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The Biologics Price Competition and Innovation Act of 2009: Legislative Imprudence, Patent Devaluation, and the False Start of a Multi-Billion Dollar Industry

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Brian F. McMahon[1]

INTRODUCTION

On March 23, 2010, the final piece of the puzzle that presumably would launch a new multi-billion dollar industry was placed. On that day, President Obama signed into law the Biologics Price Competition and Innovation Act of 2009 ("BPCIA" or "the Act").[2] The purpose of the Act was to create an abbreviated regulatory approval process through which pharmaceutical companies could obtain FDA approval to market biologic medicinal therapies substantially similar to other biologic therapies that had already received FDA approval.[3] Legislation of this kind had been enacted some twenty-five years earlier with the passage of the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act" or "Hatch-Waxman"),[4] but this legislation was limited to creating an efficient approval process only for generic synthetic drugs. At the time, limiting such a process to synthetic drugs was of little concern. Biologics comprised only a miniscule percentage of the overall pharmaceutical market.

That has since changed. Within the last decade, biologics have played an increasingly prominent role in medicine; the market for new biologic medicines has grown at twice the rate as its synthetic drug counterpart.

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2 Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, 75 Fed. Reg. 192, 61,497 (Oct. 5, 2010) [hereinafter Request for Comments].

3 *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7001(b), 124 Stat. 119, 804 (2010).

4 Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 271(e) (2006).

With no decline of this trend in sight, and with the ever-increasing cost of medicinal therapies following the same trajectory, the need to establish an abbreviated regulatory approval process for "biosimilars" had become too pressing to ignore.

The resultant Act purportedly is designed to reward innovation while reducing overall costs to consumers.[5] These twin, seemingly contradictory aims are the same as those that prompted enactment of the earlier, ultimately successful Hatch-Waxman legislation.[6] As such, the two Acts are unsurprisingly similar in certain respects. In other respects, there is stark contrast. Within both the similarities and differences, however, the BPCIA contains numerous flaws that ultimately will stifle the growth of a nascent biosimilar pharmaceutical industry, if not pharmaceutical innovation altogether.

Despite their potential deleterious effect on pharmaceutical industries and innovation, however, the flaws of the BPCIA serve a valuable purpose. At the very least they serve to underscore the virtue of incorporating "legislative prudence," a seemingly long-forgotten, originally Aristotelian notion, into the modern lawmaking process. The BPCIA also provides substantial guidance in formulating a process-oriented standard by which one can evaluate the legislative prudence of a particular Act.

It was my original intent in first drafting this article merely to identify for the reader the significant flaws of the BPCIA, some of which heretofore remained unidentified, and to submit potential solutions for consideration. As more flaws became apparent during scrutiny of the Act, however, a theme emerged: In its haste to respond to increasing external pressures for an abbreviated biosimilars regulatory approval pathway, Congress ratified this legislation merely hoping it would work. It abandoned several common-sense principles in an effort to timely respond to its constituencies. While Congressional intent may have been true, the resultant Act is potentially fatal to its intended purposes.

As such, this article is the result of an attempt to achieve two objectives. First, I hope to provide the reader with a minimal but sufficient understanding of pharmaceutical science, FDA regulatory approval processes, patent law, and today's pharmaceutical industry in order to facilitate appreciation of the subsequently identified flaws of the BPCIA and corresponding proposed solutions. Second, I will use scrutiny of the BPCIA to argue that ancient notions of legislative prudence, adapted for modern use, would serve Congress well in all future legislative endeavors.

To accomplish these objectives, Part I will provide an overview of the current domestic pharmaceutical industry, the role of legislation in that industry, the import of incentives in pharmaceutical legislation, and an

5 § 7001(b), 124 Stat. at 804.

6 *See* 35 U.S.C. § 271(e).

overview of how Hatch–Waxman has influenced the industry. Part II will explain the difference between synthetic drugs and biologic therapies, and also explain why Congress could not simply modify Hatch–Waxman to establish an abbreviated regulatory approval pathway for biologics. Part III will summarize the current terms of the BPCIA and compare them to corresponding provisions of Hatch–Waxman to illustrate how Congress is attempting to accommodate the substantial differences between synthetic drugs and biologics. Part IV will explicitly identify the most significant shortcomings of the BPCIA and proffer solutions to those flaws. Finally, Part V will explain how each shortcoming of the BPCIA is violative of general notions of legislative prudence and will provide a modern, working definition of the virtue. Further, Part V will attempt to set forth a non-exhaustive list of characteristics, deduced from the BPCIA's most notable missteps, that should comprise at least in part a modern version of the Aristotelian virtue.

I. Today's Pharmaceutical Industry & the Role of Legislation

Today's domestic pharmaceutical industry is enormous by almost any standard, and it is growing. In 2007, U.S. pharmaceutical sales amounted to more than $285 billion.[7] In the three years that followed, despite a widely-felt economic downturn, sales of U.S. pharmaceuticals grew almost thirteen percent to reach $307 billion.[8] Further still, estimates currently project annual pharmaceutical sales to reach almost $800 billion by 2015.[9]

In 2010, biologics comprised just over ten percent of the total new products approved by the FDA.[10] This marks an increase of over three percent from the previous year,[11] and an increase of over five percent from 2008.[12] While this trend might seem marginally significant to some,

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7 *See About GPhA: Facts at a Glance*, Generic Pharmaceutical Ass'n, http://www.gphaonline.org/about-gpha/about-generics/facts (last visited Aug. 14, 2011).

8 See Hossam Abdel-Kader, *Research and Markets: Pharmaceutical Industry in the United States*, PR Inside, http://www.pr-inside.com/research-and-markets-pharmaceutical-industry-r2737897.htm (last visited Aug. 14, 2011).

9 Bruce Carlson, *Biologics Pipeline Set to Replenish Coffers*, Genetic Engineering & Biotechnology News, Aug. 2010, at 14, *available at* http://www.genengnews.com/gen-articles/biologics-pipeline-set-to-replenish-coffers/3366/.

10 *See CDER Drug and Biologic Calendar Year Approvals as of December 31, 2010*, FDA, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM260585.pdf (last visited Jan. 7, 2012).

11 *CDER Drug and Biologic Calendar Year Approvals as of December 31, 2009*, FDA, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/PriorityNDAandBLAApprovals/UCM090995.pdf (last visited Jan. 7, 2012).

12 *CDER Drug and Biologic Approvals for Calendar Year 2008 Updated through December 31, 2008*, FDA, http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/

the effect the growth of biologics has had on the overall pharmaceutical industry is undeniably substantial. Due to the increased costs in research, development, and manufacturing of biologic therapies, as will be further explained herein, sales of biologics in 2010 comprised almost a quarter of the total domestic pharmaceutical sales for the year measured in dollars.[13] With annual domestic sales of pharmaceuticals reaching stratospheric levels, and with biologics becoming an increasingly significant share of those sales, it is small wonder that the passage of the BPCIA has received such tremendous attention.[14]

A. Legislative Impact on the Pharmaceutical Industry

The impact that any legislation—let alone the BPCIA—can have on the pharmaceutical industry cannot be overstated. Indeed, since at least 1962 when passage of the "Kefauver Amendments" modified the Federal Food, Drug, and Cosmetic Act ("the FDCA") to require proof of a drug's efficacy as well as safety before marketing, the industry has owed its existence to federal legislation.[15] Acts like the FDCA, The Orphan Drug Act of 1983 ("the ODA"),[16] Hatch–Waxman, and The Medicare Modernization Act of 2003 ("the MMA"),[17] along with their corresponding regulations enacted by the FDA under delegated authority, govern nearly all aspects of the medicinal drug market. Laws like the Public Health Service Act ("PHSA"),[18] the ODA, and now the BPCIA, again with corresponding regulations, govern medicinal biologics. To clearly illustrate the effect legislation has on the pharmaceutical industry, consider the following entirely fictitious hypothetical relating to the approval of a new drug under current applicable law and regulation:

> Pferck is a company with a long history of developing innovative synthetic drugs to treat various disease states. It maintains an impressive portfolio of patents, covering a variety of FDA–approved drugs indicated for the treatment of various disease

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HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM200924.pdf (last visited Jan. 7, 2012).

13 *See* Katherine N. Addison, *The Impact of the Biosimilars Provision of the Health Care Reform Bill on Innovation Investments*, 10 J. MARSHALL REV. INTELL. PROP. L. 553, 554–55 (2011).

14 *See* Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 697–98 (2010); FDA, Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products Public Meeting (Nov. 2–3, 2010) [hereinafter *Hearings*], *available at* http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm.

15 Carver et al., *supra* note 14, at 672–78.

16 Orphan Drug Act, 21 U.S.C. § 360cc(a) (2006).

17 Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108–173, 177 Stat. 2066.

18 Public Health Service Act, Pub. L. No. 78–410, 58 Stat. 682 (1944).

> states. Its most recent project is related to the development of a treatment for color blindness. After years of research and development, Pferck believes the cure for color blindness can be found in a synthetic drug of its own creation, plutoniox. Pferck believes plutoniox is both safe and effective for the treatment of color blindness, and it hopes to market its drug under the brand name ColorView.

Before Pferck can market ColorView within the United States, it must first obtain FDA approval to certify by government standards that ColorView in fact demonstrates a statistically significant therapeutic effect in treating colorblindness and that it is sufficiently safe for human consumption.[19] To do this, Pferck must submit to the FDA what is commonly referred to as a New Drug Application ("NDA").[20] The submission of an NDA by a sponsor such as Pferck is no small matter—one can certainly imagine the wealth of information required by the government before the FDA would approve a drug as safe and effective for human consumption. Indeed, an exhaustive list of information required in any given NDA is provided in the Code of Federal Regulations.[21] Practically speaking, most NDAs contain approximately 100,000 pages.[22] Before a sponsor can begin compiling this information, however, the sponsor must seek FDA permission on a different front.

Unsurprisingly, an NDA almost always requires the inclusion of data compiled from drug studies conducted in humans ("clinical trials").[23] Because drugs cannot be administered to humans even as part of a scientific study without express consent from the FDA,[24] however, the sponsor must first submit an Investigational New Drug Application ("IND") to conduct clinical trials. The information required for mere approval of an IND, though less than that included as part of an NDA, is still substantial.[25] And approval of an IND means only that the applicant can conduct what generally will be a very costly, and very lengthy, protocol in order to gather information that may or may not ultimately support approval of the yet-to-be-submitted NDA. If all goes well, a potential NDA applicant might be ready to submit its NDA approximately six years and millions of dollars following IND approval.[26]

As is readily apparent from even this quick glimpse of the regulatory approval process for a new drug, legislation affecting the pharmaceutical

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19 21 U.S.C. § 355(b)(1) (2006).

20 JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 8 (2005).

21 21 C.F.R. § 314.50 (2011).

22 *New Drug Approval Process*, DRUGS.COM, http://www.drugs.com/fda-approval-process-html (last visited Aug. 14, 2011) [hereinafter *New Drug Approval Process*].

23 21 C.F.R. § 314.50(d)(3).

24 21 C.F.R. § 312.20 (2011).

25 21 C.F.R. § 312.23 (2011).

