy to approve a follow-on application under §505(b)(2) is a fine one. Legal commentators find that FDA is not taking trade secrets without just compensation in violation of the Fifth Amendment to the Constitution.²³⁶ FDA's response to the citizen petitions related to the approval of Omnitrope declined to address trade secret and Fifth Amendment takings issues.²³⁷ Any Congressional legislation aimed at creating an abbreviated approval pathway under §351 of the PHSa should strongly consider ratifying FDA's interpretation of its authority under §505(b)(2) and applying this authority to the new pathway for follow-ons under the PHSa. No follow-on bill proposal would ratify FDA's §505(b)(2) practice. Congressional action to clarify this contentious issue under both statutes would relieve FDA from the burden to justify its legal position at each review and approval of a follow-on biologic.

Future of §505(b)(2) for Biological Drug Products. If a follow-on approval pathway is created, the question remains how FDA must handle §505(b)(2) approvals in the future. It is unclear how the previously-approved follow-on products would comply with the new provisions, or if they will be subject to them at all. H.R. 1956 permits a drug approved under §505(b)(1) to serve as a reference product for a follow-on, but explicitly forecloses any other mechanism to approve a follow-on,

²³⁴ Gitter, *supra* note 7, at p.617.

²³⁵ Hussain, *supra* note 47, at 7.

²³⁶ Yoo, *supra* note 25, at 42; Dudzinski, *supra* note 12, at 220, n. 558; Manheim, *supra* note 25.

²³⁷ May 2006 Response to Citizen Petitions, *supra* note 27.

including §505(b)(2), from the date of enactment.²³⁸ S. 1695 and H.R. 5629 would allow §505(b)(2) to operate, but only for those products submitted under that provision within ten years of enactment, after which an approved application for a biological product under §505 of the FDCA is “deemed to be a license” under §351 of the PHSA.²³⁹ Both bills prohibit a follow-on approval under §505(b)(2) during this ten-year period where there is another biological product approved under §351 of the PHSA that could be a reference product for the follow-on product.

FDA cautions against the transfer of certain products currently regulated under section §505 of the FDCA to section §351 of the PHSA.²⁴⁰ FDA comments that insulin products are proteins that have been regulated under the FDCA for more than 60 years and there could be significant regulatory implications if this product class were now to be approved or licensed and regulated under the PHSA.²⁴¹

A phase-out approach to §505(b)(2)’s utility as an abbreviated pathway for follow-on biologics approval is optimal. This 10-year window will minimize the disruption in the pipeline that may be caused by any abrupt foreclosure of § 505(b)(2) as an approval option for drugs being studied. The phase-out approach provides uniformity between the FDCA and PHSA. FDA’s argument that expertise with a particular product class will be lost by transferring the application type from an NDA to a BLA is unfounded. First, S. 1695 and H.R. 5629 explicitly permit continued applications for such product classes without change for a decade. Second, re-designating an approved NDA as a BLA after ten years does not automatically require FDA to alter the teams that review these products. FDA frequently has shifted responsibility for review of biological drug applications from CDER to CBER and has the ability to do so to maximize the scientific expertise FDA can bring to bear on a follow-on application.²⁴²

Follow-on User-Fees. FDA funding has not kept pace with its sister HHS public health agencies. For example, in 1986, FDA’s budget was \$416.7 million, or 97 percent of the CDC’s \$429.4 million budget and eight percent of NIH’s \$5.1 billion budget.²⁴³ In 2006, FDA’s budget was \$1.5 billion, or 28 percent of CDC’s \$5.2 billion budget and five percent of NIH’s \$27.7 billion budget.²⁴⁴ While these agencies perform different functions, appropriated funds are not commensurate with FDA’s regulatory responsibilities and places FDA in a difficult position to meet its public health mission.²⁴⁵ The Prescription Drug Use Fee Act (PDUFA) was enacted in 1997 to provide additional funding to FDA to expedite its review of drug applications. PDUFA funding applies to both drugs and biologics and there has been discussion of generic drug user fees as well. Either way, FDA must have the funds to review the complex follow-on applications that such an abbreviated approval pathway would generate. President George W. Bush’s Fiscal Year 2009 budget proposed that Congress provide FDA with the authority to approve follow-on biologics, calling for a pathway that includes user-fee financing structure

²³⁸ H.R. 1956, *supra* note 90, §2 (K)(3)(D).

²³⁹ S. 1695, §2(d) (2007).

²⁴⁰ June 2007 HHS Letter, *supra* note 146, at 3.

²⁴¹ *Id.*

²⁴² FDA transferred review of therapeutic products to CDER from CBER in 2004. Mathieu, *supra* note 48, at 56.

²⁴³ COALITION FOR A STRONGER FDA. JUST THE FACTS: *available at:* <http://www.fdacoalition.org/facts.php> (last visited April 30, 2008).

²⁴⁴ *Id.*

²⁴⁵ *Id.*

to pay for the system.²⁴⁶ Only S. 1695 and H.R. 5629, would authorize follow-on user-fees and do so in conjunction with the next reauthorization of PDUFA, set for 2012, as outlined in FDAAA. The 111th Congress should extend FDA's authority to collect user-fees to expedite its review of follow-on biologic applications or appropriate funds to do so.