26 *See New Drug Approval Process*, *supra* note 22.

industry has imposed tremendous costs on those seeking to market pharmaceuticals. Laws like the FDCA, PHSA, and related acts therefore can readily stifle the growth of the industry if not carefully balanced with appropriate incentives. The additional costs incurred in developing new pharmaceuticals due to legislative requirements must be offset by appropriate legislative incentives in order to ensure and promote the industry's future. Historically the U.S. Government has done well in this regard. For instance, a 2010 study recently revealed that only thirteen percent of potential synthetic drugs survive the scrutiny imposed by government-required IND trials.[27] Of those that pass IND muster to become the subject of an NDA, less than three-quarters will receive FDA approval for commercial marketing.[28] Despite these long odds for commercialization of new products, however, the number of NDAs submitted each year continues to grow. As of July 8, 2011, the FDA had approved almost as many new drugs in 2011 as it had in all of 2010.[29] The rationale to pursue NDAs in the face of probable failure can be found in the incentives awaiting NDA applicants should they succeed—guaranteed market exclusivity.

B. The Need for Incentives in Pharmaceutical Legislation

Market exclusivity, in its most general sense, is the period of time during which a sponsor's product is the only drug product FDA-approved and commercially available to treat any particular condition or disease state. For example, reverting to the aforementioned hypothetical briefly, the market exclusivity for ColorView (plutoniox) is the period of time beginning from when ColorView (plutoniox) is first approved by the FDA for commercial marketing and ending when a competing product similar to ColorView (e.g., a "generic" plutoniox) is commercially launched. The longer the market exclusivity of a particular FDA-approved product, the longer the drug sponsor can charge a premium for its drug product without fear of competition. This benefit is crucial to innovative drug companies, as it is the primary mechanism by which it may recoup costs for its other failed drug products.[30] Also, the longer the time to charge a premium, the lower

27 *See* JA DiMasi et al., *Trends in Risks Associated with New Drug Development: Success Rates for Investigational Drugs*, 87 CLINICAL PHARMACOLOGY & THERAPUTICS 272, 272, 276–77 (2010).

28 *FDA Is Rejecting More New Drugs than in Past*, MSNBC (Aug. 17, 2007, 4:16 PM), http://www.msnbc.msn.com/id/20321830/.

29 *FDA's Drug Approval Rate for 2011 on Pace to Exceed 2010*, FOX NEWS (July 8, 2011), http://www.foxnews.com/health/2011/07/08/fdas-drug-approval-rate-for-2011-on-pace-to-exceed-2010/.

30 *See* CONG. BUDGET OFFICE, RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 47 (2006), *available at* http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf.

the premium needs to be. Protracted market exclusivity therefore can be instrumental in lowering the initial costs of new drugs.

Market exclusivities can take many forms. Before explaining the various types of market exclusivities, however, certain definitions are in order. The term "market exclusivity" has meant many things to many authors, depending on the context of their works. For instance, market exclusivity has been used to mean a right vested through regulation that prohibits others from market entry, distinguishing the term from that of "data exclusivity."[31] The term has also been used more loosely to encompass all forms of regulatory exclusivity.[32] With various understandings of the term in circulation, continued discussion of exclusivities requires a more rigidly defined lexicon. As such, the term "market exclusivity" will be used herein, but only with modifiers properly attributable to the distinguished philosopher John Rawls.[33]

1. Pure Market Exclusivity Defined.—Pure market exclusivity is the right afforded a market participant to be the single provider of a particular good or service within a specific market for a time certain. The right may be vested by way of ownership of one or more enforceable patents, by way of possessing a singular exclusive license of any relevant patents, by way of a regulatory grant of exclusivity, or by any other means. Within pharmaceutical legislation, to the extent it can be achieved, pure market exclusivity generally comes in two forms: patent exclusivity[34] and regulatory exclusivity.[35]

2. Patent Exclusivity vs. Regulatory Exclusivity.—

(a) Patent Exclusivity

Patent exclusivity is derived from the Patent Act of 1952,[36] which in part provides that the holder of a patent shall have "the right to exclude others from making, using, offering for sale, or selling" the invention claimed by

31 *See* Maxwell R. Morgan, *Regulation of Innovation Under Follow-On Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism*, 11 COLUM. SCI. & TECH. L. REV. 93, 98 (2010); *see also* Addison, *supra* note 13, at 567 (citing Morgan, *supra*, at 100).

32 *See, e.g.*, Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 365 (2007).

33 JOHN RAWLS, A THEORY OF JUSTICE 73–77 (Harvard Univ. Press rev. ed. 1971).

34 *See, e.g.*, 21 U.S.C. § 355(b)(1) (2006) (extending patent protection to new drug applications under certain conditions).

35 *See, e.g.*, § 355(c)(3)(E)(ii), (j)(5)(F)(ii) (extending a five year regulatory exclusivity period for new chemical entities); § 355(c)(3)(E)(iii), (j)(5)(F)(iii) (extending a three year regulatory exclusivity period for new clinical studies conducted on drug products).

36 Patent Act of 1952, Pub. L. No. 82-593, 66 Stat. 792.

the patent.[37] Those in the pharmaceutical industry typically have regarded this right as an extremely valuable one, particularly when the right is combined with the required pre–market approval process at the FDA. For reasons that will be discussed in greater detail below, patent rights in the pharmaceutical context can be an effective deterrent to others hoping to compete in a profitable market space.

The standards for obtaining a patent are well promulgated, and a patentee "shall be entitled to a patent unless" certain conditions of non–patentability are found.[38] Among those conditions are lack of novelty,[39] obviousness,[40] and perhaps most relevant for purposes of this discussion, lack of enablement.[41] Specifically, the enablement requirement of the Patent Act requires a patentee to disclose sufficient information about the invention in the patent itself such that one of ordinary skill in the relevant art, after reading the disclosures made in the patent, could practice or make the invention without unnecessary experimentation.[42] In exchange for the disclosure explaining how to make or practice the invention, the patentee is entitled to the aforementioned right to exclude for a period of twenty years.[43] The twenty–year period begins on the day the earliest related patent application is filed.[44] Upon expiration of the patent's term, the public is then free to practice or make or even improve upon the previously patented invention, and the Constitutional objective of the Patent Act to "promote the Progress of Science and useful Arts" is therefore achieved.[45]

The statutory term of a patent's right to exclude has been deemed the "'quid pro quo'" for the full disclosure of the invention to the public,[46] but pharmaceutical patent holders could never reap the benefit of a patent's

37 35 U.S.C. § 154(a)(1) (2006).

38 35 U.S.C. § 102 (2006).

39 *Id.*

40 35 U.S.C. § 103 (2006).

41 35 U.S.C. § 112 (2006).

42 N. Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 941 (Fed. Cir. 1990).

43 *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 731 (2002); *see also* J.E.M. AG Supply, Inc. v. Pioneer Hi–Bred Int'l, Inc., 534 U.S. 124, 142 (2001) (quoting Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 484 (1974)).

44 35 U.S.C. § 154(a)(2) (2006). The Patent Act of 1952 originally awarded a patent term of seventeen years from the date the patent issued. *See* Patent Act of 1952, Pub. L. No. 82–593, 66 Stat. 792, 804. As a result of a Patent Cooperation Treaty entered into as part of the Uruguay Round of multilateral trade agreements, however, the Uruguay Round Agreements Act was enacted in an effort to harmonize domestic patent laws with corresponding international laws. Thereafter, patents issuing from applications submitted after June 8, 1995, receive a twenty year term measured from the date the earliest patent application is filed. Uruguay Round Agreements Act, Pub. L. No. 103–465, 108 Stat. 4809 (1994).

45 U.S. CONST. art. I, § 8, cl. 8.

46 *J.E.M. AG Supply, Inc.*, 534 U.S. at 142.

full statutory term—at least not prior to enactment of Hatch–Waxman.[47] Because pharmaceutical products require regulatory approval before commercial use, and because NDA approvals commonly issued well after a relevant patent's statutory term had begun, NDA applicants were forced to launch their innovative patented pharmaceutical products commercially often with less than half of the original patent term remaining.[48] Through no fault of the NDA applicants, the regulatory approval process was nullifying a significant portion of their patents.[49] The truncated duration of their right to exclude would in turn drive initial costs of newly commercialized drugs higher than they would have been otherwise. The NDA holders were forced to charge more for their product because they had less time to recoup their costs before generic competitors would reach the market. The net effect was that the public suffered. The "Patent Term Restoration" portion of the Hatch–Waxman Act remedied this defect by affording NDA holders the opportunity to extend the life of one affected patent for up to five years, depending on the period of exclusivity lost due to the regulatory approval process.[50]

The portion of the Hatch–Waxman Act dedicated to establishing an abbreviated approval process for generic drugs also affects the significance of patent exclusivities in the development of new synthetic drugs. For example, rare is the case where a sponsor submits an NDA for a drug product that is not covered by the scope of at least one issued U.S. patent either owned or exclusively licensed by the sponsor. To ensure that the FDA is aware of any relevant patents pertaining to the drug product, and to prevent the FDA from inadvertently approving for commercial launch a generic drug product arguably within the scope of one of these patents, the terms of the Hatch–Waxman Act require a sponsor to file with its NDA "the patent number and the expiration date of any patent which claims the drug" product or "a method of using such drug" that is the subject of the NDA.[51] The Hatch–Waxman Act also requires the sponsor to timely supplement this information should any relevant patent issue after the NDA is filed but before it is approved.[52] Upon approval of the NDA, the FDA publishes this patent information in its *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the "Orange Book."[53] By virtue of this publication, the FDA shifts the burden to any

47 Alan D. Lourie, *Patent Term Restoration*, 66 J. PAT. OFF. SOC'Y 526, 527 (1984).

48 *Id.*

49 *Id.*

50 *See* 35 U.S.C.A. § 156 (West Supp. 2011); *see also* Alfred B. Engelberg et al., *Balancing Innovation, Access, and Profits – Market Exclusivity for Biologics*, 361 NEW ENG. J. MED. 1917 (2009).

51 21 U.S.C. § 355(b)(1) (2006).

52 *Id.*

53 *Id.*; *see* THOMAS, *supra* note 20, at 327; *see also* FDA, ORANGE BOOK: APPROVED DRUG

applicant wishing to obtain approval of a generic version of the new drug product to represent that commercialization of the generic version of the drug product will not impinge on the patent rights of the new drug sponsor. This will be addressed in more detail in Part III, *infra*.

(b) Regulatory Exclusivity

Regulatory exclusivity, at least for purposes of this article, is somewhat of a misnomer. In the context of pharmaceutical legislation, regulatory exclusivity is actually a statutory edict prohibiting either potential market competitors from filing an application seeking FDA approval to compete, or the FDA from approving an application of a potential market competitor in certain circumstances. Also, depending on the type of regulatory exclusivity at issue, the prohibition may nevertheless permit more than one market participant at a given time. Others have referred to the different types of regulatory exclusivities as either "data exclusivity" or "market exclusivity."[54] Herein, three types of regulatory exclusivities will be discussed: "data exclusivity," "procedurally perfect market exclusivity," and "procedurally imperfect market exclusivity." The distinctions will prove useful in discussing the various incentives within both Hatch–Waxman and the BPCIA, *infra*.

(i) Data Exclusivity

Data exclusivity has already been well–defined, and its definition is appropriate for use herein. It is a type of regulatory exclusivity that prevents any later–filing FDA applicant from relying on clinical data submitted by a first applicant in order to obtain FDA approval.[55] More simply, it prevents "piggy–backing." Data exclusivity therefore does not necessarily prevent potential market competitors from entering a given market. Rather, it renders entry to the market to be nearly as costly for later entrants as it was for the first. If a later–filing FDA applicant is willing to bear the cost of conducting its own clinical trials, for example, data exclusivity will not prohibit that applicant from submitting its product to the FDA for review, and it will not bar the FDA from approving that application. The award of data exclusivity therefore is not as valuable to a first applicant as other types of regulatory exclusivity, in part because it is generally conferred for a

PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (2001), *available at* http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

54 *See* Addison, *supra* note 13, at 567; *see also* Steven Lendaris, *Fine–Tuning the Generic Biologic Approval Process*, NAT'L L.J., Mar. 14, 2011, *available at* http://www.bakerbotts.com/file_upload/documents/LendarisNLJarticleMarch2011.pdf.

55 *See* Morgan, *supra* note 31, at 98.

relatively short period of time. In practice, however, data exclusivity is still an effective deterrent for later–filers.

In the context of Hatch–Waxman, data exclusivity is awarded in certain circumstances for periods of three, four, or five years.[56] As found in the BPCIA, such exclusivity is awarded for four.[57] By conferring data exclusivity for so brief a time, the value of data exclusivity can nearly equal that of pure market exclusivity. So long as the cost to a later filer for conducting its own clinical trials is greater than the profits it might realize during the period of data exclusivity, a later–filer would be fiscally foolish to seek FDA approval prior to the expiration of the data exclusivity period. Note also that cost is measured both in terms of dollars and time. Therefore, a later–filer's pursuit of FDA approval during a data exclusivity period makes sound business sense only in the rarest of cases: where clinical data could be gathered and submitted in sufficient time such that it could recoup the costs for such data before expiration of remaining period of data exclusivity. Where periods of exclusivity generally run only four to five years, such circumstances are difficult in practice to realize.

(ii) Procedurally Perfect Market Exclusivity

Procedurally perfect market exclusivity is a statutory edict that prohibits the FDA from approving for a time certain any competing product that is the subject of a later–filer's application. This type of regulatory exclusivity is absolute, and the recipient of such exclusivity is guaranteed to be the sole purveyor in a given market for the duration of the exclusivity. Numerous advantages obviously flow from the award of procedurally perfect market exclusivity, not least of all the ability of the recipient to forecast with minimized variables anticipated revenues for the exclusivity's duration. For this and other reasons, some have suggested that this type of exclusivity is "superior" to other types of regulatory and patent exclusivities in the context of incentivizing biologic innovation.[58] For reasons articulated, *infra*, this position necessarily fails to appreciate complexities inherent in biologic

56 21 U.S.C. § 355(c)(3)(E)(iii)–(iv), (j)(5)(F)(iii)–(iv) (2006) (providing for three years of data exclusivity for any approved drug that was the subject of an FDA application containing data from new clinical studies that were essential to approval); § 355(c)(3)(E)(ii), (j)(5)(F)(ii) (awarding five years of data exclusivity for any approved drug deemed by the FDA to be a New Chemical Entity ("NCE"), in that it contains an active pharmaceutical ingredient that had not been approved previously by the FDA). In cases where a generic drug applicant seeks to challenge any Orange Book–listed patent related to the NCE, however, the exclusivity is reduced to four years. *Id.*

57 42 U.S.C.A. § 262(k)(7)(B) (West 2011).

58 *See* Morgan, *supra* note 31, at 98–106.

research, development, and manufacture. It also overlooks the dangers in awarding such an impregnable market exclusivity.

Procedurally perfect market exclusivity, by definition, can be awarded only to a new, innovative product. Notably, Hatch–Waxman does not award this type of regulatory exclusivity under any circumstance.[59] The ODA awards a period of seven years.[60] The award and duration of this exclusivity was the topic of considerable Congressional debate in forging the terms of the BPCIA,[61] and the Act currently confers a period of twelve years.[62]

(iii) Procedurally Imperfect Market Exclusivity

In contrast to the procedurally perfect market exclusivity, procedurally imperfect market exclusivity is awarded only to later–filing applicants. The "imperfect" designation connotes that the exclusivity awarded is not truly exclusive. Rather, the award guarantees a later–filing applicant that the only competing product it will face in a given market for a time certain is the innovative product of the first–filer. This regulatory exclusivity is conferred generally to incentivize later filers to file their FDA applications as quickly as possible. The "first later–filer," by virtue of this exclusivity, will be free to set a price for its product substantially lower than the first–filer (*i.e.*, at roughly "generic" prices) without fear of competition from other products set at substantially the same price.

The Hatch–Waxman Act, as modified by the MMA, awards this exclusivity to last no longer than 180 days from the date of commercial launch of the first later–filer's product.[63] The BPCIA allows for an exclusivity of this type to last up to one year.[64]

C. An Overview of Hatch–Waxman and Its Effect on the Pharmaceutical Industry

Prior to enactment of the Hatch–Waxman Act, the process of obtaining regulatory approval for generic drugs was confounding at best. Until 1962, for example, governing law required that all drugs, not just generic versions of new drugs, be "approved for safety only."[65] Only with the "Kefauver" Amendments passed in 1962 did the Federal Food, Drug, and Cosmetic Act

59 *See* Eisenberg, *supra* note 32, at 359–60.

60 *Id.* at 359; Orphan Drug Act, 21 U.S.C. §360cc(a) (2006).

61 *See* Carver et al., *supra* note 14, at 735–36.

62 42 U.S.C.A. § 262(k)(7)(A) (West 2011).

63 21 U.S.C. § 355(j)(5)(B)(iv)(I) (2006).

64 42 U.S.C.A § 262(k)(6).

65 Gerald J. Mossinghoff, *Overview of the Hatch–Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 187 (1999).

require approval on the basis of both safety and efficacy.[66] Even with the Kefauver Amendments, however, there were still no provisions establishing an abbreviated approval process for generic drugs identical to previously approved innovator drugs.[67] Generic drug companies therefore generally had to file NDAs, thereby incurring the same costs of an innovator, to show the safety and effectiveness of their generic products.[68] Those parties could submit "paper NDAs," or NDAs relying on already-published data showing that the chemical comprising their proposed generic drugs was both safe and effective, but such data was not always available for the particular chemical sought to be approved.[69] Additionally, even if such data were available, the FDA was nevertheless free to require additional clinical studies addressing safety or efficacy issues arising out of that clinical data or from adverse event reports presented during pendency of the application itself.[70] Indeed, after 1962, as many as 150 drugs no longer protected by patents had no generic competition because companies would not invest the resources necessary to collect the requisite data for approval of such drugs.[71] That stood to reason—seeking permission to market a generic version of an FDA-approved drug product would often rival the cost of obtaining permission of the reference product.

With the future of the generic pharmaceutical industry uncertain leading up to the early 1980s,[72] a movement in the Ninety-seventh Congress (1980–82) caused the introduction of legislation that would further cast the viability of the industry in doubt. The proposed legislation would have permitted patent term extensions for pharmaceutical patents for periods of up to seven years to compensate their owners for exclusivity lost during the required FDA regulatory approval process.[73] An amended version of that legislation passed in the Senate, and it is said that only the efforts of Representative Henry Waxman (D-Cal.) and then-Representative Albert Gore, Jr. (D-Tenn.), with some help from inclement weather, prevented its enactment.[74] The bill fell only five votes short in the subsequent House

66 *Id.* at 187; Carver et al., *supra* note 14, at 674.

67 Alfred B. Engelberg, *Special Patent Provisions for Pharmaceuticals: Have They Outlived Their Usefulness? A Political, Legislative and Legal History of U.S. Law and Observations for the Future*, 39 IDEA 389, 396 (1999).

68 *Id.* at 396–97.

69 *Id.* at 397; Carver et al., *supra* note 14, at 675.

70 Engelberg, *supra* note 67, at 397.

71 *See* Mossinghoff, *supra* note 65, at 187.

72 *See* Engelberg, *supra* note 67, at 397.

73 *Id.*

74 *Id.* at 397–98; Lourie, *supra* note 47, at 532.

of Representatives tally; fog had prevented many in favor of the bill from reaching Washington to cast their votes.[75]

Around the beginning of the Ninety-eighth Congress, a district court decision in *Roche Products, Inc. v. Bolar Pharmaceuticals Co.*, and the subsequent appellate decision from the United States Court of Appeals for the Federal Circuit, *ex poste* and quite coincidentally demonstrated the good fortune of that bill's failure. In the district court action, plaintiff Roche Products, Inc. ("Roche"), the NDA holder for sleep medication Dalmane (flurazepam hcl) and the owner of U.S. Patent No. 3,299,053 ("the '053 Patent") for that pharmaceutical compound, sued to enjoin Bolar Pharmaceuticals Company ("Bolar") from manufacturing and using the compound for purposes of preparing its own FDA application.[76] Bolar did not dispute that it was using flurazepam hcl for that purpose, and there was no dispute that Bolar did not intend to commercially market its flurazepam hcl product until after expiration of the '053 Patent.[77]

Roche contended that even though Bolar's manufacture and use was strictly for purposes of obtaining government approval to market a competing flurazepam hcl product, it nevertheless still constituted infringement under 35 U.S.C. § 271(a).[78] The district court disagreed and denied the injunction.[79] On appeal, the Federal Circuit reversed.[80] The court reasoned that "use" as provided in section 271(a) of the Patent Act covered Bolar's activities, and the judicially created "experimental use" exception to that provision did not apply—Bolar's activities were for commercial reasons, and as such they were sanctionable.[81] As a result of this holding, patent law would now prohibit generic pharmaceutical companies from even preparing to seek FDA approval to market a generic competitor to an FDA-approved, patent protected pharmaceutical compound until the expiration of the relevant patents. This effectively would extend market exclusivity for NDA holders beyond the statutory patent term to include the period of time post-expiry of a patent that it took for a generic applicant to both prepare its application and to obtain FDA approval.[82] Had the legislation introduced in the Ninety-seventh Congress to extend patent terms not been defeated, the *Roche* decision could have amounted to a death knell for generic pharmaceuticals.

With the interests of appropriate patent term durations on the minds of innovator companies, and with the interests of ensuring the preservation

75 Lourie, *supra* note 47, at 532.

76 Roche Prods., Inc. v. Bolar Pharm. Co., 572 F. Supp. 255, 256 (E.D.N.Y. 1983).

77 *Id.*

78 *Id.* at 257.

79 *Id.* at 258.

80 Roche Prods., Inc. v. Bolar Pharm. Co., 733 F.2d 858, 867 (Fed. Cir. 1984).

81 *Id.* at 863.