Barriers to Competition Include Blocking Petitions & "Authorized Generics." Finally, any follow-on regulatory scheme enacted by 111th Congress must consider two problems now facing the generic review and approval and prevent their extension to follow-on biologics: authorized generics²⁴⁷ and blocking petitions.²⁴⁸ The use of authorized generics is increasing,²⁴⁹ and nearly every time a generic company receives its 180-day marketing exclusivity, an authorized generic is marketed.²⁵⁰ Marketing an authorized generic during the 180-day exclusivity period cuts generic company profit in half, making it harder to recoup costs associated with bringing a generic to market.²⁵¹ There are divergent opinions on the authorized generic issue, with the FTC arguing that this is pro-competition and the GPhA asserting that this conduct is aimed to convince generic companies to avoid bringing a drug to market.²⁵²

"Blocking petitions" are often submitted at the last minute before an approval and contain little substantive information that FDA has not already considered.²⁵³ In fear of judicial review, FDA is compelled to painstakingly review each citizen petition prior to taking an approval action, thus delaying generic drug approvals. FDA has frequently acknowledged this problem and is working to implement provisions of FDAAA that attempt to resolve it.²⁵⁴ Only H.R. 1038 would address authorized generics and citizen petition problems. Any follow-on biologics legislation in the 111th Congress should extend these remedies to anticompetitive practices to both the FDCA and PHSA.

V. CONCLUSION

It is not a matter of "if," but "when" Congress will grant FDA the authority to review abbreviated applications for follow-on biologics whose reference innovator is licensed under §351 of the PHSA. There is a growing consensus that the complex scientific, legal, and policy challenges to such an abbreviated approval pathway can be overcome. In creating a follow-on biologics approval pathway, the 111th Congress will need to strike a balance between patient safety, incentives for product innovation, price competition, and the need for a flexible, transparent process that capitalizes on FDA's growing expertise with §505(b)(2) follow-on biologics approvals. Like European and Canadian regulatory approaches, a flexible, case-by-case evaluation of the similarity of a follow-on biologic to its reference innovator best achieves this balance.

²⁴⁶ OFFICE OF MANAGEMENT AND BUDGET. THE BUDGET OF THE UNITED STATES GOVERNMENT FOR FISCAL YEAR 2009: HHS, 65, available at: <http://www.whitehouse.gov/omb/budget/fy2009/pdf/budget/hhs.pdf>. (last visited on Nov. 30, 2008).

²⁴⁷ An "authorized generic" is an innovator product repackaged and marketed at a lower price just prior to concurrent with the running of the 180-day exclusivity period of the generic drug.

²⁴⁸ Citizen petitions submitted just prior to the approval of a generic drug application are also delaying competition in the marketplace.

²⁴⁹ Baghadi, Ramsey, *The War On Generics: Part 1*, 1 THE RPM REPORT, 9, 3 (Sept. 2006).

²⁵⁰ *Id.* at 6.

²⁵¹ *Id.*

²⁵² *Id.*

²⁵³ Kaufman, Marc, *Petitions to FDA Sometimes Delay Generic Drugs: Critics Say Companies Misusing Process*, WASH. POST, (July 3, 2006).

²⁵⁴ FDAAA, P.L. 110-85, §914, 121 Stat. §953-957.

Considering the need for flexibility in light of ever-improving scientific expertise, a hybrid guidance approach provides for notice and comment but does not operate with the force and effect of law. Such an approach should be a first step to develop an abbreviated approval pathway for follow-on biologics. However, Congress must eventually require FDA to promulgate regulations, pursuant to the APA, to provide the biological drug industry (innovators and follow-ons alike) with a predictable application process and approval standards.

An approach that gives FDA a high degree of flexibility and discretion to require any data it deems necessary, including clinical trials, to support a follow-on application's approval will best protect patient safety. A follow-on statute should allow FDA to make interchangeability determinations for a follow-on biologic and encourage product applications with exclusivity if interchangeability is demonstrated. However, FDA must be given discretion to conclude, when appropriate, that science does not permit interchangeability determinations. Furthermore, any follow-on approval pathway must require strong warnings on the FDA-approved labeling of any follow-on biologic against unintended substitution with the innovator or another follow-on.

The biological drug industry depends on incentives to innovate. Both innovator and follow-on companies should be given exclusivity to propel the development of science and techniques in the field to encourage development of safe, pure, potent, and effective products. Such incentives will, over time, reduce the cost of biological drugs for patients and the federal government. Legislation should give FDA discretion to determine which products are eligible for abbreviated approval and which are not, with periodic FDA reports to Congress on this issue.

There is concern that enacting an abbreviated approval pathway under §351 of the PHS Act leaves unanswered certain questions pertaining to FDA's interpretation and use of §505(b)(2) of the FDCA. The 111th Congress should achieve uniformity between the FDCA and the PHS Act by harmonizing post-market safety requirements, de-linking patent dispute resolution from FDA review and approval, and ratifying FDA's interpretation of its authority under §505(b)(2) of the FDCA. A statute should achieve further uniformity by authorizing user-fees for follow-on application review and eliminating barriers to competition, such as authorized generics and blocking petitions that will continue to undermine both statutory schemes as they evolve. The hallmarks of an abbreviated approval pathway for follow-on biologics should be FDA flexibility and discretion. If based on these principles, a follow-on biologics pathway will age as well as, if not better, than the original Hatch-Waxman Amendments.