82 *See* Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 670 (1990).

of their industry on the minds of generic pharmaceutical companies, the deliberation over what would become known as the Hatch–Waxman Act began in earnest. The goal was to reconcile "two seemingly contradictory objectives, namely, 1) to make lower–costing generic copies of approved drugs more widely available and 2) to assure that there were adequate incentives to invest in the development of new drugs."[83]

The resulting Hatch–Waxman statutory framework is an incredibly complex, but arguably efficient, mechanism whereby parties seeking to market generic versions of FDA–approved drugs can do so through clearly established and well–defined means. Hatch–Waxman artfully blends awards of patent exclusivity and regulatory exclusivity in an effort to balance between its two seemingly contradictory objectives. The innovative NDA holders are required to identify in their NDA any relevant patent information to be listed in the FDA's Orange Book,[84] and potential generic competitors have the obligation to certify to the FDA as part of their Abbreviated New Drug Application ("ANDA") that their product will not infringe any valid and enforceable patents listed in the Orange Book.[85] Pure market exclusivity is then determined on the basis of applicable regulatory exclusivity periods and any patent exclusivity that might be relevant.[86] Also, to eliminate the potential effect that the *Roche* decision would have had on the development of generic pharmaceutical drug candidates prior to filing an ANDA, the Hatch–Waxman Act also created what is considered to be "an artificial act of infringement" in creating 35 U.S.C. § 271(e).[87]

Section 271(e) defines the filing of an ANDA with the FDA, where the intent of the ANDA is to market a generic product prior to expiration of any relevant patent, to be an act of patent infringement.[88] This is not to say that a generic company is liable for patent infringement merely because it files an ANDA—thus the "artificial" component to the act of patent infringement. Rather, the statute was enacted merely to confer subject matter jurisdiction in federal district court over a patent infringement action. The innovator company thus is able to seek adjudication of potential patent infringement against an ANDA filer before commercial launch of the generic competitor, to the benefit of both the innovator and generic companies alike.

The innovator NDA holder enjoys numerable benefits from the various provisions in Hatch–Waxman: First, it is entitled to receive notice of any ANDA application that raises a patent challenge against any of its patents listed in the Orange Book, and it must receive such notice within 20

83 Engelberg, *supra* note 67, at 389.

84 21 U.S.C. § 355(b)(1) (2006).

85 § 355(j)(2)(B)(iv)(II).

86 *See* § 355(b)(1); sources cited *supra* note 56.

87 *See* Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 271(e)(2)(A) (2006).

88 *Id.*

days from the date the FDA accepts such an ANDA for consideration.[89] This absolves the NDA holder from the sometimes arduous task of monitoring markets to determine whether potential patent infringement is afoot. Second, while the NDA holders are not obligated to bring suit, they are incentivized do so within forty–five days of receiving notice.[90] If they do, a statutory 30–month stay is triggered that prohibits the FDA from approving that ANDA during its pendency.[91] The stay serves as a *de facto* preliminary injunction against the ANDA applicant to prevent any commercialization of any competing product for the duration of the stay. Third, the Act effectively requires the ANDA applicant to offer the NDA holder confidential access to proprietary documents necessary to form an opinion as to whether and how the proposed generic drug product might infringe any of the Orange Book–listed patents.[92] Thus, the sometimes combative and uncertain initial steps to patent litigation are accounted for by statute. The NDA holder is effectively informed of potential bases for bringing a patent infringement suit rather than having to discover them independently.

The benefits enjoyed by generic pharmaceutical companies are equally valuable, if not more so. Hatch–Waxman not only provides a path certain by which generic companies may file less costly abbreviated new drug applications, but the artificial act of infringement created by section 271(e) saves generic drug applicants from exposure to potentially crippling damages awards for infringement. Again, section 271(e) permits patent infringement suits by innovator companies prior to commercial launch of a competing generic product. So long as the innovator files suit prior to commercial launch of the generic competitor, no basis for damages can be pled, and the only relief the innovator may seek is injunctive. The reward of a 30–month stay of FDA approval for timely filing suit incentivizes innovator companies to file early enough to prevent damages from becoming an issue. The resulting worst case scenario for a generic company should they lose the ensuing patent infringement suit, then, is that it must delay its intended commercialization of its product until after expiration of the relevant patents. While many generic drug companies will state that this loss is not insignificant, none will contest that such a loss pales in comparison to the damages award it would otherwise have to pay if suit could not be brought prior to commercial launch.

Additional benefits are conferred upon generic drug applicants as well. For instance, enactment of section 271(e) superseded the decision of the

89 21 U.S.C. § 355(b)(3)(B)–(C), (j)(2)(B)(ii)–(iii).

90 *See* § 355(c)(3)(C), (j)(5)(B)(iii).

91 *Id.*

92 *See* 21 U.S.C. § 355(c)(3)(D)(i)(III) (West Supp. 2011); *see also* § 355(j)(5)(C)(i)(I)(cc) (West Supp. 2011) (barring generic applicant from seeking declaratory judgment of non–infringement if "offer of confidential access" is not provided).

Federal Circuit in *Roche*.[93] Therefore, generic drug companies may now manufacture and use patented pharmaceutical compounds and their uses without fear of infringement, so long as the manufacture and use is solely for purposes of preparing its ANDA application.[94] In certain circumstances, generic applicants are also eligible for procedurally imperfect market exclusivity periods, which keep other competing generic drug products from the market for up to 180 days from the time the first generic drug product is commercially launched.[95] Considering the explosion in ANDA filings within the last decade,[96] one can safely say that sufficient incentives have been enacted to enable the generic pharmaceutical industry to thrive.

After considering the background of, and the incentives contained in, the Hatch–Waxman Act, one must look at the data required as part of an ANDA in order to understand the motivation to enact the BPCIA. Like innovative drug products submitted as part of an NDA, generic drug products must be deemed both safe and effective in order to merit FDA approval for commercial marketing.[97] Unlike the innovative drug products, however, generic drug products (because of Hatch–Waxman) generally do not have to be subject to the wealth of studies and clinical evaluations required for a reference, innovator product. Instead, generic drug products need only be sufficiently similar to the reference product (the latter already having been FDA approved as safe and effective) to garner FDA approval. Specifically, a generic drug applicant must show merely that the proposed generic drug is comprised of the same active ingredient, is available in the same strength and dosage form, and uses the same route of administration as the reference drug.[98] The generic drug applicant must also submit "bioequivalence" data in support of its application.[99] If the FDA deems the generic drug to be bioequivalent to the innovative drug, the generic drug receives a "Therapeutic Equivalent" designation and can be "substituted for" the innovative drug with the expectation that it will produce the same effect.[100] If bioequivalence cannot be established, the generic drug may

93 *See* Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 670–71 (1990).

94 35 U.S.C. § 271(e)(1) (2006).

95 21 U.S.C. § 355(j)(5)(B)(iv) (2006).

96 David E. Korn et al., *A New History and Discussion of 180" Exclusivity*, 64 FOOD & DRUG L.J. 335, 384–85 (2009).

97 *See* 21 U.S.C. § 355(a), (b).

98 § 355(j)(2)(A)(ii)–(iv).

99 § 355(j)(2)(A)(iv).

100 FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS iii–iv (31st ed. 2011) (on file with author).

still be approved, but it would receive a lesser rating of "Pharmaceutical Equivalent."[101]

The FDA defines "Bioequivalence" as follows:

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.[102]

While this definition is far from precise (e.g., "absence of significant difference"), it is unmistakably clear in at least one respect. Using "bioequivalence" as "an effective surrogate"[103] to determine safety and efficacy of a proposed generic drug product obviates the need for human clinical trials—"bioequivalence . . . [can be] demonstrated though relative simple analyses such as blood level testing."[104] Therefore, a generic drug applicant can forego the immense expense of conducting clinical trials to prove the safety and efficacy of its proposed generic drug product, invest far less in obtaining the necessary approvals to ready that product for commercialization, and ultimately charge the customer significantly less for its drug than the innovator would for its own.

These cost savings have passed through to consumers. Since its enactment, the Hatch–Waxman Act has saved the public, and notably the government, hundreds of billions of dollars. In the last decade alone, over $700 billion in savings were realized "without the disastrous effects on pharmaceutical innovation that were predicted when [the ANDA/generic] pathway was initially being developed."[105] Indeed, investment in research

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101 *Id.*

102 Bioavailability and Bioequivalence Requirements, 21 C.F.R. § 320.1(e) (2011).

103 *See* Mossinghoff, *supra* note 65, at 191.

104 *How Do Drugs and Biologics Differ?*, BIOTECHNOLOGY INDUS. ORG. (Nov. 10, 2010), http://www.bio.org/node/53.

105 *Hearings*, *supra* note 14, at 116 (Nov. 2, 2010 testimony of Sara Crager).

and development by innovator pharmaceutical companies has steadily and rapidly increased since the Act's passage in the 98th Congress.[106]

Despite the success it has achieved in promoting drug innovation while lowering costs to consumers for drug products, Hatch–Waxman is not without its limitations. Most notably, and as noted earlier, the Hatch–Waxman Act was not designed to accommodate abbreviated applications for biologic medicinal therapies. Indeed, Hatch–Waxman amended and supplemented provisions of the FDCA, the Act that has required government approval to market synthetic drugs since its passage in 1938.[107] Hatch–Waxman did not affect the PHSA, the 1944 revision and recodification of the Biologics Act of 1902, under which innovative biologic medical therapies have been subject to governmental scrutiny.[108] However, limiting Hatch–Waxman's reach to synthetic drugs only was not mere oversight. Understanding the fundamental differences between drugs and biologics reveals that regulating drug and biologic treatments under different sections of the United States Code is not a result of stereotypical government inefficiencies.

II. Synthetic Drug vs. Biologic Formulation: Why Hatch–Waxman Cannot Accommodate Biosimilars Applications

While drugs and biologics are both used to treat various disease states and must be FDA–approved for such use before commercial marketing in the United States, the similarities arguably end there. Nearly all aspects of biologics differ from drugs[109]: "The inherent differences between these two classes include product and active agent sources, identity, structure, composition, manufacturing methods and equipment, intellectual property, formulation, handling, dosing, regulation, and marketing."[110] Because the purpose of this article is to provide the reader only with sufficient knowledge to understand the inapplicability of the Hatch–Waxman statutory and regulatory regime to biologics, not to explain in exhaustive detail the myriad differences between the two classes of medicinal therapies, most of these differences are irrelevant here. For this purpose, a brief examination of the differences in structure and composition, product and active agent sources, and manufacturing methods and equipment will suffice.

With respect to structure and composition, drugs are smaller and far less complexly organized than biologics. Drugs generally have very few atoms comparatively, and their structures are easily displayed graphically by

106 *See* Cong. Budget Office, *supra* note 30, at 17.

107 *See* Carver et al., *supra* note 14, at 671, 673.

108 *See id.* at 677, 682–83.

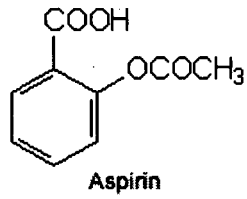
109 Ronald A. Rader, *(Re)defining Biopharmaceutical*, 26 Nature Biotechnology 743, 744 (2008).

110 *Id.*

way of diagrams showing bonds of specific atoms.[111] By contrast, biologics contain a far greater number of atoms, having molecular masses "two to three orders of magnitude greater" than drug counterparts, "and involve many additional levels of structural complexity."[112] The complex nature of biologics is attributable to many factors, including the fact that biologics "invariably consist of more than one molecular entity, and are usually mixtures of many closely related molecular species."[113] Some biologics are even more complex and are impossible to completely characterize with current technology.[114]

To better illustrate the differences in size and structural complexity when comparing drugs with biologics, consider the comparison of Aspirin (drug) and Aranesp® (biologic):

Aspirin, perhaps less commonly known as acetylsalicylic acid, is an "analgesic, anti-inflammatory, antipyretic and . . . inhibitor of platelet aggregation."[115] In common parlance, Aspirin is used for pain relief, reduction of swelling, reduction of fever, and to a lesser extent for blood thinning. The structural composition of Aspirin is easily described as $C_9H_8O_4$, its molecular weight is equal to approximately 180.1574 Daltons, and its skeletal diagram is uncomplicated as shown in Figure 1:



Aspirin

Figure 1[116]

Aranesp®, less commonly known as darbepoetin alfa, is an erythropoiesis-stimulating protein manufactured and commercialized by Amgen, Inc. that is FDA-approved for the treatment of anemia (i.e., a shortage of red blood cells or hemoglobin in the body) stemming from either chronic kidney

111 LUBERT STRYER, BIOCHEMISTRY 2–3 (2d ed. 1981).

112 Rader, *supra* note 109, at 744. *See generally* STRYER, *supra* note 111, at 11–37 (providing further explanation of this difference).

113 Austl. Gov't Dep't of Health & Ageing, *Discussion Paper on Similar Biological Medicinal Products*, PHARMACEUTICAL BENEFITS SCHEME (July 1, 2010), http://www.pbs.gov.au/info/publication/factsheets/shared/2010-07-01-Discussion_paper_on_SBMPs.

114 JUDITH A. JOHNSON, FDA REGULATION OF FOLLOW-ON BIOLOGICS 2 (2010), *available at* http://www.primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.pdf.

115 *What is Aspirin?: The Chemistry of Aspirin*, ASPIRIN FOUND., http://www.aspirin-foundation.com/what/chemistry.html (last visited Aug. 13, 2011).

116 *Id.*

disease or the effects of certain chemotherapy.[117] Aranesp® is designed to stimulate erythropoiesis (the process of red blood cell [erythrocyte] production) by the same mechanism as endogenous erythropoietin ("EPO"),[118] a cytokine hormone and glycoprotein ordinarily produced naturally from endothelial cells in human kidneys, and to a lesser extent, the liver.[119] Amgen's manufactured EPO resembles endogenous EPO, and can be used generally in instances where a human's natural production of endogenous EPO is deficient.[120] (EPO, such as recombinant human EPO ["rHuEPO"] is also the substance used by some high–performance athletes for purposes of "blood doping," or creating extra oxygen–carrying hemoglobin found in red blood cells for prolonged endurance.)[121]

Unlike Aspirin, the structural composition of Aranesp® or any other EPO is difficult to describe. Without pictures or diagrams, it is realistically impractical.[122] According to Paolo DaSilva and David Marcey of the Biology Department of California Lutheran University, a brief description of EPO includes the following:

> EPO contains a four–helical bundle with a topology shared with other cytokines. The four helices of this bundle are termed A, B, C, and D. The A and D helices are linked by a disulphide bridge.

117 *Highlights of Prescribing Information for Aranesp*, FDA (June 2011), http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951Orig1s5173_103951Orig1s5258lbl.pdf.

118 *Id.*

119 Paolo DaSilva & David Marcey, *Erythropoietin Bound to the Extracellular Domains of Two EPO Receptors*, (2011), http://www.callutheran.edu/BioDev/omm/jmol/epo/epo.htm.

120 *See Highlights of Prescribing Information for Aranesp*, *supra* note 117.

121 *See, e.g.*, Siamak T. Nabili, *Erythropoietin (EPO) & the EPO Test*, MEDICINENET.COM, http://www.medicinenet.com/erythropoietin/page3.htm (last visited Aug. 14, 2011).

122 Even the U.S. Court of Appeals has recognized as much, noting that "providing a description in written form is not practicable" for biologic inventions. Enzo Biochem, Inc. v. Gen–Probe Inc., 323 F.3d 956, 970 (Fed. Cir. 2002).

> The B and C helices are linked by a short loop. In addition to the A–D helices, EPO contains two short helices, B' and C'.[123]

See Figure 2:

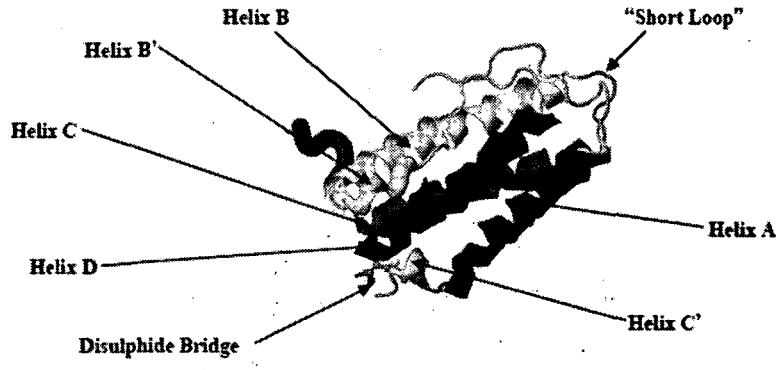


Figure 2[124]

DaSilva and Marcey explain, "The structure of EPO is further stabilized by numerous hydrophobic interactions. For example, aromatic and hydrophobic amino acids of the D–helix pack against hydrophobic residues of helices A, B, and C, helping to form the hydrophobic core of EPO."[125] See Figure 3:

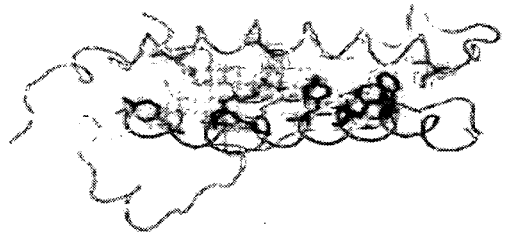


Figure 3 (Graphic representation of hydrophobic interactions within EPO)[126]

As is evident from even a cursory comparison of Figure 1 with Figures 2 and 3, the structural differences between Aspirin (drug) and an EPO like Aranesp® (biologic) are vast. Aspirin contains only a benzene ring, three

123 DaSilva & Marcey, *supra* note 119.

124 *Id.*

125 *Id.*

126 *Id.* (top view).

additional carbon atoms, eight hydrogen atoms, and four oxygen atoms;[127] EPO, among other components, contains 165 amino acids and multiple carbohydrate (oligosaccharide) side chains.[128] The difference in the sizes is equally disparate—the molecular weight of Aranesp® is approximately 37,000 Daltons, roughly 205 times greater than Aspirin.[129] Pictorially, the relative size and complexity of the two products can be seen in Figure 4 below.

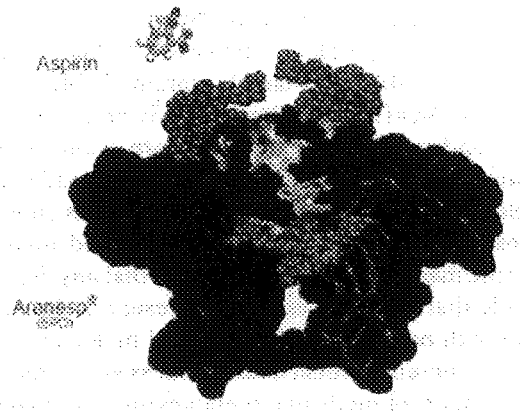


Figure 4 (Comparison between structures of aspirin and erythropoietin)[130]

The disparities in size and structure between Aspirin and Aranesp® are not unique to these products, and they are characteristic of the differences between the classes of drug and biologics at large. "Compared with drugs, bio[logics] are composed of many more atoms . . . . Most bio[logics] involve proteins or other biopolymers comprising many, usually hundreds or thousands, of chemical subunits or monomers (e.g., amino acids or nucleotides), with each subunit a potential site for structural variation."[131] Simply put, biologics are immeasurably more complex in size and structure than are drugs.[132]

In addition to the disparity in size and structure between the two classes, the disparity in product and active agent sources among drugs and biologics, as well as the differences in their respective manufacturing methods and equipment, are no less significant. Active agents of biologics, for instance,

127 *See What is Aspirin?*, *supra* note 115.

128 *See* DaSilva & Marcey, *supra* note 119; Wael Ebied, *Production of Biosimilars/Biogenerics in Developing Countries: Challenges and Opportunities, SEDICO Case Study Egypt* (Oct. 2010), eps-egypt.net/files/pdf/law/drebid.ppt [hereinafter Ebied Presentation].

129 *See Highlights of Prescribing Information for Aranesp*, *supra* note 117.

130 Ebied Presentation, *supra* note 128.

131 Rader, *supra* note 109, at 744.

132 *See* Austl. Gov't Dep't of Health & Ageing, *supra* note 113.

generally are "a complex mixture of molecular subspecies with a range of variations in structural aspects (e.g., due to amino acid substitutions, twists and turns in chain structures, intra– and inter–chain linkages, side–chain modifications and aggregation)," and they are therefore extraordinarily difficult to analyze or sometimes identify.[133] Active agents of drugs, in contrast, are easily identified and analyzed. This difference stems largely from the way in which these classes of drugs are manufactured.

Manufacturing a drug is, relatively speaking, quite straightforward. Typically it involves chemical synthesis, "made by combining specific chemical ingredients in an ordered process."[134] The process is very predictable, easily repeatable, and largely unremarkable. In some cases, such as in the formulation of Aspirin, the process is so easy as to be available on the internet,[135] and student laboratory kits are available to make it at home.[136] In the uncommon instances where drugs are made at least in part from specific biological, rather than chemical, ingredients, those ingredients are usually exposed to conditions (extreme heat) and involve materials (solvents) during the manufacturing process such that any organism or other biological molecule that might otherwise be present in the drug would be destroyed.[137] And with no organism or biological molecule in the finished drug product, the "inherent diversity, randomness and complexity" found in biological components of medicinal therapies are eliminated.[138]

Manufacturing a biologic is exponentially more complicated, ostensibly by definition: "A biologic is manufactured in a living system such as a microorganism, or plant or animal cells."[139] The process involves several steps, and even a mere overview of the protocol often used to develop a biologic is indicative of the stark contrast between drugs and biologics. It also reveals why the bioequivalence measure used to identify and approve generic drugs under Hatch–Waxman is inappropriate to extend to the identification and approval of biosimilars.

To manufacture a biologic, a seven–step process generally is employed: host cell development; establishment of a cell bank; protein production; purification; analysis; formulation; and finally, storage and handling.[140] The specifics of each step are far beyond the scope of this article, but the

133 Rader, *supra* note 109, at 745.

134 *See How Do Drugs and Biologics Differ?*, *supra* note 104.

135 *See Aspirin*, How Products Are Made, http://www.madehow.com/Volume-1/Aspirin.html (last visited Aug. 13, 2011).

136 *See Synthesis of Aspirin – Student Laboratory Kit*, Flinn Sci., Inc., http://www.flinnsci.com/store/Scripts/prodView.asp?idproduct=16820&noList=1 (last visited Aug. 1, 2011).

137 Rader, *supra* note 109, at 744.

138 *Id.*

139 *See How Do Drugs and Biologics Differ?*, *supra* note 104.

140 Siriwan Chaisomboonpan, *Biosimilar* (Dec. 25, 2008), www.dmsc.moph.go.th/webroot/drug/km/docs/Biosimilar.ppt [hereinafter Chaisomboonpan Presentation].

yield of the protocol is significant: through identification and selection of a particular human gene sequence, introduction of that gene sequence to a host cell, production by that host cell of a complex protein structure, and processing of that protein structure into the final biologic product, it follows that the final biologic product necessarily will be unique to the *particular* host cell selected in the initial stages of production (as well as a function of particular conditions to which the particular host cell is exposed during protein production, and of numerous other factors).[141] It is for this reason that "for biologics, 'the product is the process.'"[142]

Consider the manufacturing processes of Aranesp®, for example. The particular gene sequence selected and isolated is erythropoietin, and that gene is introduced into a Chinese Hamster Ovary ("CHO") cell for development.[143] The resultant byproduct of that CHO cell is unique to that very cell.[144] The same erythropoietin gene sequence introduced into different CHO cells will admittedly result in very similar byproducts, but they will not be identical.[145] Moreover, the same erythropoietin gene sequence introduced to the same CHO cell can result in similar but ultimately different byproducts if the conditions to which the CHO cell is exposed are varied during protein production.[146] And if the steps conducted in subsequent purification of the protein, formulation, and even storage and handling vary, the resultant biologic product will vary accordingly.[147] To prevent these variations to the extent possible, "biologics manufacturers [like Amgen] . . . tightly control the source and nature of starting materials, and consistently employ hundreds of process controls that assure predictable manufacturing outcomes."[148]

As alluded to earlier, however, employment of hundreds of process controls by one manufacturer will not prevent variation among biologics where they are produced by different manufacturers. An example of such variation can be seen in Figure 5, *infra*. Figure 5 compares pictorially recombinant human erythropoietin ("rHuEPO") manufactured by a third party with Amgen's Aranesp®.[149] Both are made by way of introducing the erythropoietin gene sequence into CHO cells; both are very similar in appearance, but they are not the same.[150] Aranesp®, as shown in Figure 5,

141 *Id.*

142 *See How Do Drugs and Biologics Differ?*, *supra* note 104 (quoting another source).

143 *See Highlights of Prescribing Information for Aranesp*, *supra* note 117.

144 *See* Ebied Presentation, *supra* note 128.

145 *See* Chaisomboonpan Presentation, *supra* note 140.

146 *Id.* at 8.

147 *Id.* at 9, 13; *see How Do Drugs and Biologics Differ?*, *supra* note 104.

148 *See How Do Drugs and Biologics Differ?*, *supra* note 104.

149 *See* Ebied Presentation, *supra* note 128.

150 *Compare id.*, *and Highlights of Prescribing Information for Aranesp*, *supra* note 117, *with EPO, Human Recombinant, Ultra Pure*, CELLSCIENCES.COM, http://www.cellsciences.com/PDF/

contains five N–linked oligosaccharide chains, whereas rHuEPO contains only three. The clinical significance of this difference may be insubstantial, but it may not be. Without lengthy and costly evaluation of the potentially clinically significant differences between the two biologics, deeming one to be "biosimilar" to the other could be considered irresponsible. Certainly deeming one "bioequivalent" or "generic" to the other would be.[151]

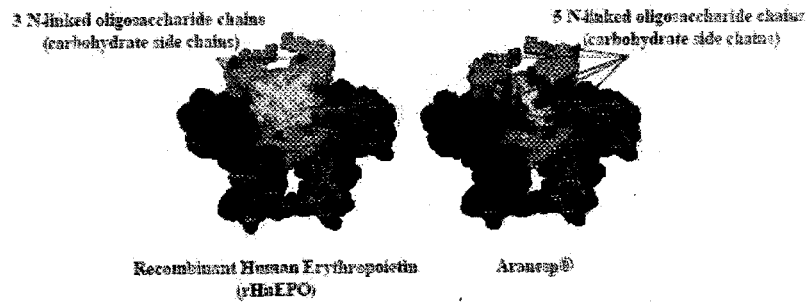


Figure 5 (Comparison between structures of rHuEPO and Aranesp®)[152]

Therein lies the problem with applying Hatch–Waxman standards for bioequivalence to biologics: The complex nature of manufacturing, characterizing, and evaluating biologics resulting from necessarily different processes (e.g., different host cells, different ambient environments during production) among different manufacturers, where "the process is the product,"[153] makes bioequivalence determinations unrealistic. From merely a cost perspective, conducting the tests necessary for a biologic to be deemed bioequivalent would be prohibitive—the end cost of producing a "bioequivalent biologic" would be roughly the same as producing an innovative biologic.[154] The cost of producing an innovative biologic, however, is precisely what made the passage—and what makes the success—of a streamlined approval process for biosimilars so critical. The expense involved in manufacturing biologics—including costs for the maintenance of the requisite process controls to ensure production of consistent biologic products, the lengthy and numerous clinical studies necessary to accurately assess safety and efficacy, and even the state of the art assays required to merely categorize the biologic—all result in rendering the average annual cost of a biologic treatment regimen to be 72 times

CRE600B.pdf (last visited Aug. 14, 2011).

151 *See Hearings*, *supra* note 14, at 16–18, 22–28, 40–42, 97–101, 199–202, 308–10 (Nov. 2, 2010 testimony of Marcia Boyle, Janet Wyatt, Seth Ginsberg, Laszlo Endrenyi, Gregory Schimizzi, and James Sykes); *see also* JOHNSON, *supra* note 114.

152 Ebied Presentation, *supra* note 128.

153 *See* Rader, *supra* note 109, at 745–46.

154 *Hearings*, *supra* note 14, at 116 (Nov. 2, 2010 testimony of Sara Crager).

more expensive than its small molecule drug treatment counterpart.[155] The BPCIA is supposed to reduce this disparity. Unfortunately, the terms of the current BPCIA may not result in such a reduction.

III. The Terms of the BPCIA and Corresponding Provisions of Hatch–Waxman

In its broadest sense, the BPCIA can be viewed as containing three distinct but interrelated components. One outlines the necessary information biosimilars applicants must provide to the FDA as part of their application (hereinafter, "subsection (k) applications"); a second provides for the regulatory exclusivities that will be awarded to either initial biologics applicants ("reference product sponsors") or first subsection (k) applicants; and the third outlines the patent litigation framework that will apply should such a suit result from the filing of a subsection (k) application. Each distinct component of the BPCIA will be addressed and compared to the corresponding Hatch–Waxman provisions in turn.

A. The Abbreviated Applications

The very purpose of the BPCIA was to create an abbreviated FDA approval process for biosimilars, and the Act provides potential subsection (k) applicants two options from which to choose. The first option allows for an applicant to submit its proposed "Follow–on" biologic ("FOB") for designation merely as a "biosimilar."[156] The second permits the applicant to submit its proposed FOB to heightened scrutiny to potentially receive the designation of "interchangeable."[157] In either case, the applicant must provide considerable information. Analytical studies, animal studies, and/or clinical studies comprise only one subset of the data that must be included within any subsection (k) application.[158] Information demonstrating that the FOB utilizes the same mechanism(s) of action and the same route of administration as the reference product is also required.[159] In addition, the subsection (k) applicant must verify that the FOB is to be used only for the same conditions as previously approved for the reference product, that the dosage form and strength of the FOB is the same as the reference product,

155 Gopal Dasika, *Biologics with a Greater Reach*, BioSpectrum, Nov. 6, 2009, http://biospectrumindia.ciol.com/content/BioSpecial/10911062.asp.

156 *See* 42 U.S.C.A. § 262(k)(2)(A) (West 2011).

157 § 262(k)(2)(B), (k)(4); *see also* Request for Comments, *supra* note 2, at 61497–98.

158 § 262(k)(2)(A)(i)(I).

159 § 262(k)(2)(A)(i)(II), (IV).

and that the facility in which the proposed FOB is manufactured meets applicable government standards.[160]

For an FOB to achieve an interchangeability determination, additional data is required. Beyond the information required to show that the FOB is "biosimilar to the reference product," a subsection (k) applicant must provide sufficient information to demonstrate that the FOB "can be expected to produce the same clinical result as the reference product in any given patient."[161] For those FOBs that will be administered more than once in any given patient, the subsection (k) applicant must also show that the patient would respond to repeated treatment alternating between the reference product and the FOB, or switching from the reference product to the FOB, in the same manner as he or she would if given repeated treatment with the reference product alone.[162]

The options and requirements of the BPCIA for abbreviated biologics applications essentially mirror those contained in Hatch–Waxman for abbreviated drug applications, except that the BPCIA codifies in statutory language what the FDA has imposed through its delegated regulatory powers.[163] The distinction between the designations "biosimilar" and "interchangeable" under the BPCIA is roughly akin to the distinction made by the FDA in determining whether a drug is a "Pharmaceutical Equivalent" or a "Therapeutic Equivalent" under Hatch–Waxman.[164] As will be addressed in detail in Parts V and VI, however, this is one of the most glaring flaws of the BPCIA. The legislature seems to have presumed that because the distinction between similarity and substitutability can be made in the synthetic drug context, it follows that a similar distinction can be made with biologics. This presumption is potentially fatal to the success of the BPCIA.

B. The Market Exclusivities

The BPCIA appears to contain generous incentives to stimulate biologic innovation as well as competition. As a reward for innovation, the BPCIA provides both data exclusivity and procedurally perfect market exclusivity for any reference product that ultimately obtains FDA approval.[165]

160 § 262(k)(2)(A)(i)(III)–(V).

161 § 262(k)(4)(A).

162 § 262(k)(4)(B).

163 *Compare* § 262(k)(2) (providing for "biosimilar" and "interchangeable" designations), *with Orange Book Preface*, *supra* note 100 (providing for "pharmaceutical equivalent" and "therapeutic equivalent" designations).

164 *Compare* § 262(k)(2) (providing for "biosimilar" and "interchangeable" designations), *with Orange Book Preface*, *supra* note 100 (providing for "pharmaceutical equivalent" and "therapeutic equivalent" designations).

165 *See* § 262(k)(7)(A)–(B).

The data exclusivity provision forbids a subsection (k) application from submitting its application any earlier than four years after the date the reference product was first approved by the FDA.[166] The procedurally perfect market exclusivity provision bars the FDA from approving any subsection (k) application for a period of twelve years following FDA approval of the reference product.[167] Interestingly, the practical effect of concomitant data and procedurally perfect market exclusivities is that the data exclusivity provision is rendered almost entirely superfluous. From a market perspective, no competitor can enter the market for twelve years regardless of whether data exclusivity applies. Query then what purpose the data exclusivity provision serves.

To reward early biologic competition, the BPCIA awards the first subsection (k) application that successfully obtains an interchangeability determination up to one year of procedurally imperfect market exclusivity.[168] When viewed in context of the forfeiture provisions surrounding the grant of exclusivity, however, the grant is completely illusory. This is another of the most glaring flaws of the BPCIA, and it, too, will be addressed in detail in Part IV, *infra*.

By comparison, all grants of exclusivity conferred under the Hatch–Waxman statutory regime are real. Hatch–Waxman confers no procedurally perfect market exclusivities, and instead it relies on a combination of patent exclusivity and data exclusivity to incentivize synthetic drug innovation.[169] To encourage synthetic drug competition, Hatch–Waxman provides for up to 180 days of procedurally imperfect market exclusivity.[170]

C. The Contemplated Patent Litigation Framework

The contemplated patent litigation framework contained in the BPCIA comprises nearly a third of the total provisions of the Act itself.[171] This component of the Act constitutes a radical departure from the patent litigation framework contemplated under the Hatch–Waxman Act. Indeed, the litigation framework of the BPCIA constitutes a radical departure from traditional patent litigation procedure in any respect, for reasons that will be readily apparent.

Like Hatch–Waxman, the BPCIA has modified the Patent Act such that the filing of an abbreviated application with the FDA shall constitute

166 § 262(k)(7)(B).

167 § 262(k)(7)(A).

168 § 262(k)(6).

169 *See supra* note 56 and accompanying text.

170 *See* 21 U.S.C. § 355(j)(5)(B)(iv) (2006).

171 *Compare* 42 U.S.C.A. § 262(l) (West 2011), *with* Patient Protection and Affordable Care Act, Pub. L. No. 111–148, § 7001(b), 124 Stat. 119, 804 (2010) (to be codified at 42 U.S.C. § 271(e)).

an artificial act of patent infringement, presuming of course that relevant patent rights exist.[172] Also like Hatch–Waxman, the BPCIA requires that upon FDA receipt of the abbreviated application, the applicant has twenty days to notify the reference product sponsor of the FDA's acceptance of the application.[173] The remainder of the BPCIA litigation framework diverges significantly from what has been proposed and practiced under the Hatch–Waxman Act.

Under the BPCIA, the next step is the first in a series of steps designed to serve as pre–litigation "good faith" negotiations. Recall that under Hatch–Waxman the NDA holder has the obligation to submit to the FDA patents relevant to the approved product for listing in the Orange Book.[174] The ANDA applicant therefore receives notice that the manufacture, use, sale, or offer for sale of the product described in any ANDA submission might result in infringement of one or more of the Orange Book–listed patents. Under the BPCIA, the subsection (k) applicant receives no like notice.[175] The Orange Book protocol of Hatch–Waxman has been eliminated. The BPCIA instead requires that the reference product sponsor and the subsection (k) applicant engage in serial communications to identify the patents that should be subject to litigation.[176] Further, the BPCIA contemplates potentially two separate patent infringement actions for each subsection (k) application submitted.[177] An overview of the protocol follows:

> Step 1: The FDA accepts the subsection (k) application for filing.[178]
>
> Step 2: The subsection (k) applicant notifies the reference product sponsor about the subsection (k) application within 20 days of step 1.[179]
>
> Step 3: Within 60 days of receipt of notice, the reference product sponsor provides the subsection (k) applicant

172 *See* Patient Protection and Affordable Care Act § 7002(c)(1).

173 42 U.S.C.A. § 262(l)(2) (West 2011).

174 *See* 21 U.S.C. § 355(b)(1) (2006).

175 *See generally* 42 U.S.C.A. § 262(l) (West 2011) (leaving to private parties the task of identifying patents relevant to any BLA and subsequent subsection (k) application).

176 *See id.*

177 *See id.* § 262(l)(6), (8).

178 *Id.* § 262(l)(2)

179 *Id.*

with a list of patents potentially infringed by the product described in the subsection (k) application.[180]

Step 4: Within 60 days of receiving the reference product sponsor's list, the subsection (k) applicant provides its own list of any patents it believes are relevant to the application but that may have been omitted from the reference product sponsor's list. The subsection (k) applicant also must provide a detailed statement concerning its non-infringement, invalidity, and unenforceability positions.[181]

Step 5: Within 60 days of receiving the subsection (k) applicant's list and statement, the reference product sponsor must provide the subsection (k) applicant with a detailed statement concerning its infringement positions and a response to any invalidity or unenforceability arguments previously raised by the subsection (k) applicant.[182]

Step 6: After the subsection (k) applicant's receipt of the statement described in step 5, the parties must engage in "good faith negotiations" in an attempt to agree on a list of patents that should be the subject of an "immediate patent infringement action."[183] The parties have 15 days to negotiate.[184] If the parties reach an agreement on the inventory of patents that should serve as the basis for an immediate action, then the parties skip Step 7, and the reference product sponsor has 30 days from the date of agreement to bring suit on the identified patents under Step 8.[185] Any patents previously identified in Steps 3 and 4 that are not part of the immediate action may be brought in a later action.[186] If the parties fail to reach agreement within 15 days, they proceed to Step 7.[187]

Step 7: In light of the parties' disagreement about which patents to litigate immediately, the BPCIA provides that

180 § 262(l)(3)(A)(i).
181 § 262(l)(3)(B)(i)&(ii)(I).
182 § 262(l)(3)(C).
183 § 262(l)(4)(A).
184 § 262(l)(4)(B).
185 § 262(l)(6)(A).
186 § 262(l)(8)(B).
187 § 262(l)(4)(B).

the subsection (k) applicant shall, after reaching 15 days of disagreement, provide the reference patent sponsor with the number—and just the total number—of patents that it believes should be the subject of immediately litigation.[188] After no later than five days, the parties are to simultaneously exchange identification of the specific patents, up to the number provided by the subsection (k) applicant, that will be litigated immediately.[189] For example, if the subsection (k) applicant provided the number "1," then each side may select one patent to litigate immediately. Because each side may select a different patent (depending on the number of relevant patents at issue disclosed in Steps 3 and 4), a total of two patents might be litigated. Each party might select a different patent for immediate litigation. In the event the subsection (k) applicant selects the number "0," the reference product sponsor may select one patent for immediate litigation.[190] Any patents not selected for immediate litigation at this stage are then eligible to serve as the subject of a second litigation.[191]

Step 8: The reference product sponsor must file suit within 30 days of either the date the parties reached an agreement on the patents to be litigated immediately, or if no agreement was reached in Step 6, from the date

188 § 262(l)(5)(A).

189 § 262(l)(5)(B).

190 § 262(l)(5)(B)(ii)(II).

191 § 262(l)(8)(B).

the parties exchanged identification of the patents to be litigated immediately.[192]

An illustration of the lengthy and complicated pre–litigation framework of the BPCIA described thus far is depicted below in Figure 6:

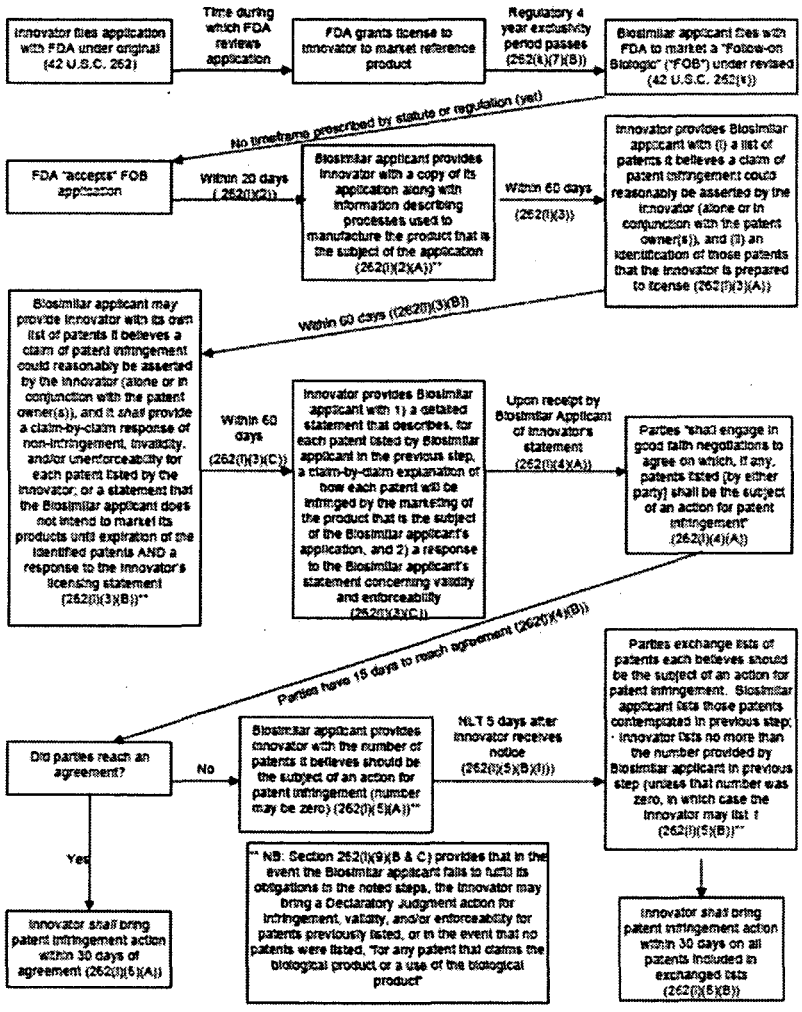


Figure 6 (Overview of BPCIA Litigations, Part I)

As mentioned, the BPCIA also accounts for the possibility of a second litigation stemming from a single subsection (k) application. The purpose

192 § 262(l)(6)(A), (B).

of the second litigation is to account for any patent identified during the good-faith negotiations of steps 3 and 4, *supra*, but not asserted as part of the immediate action.[193] The second litigation would also include claims for the infringement of any patents that might have issued only after the parties identified relevant patents in Steps 3 and 4.[194] The timing of the second action may occur at any time between the subsection (k) applicant's announcement that it intends to launch commercially its FOB product and the time of the actual commercial launch.[195] The BPCIA requires the subsection (k) applicant to give the reference product sponsor notice of its intention to launch no later than 180 days before the intended date.[196] A

193 *See id.* § 262(l)(8)(B).

194 *Id.*

195 § 262(l)(8)(A), (B).

196 § 262(l)(8)(A).

graphic illustration of the circumstances that might surround this second litigation is represented in Figure 7.

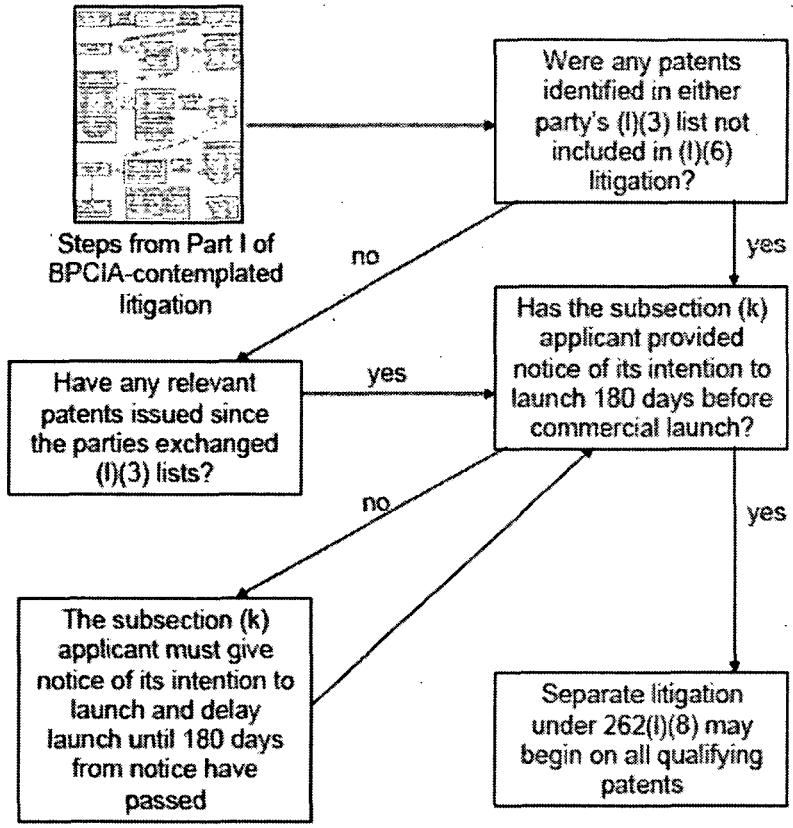


Figure 7 (Overview of BPCIA Litigations, Part II)

IV. The Flaws of the BPCIA and Proposed Solutions

A. Flaws

1. Designation of Interchangeability.—Not least among the flaws contained within the current BPCIA is whether it is realistic to expect the FDA to fashion guidelines by which a proposed FOB can be deemed "interchangeable" as opposed to merely "biosimilar."[197] As explained in

197 *See Hearings*, *supra* note 14, at 90–95 (Nov. 2, 2010 testimony of Marcia Boyle, Janet

Part II, *supra*, a proposed biologic is immeasurably more difficult to evaluate than is a drug. Yet the BPCIA would have the FDA require sufficient clinical data of a subsection (k) applicant such that the FDA could determine conclusively whether a proposed FOB "can be expected to produce the same clinical result as the reference product in *any given patient*."[198] Such a showing is not even required in the drug context, as Hatch–Waxman is entirely silent in distinguishing between Therapeutic Equivalents (interchangeables) and Pharmaceutical Equivalents (biosimilars).[199] In the context of biologics, demonstrating interchangeability under this standard currently is a practical impossibility.[200] Moreover, even if the standard is achievable, it will come at a cost that makes a subsection (k) application fiscally irresponsible to pursue.

A great deal has been published already imploring the FDA to require robust clinical data to accompany any subsection (k) application.[201] Many believe that bestowing a designation of even mere biosimilarity—let alone interchangeability—would be scientifically irresponsible without such clinical data.[202] The demand for data is unsurprising, again, given the complexities inherent in most biologic products. The difficulty the FDA faces, however, is that the greater the amount of clinical data required in a subsection (k) application, the less fiscal sense it makes for a party to file a subsection (k) application. Indeed, if the cost is too great for a subsection (k) applicant to demonstrate biosimilarity—whether because the clinical trials potentially required are too lengthy and costly to conduct, or for any other reason—the subsection (k) applicant would be better served in pursuing other options.

One alternative a prospective subsection (k) applicant might consider, for example, would be to submit its own Biologic License Application ("BLA") to the FDA instead of a subsection (k) application. Prior to enactment of the BPCIA, the PHSA required an FDA-approved BLA of every biologic prior to its commercial marketing in the United States.[203] The BPCIA now provides merely an alternative approval pathway for FDA applicants with FOBs; it is not the only approval pathway for such a product. Any biologic may still be approved as the subject of a BLA. As such, if the cost to submit

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Wyatt, Seth Ginsberg, Laszlo Endrenyi, Gregory Schimizzi, and James Sykes); *see also* JOHNSON, *supra* note 114, at 10–11.

198 42 U.S.C.A. § 262(k)(4)(A)(ii) (West 2011) (emphasis added).

199 *See generally* 21 U.S.C. § 355 (2006) (no distinction between Therapeutic and Pharmaceutical Equivalents); *see also Orange Book Preface*, *supra* note 100 (where distinction is made by regulatory guidance).

200 *See* Steven Kozlowski et al., *Developing the Nation's Biosimilars Program*, 5 NEW ENG. J. MED. 365, 385 (2011) (noting that advancements in technology currently permit assessment of whether products are merely "highly similar").

201 *See Hearings*, *supra* note 14; JOHNSON, *supra* note 114.

202 *Hearings*, *supra* note 14; JOHNSON, *supra* note 114.

203 § 262(a)(1).

a subsection (k) application becomes just as great as it would be to submit a BLA, then the incentive to submit a subsection (k) application will be eliminated. Moreover, prospective subsection (k) applicants opting to file BLAs would avoid the twelve–year procedurally perfect market exclusivity period that they would otherwise face, so they could commercialize their FOBs more quickly. Further still, they would not subject themselves to the otherwise required pre–litigation good–faith negotiations of the BPCIA, and they could avoid the multiple patent infringement suits contemplated by the BPCIA. The ensuing "brand–to–brand" competition that would result from filing a BLA instead of a subsection (k) application would make immeasurably more financial sense to any FOB applicant.[204]

The good news is that the FDA is all too aware of this conundrum, and it has sought assistance from the public at large to recommend courses of action in order to balance successfully the need for subsection (k) clinical data with the need to make the filing of subsection (k) applications a financially responsible option.[205] The bad news is that regardless of the data required to demonstrate biosimilarity of an FOB with a reference product, it will be even more costly to obtain a designation of "interchangeability."[206] And unless a party can obtain status as "interchangeable," which would permit a pharmacist to fill any prescription for the reference product with the FOB without requiring physician approval,[207] the incentive to file a subsection (k) application is faint at best.

2. Illusory Incentives.—Another problem inherent in the current BPCIA is that, even if the standard to obtain an "interchangeability" determination is fiscally responsible to pursue, the incentive to be the first subsection (k) applicant to achieve that designation is illusory. Recall that the BPCIA awards procedurally imperfect market exclusivity to the first subsection (k) applicant to receive the "interchangeability" designation for its FOB. The exact duration of the procedurally imperfect market exclusivity depends on specific circumstances outlined in the Act, but in no event will it last longer than one year.[208] Section 262(k)(6) provides the conditions upon which the duration of the exclusivity period hinges.[209] It specifically

204 *See Hearings*, *supra* note 14, at 117–18 (Nov. 2, 2010 testimony of Sara Crager).

205 Press Release, U.S. Dep't of Health & Human Servs., FDA Requests Input on Development of User Fee Program for Biosimilar and Interchangeable Biological Products (May 9, 2011), *available at* http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm254572.htm#.TqxjF–rJpwk.email; Biologics Price Competition and Innovation Act of 2009; Options for a User Fee Program for Biosimilar and Interchangeable Biological Product Applications for Fiscal Years 2013 Through 2017; Request for Comments, 76 Fed. Reg. 27,062 (May 10, 2011).

206 *Compare* § 262(k)(2)(A), *with* § 262(k)(4).

207 Request for Comments, *supra* note 2, at 61,498.

208 § 262(k)(6).

209 *Id.*

prohibits the FDA from making a determination of "interchangeability" for a second FOB until the earliest of three "triggering events" occurs—A) the one year anniversary of the first commercial marketing of the first interchangeable FOB; B) eighteen months have passed since either (i) a final court decision on all patents included in an (l)(6) litigation or (ii) a dismissal with or without prejudice of such an action; or C) (i) forty–two months have passed since the first FOB was deemed interchangeable, if the FOB applicant has been sued under section (l)(6) and the litigation is still pending, or (ii) eighteen months have passed since the first FOB was deemed interchangeable and the FOB applicant has not been sued under (l)(6).[210] This is not at all straightforward, so we return to the hypothetical first introduced at the beginning of this article to illustrate the illusory nature of this incentive. For these purposes, however, assume that Pferck's ColorView (plutoniox) for the treatment of colorblindness is a biologic rather than a drug.

> Because its product is properly regulated under the PHSA rather than the FDCA, Pferck submits to the FDA a BLA to market ColorView (plutoniox) for the treatment of colorblindness. To ensure it maintains market exclusivity to the fullest extent possible, Pferck holds three issued patents covering plutoniox, and it has two patent applications for methods of treating colorblindness with plutoniox currently pending. Pferck obtains FDA approval to market ColorView (plutoniox) on Tuesday, January 4, 2011.

Under these circumstances, any party that wishes to file a subsection (k) application to compete with ColorView for treating colorblindness must wait until Monday, January 5, 2015 to so file.[211] Now assume that a company called BioSame has developed a biologic called plutoniax, and this company has gathered data sufficient to conclusively show that plutoniax is interchangeable with plutoniox for the treatment of colorblindness in accordance with all FDA–imposed standards. BioSame files its subsection (k) application for plutoniax on the first day it is eligible to do so, January 5, 2015. The FDA accepts BioSame's subsection (k) application for filing, deeming it complete and in accordance with all FDA–imposed standards for filing, on Monday, February 2, 2015. Step 1 of the BPCIA pre–litigation protocol, described *supra*, is complete. Twenty days later, on Monday, February 23, 2015,[212] Pferck receives notification from BioSame that it has filed, and the FDA has accepted, a subsection (k) application for plutoniax.[213]

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210 *Id.*

211 *See* § 262(k)(7)(B).

212 More accurately, this date is twenty–one days later. Twenty days after the deadline is a Sunday. For purposes herein, we shall assume that if the deadline falls on a weekend, it is extended to the next business day.

213 § 262(l)(2).

BioSame also includes a copy of the subsection (k) application.[214] Step 2 has been satisfied.

For sake of simplicity, assume now that both parties comply strictly with the good faith negotiations required by the BPCIA before Pferck can file suit, and assume that neither party attempts any gamesmanship during the negotiations (such as belatedly disclosing infringement or invalidity contentions, belatedly and improperly identifying new patents late in the negotiations, etc.). Pferck informs BioSame, sixty days later on Friday, April 24, 2015, that its subsection (k) application infringes Pferck's three patents, and Pferck informs BioSame that it is not willing to license any of the three.[215] Step 3 is complete. Sixty days thereafter, on Tuesday, June 23, 2015, BioSame responds as it must with its non–infringement, invalidity, and unenforceability positions.[216] Step 4 is complete. Sixty days thereafter, on Monday, August 24, 2015,[217] Pferck provides BioSame with its infringement positions as well as its counters to BioSame's invalidity and unenforceability positions.[218] Step 5 is satisfied.

At this point under Step 6, the parties now have fifteen days, until Tuesday, September 8, 2015, to agree on which patents should be subject to immediate litigation.[219] Assume that they do not agree, and they move to Step 7; Pferck wants to litigate all three immediately, whereas BioSame wants to litigate only one. Therefore, on September 8, 2015, BioSame informs Pferck to select "one" patent for immediate litigation. Within five days, or specifically on Friday, September 11, 2015, Pferck and BioSame exchange the identity of the single patent each has selected for litigation.[220] The patents are different, so two patents are properly the subject of the ensuing (l)(6) litigation.[221] Pferck files suit against BioSame on those two patents twenty–eight days later, on Friday, October 9, 2015, as required under Step 8.

With these dates set, we now calculate the dates of the triggering events. The BPCIA does not permit FDA approval of BioSame's plutoniax to be any earlier than Wednesday, January 4, 2023, twelve years from the date ColorView (plutoniox) became FDA–approved. Assume plutoniax receives FDA approval on that date. Further assume that BioSame first commercially launches plutoniax on that date—its earliest available opportunity. Under these circumstances, the first triggering event is Thursday, January 4, 2024, the one–year anniversary of the first commercial marketing of the

214 § 262(l)(2)(A).

215 § 262(l)(3)(A).

216 § 262(l)(3)(B).

217 This is actually sixty–two days. Sixty days falls on a Saturday. *See supra* note 212.

218 § 262(l)(3)(C).

219 § 262(l)(4).

220 § 262(l)(5)(B)(i).

221 § 262(l)(6)(B).

FOB plutoniax.[222] No subsequent FOB can be deemed interchangeable any earlier unless one of the other two remaining triggering events occurs earlier.

To calculate the date of the second triggering event, we would need to know the date the litigation commenced in Step 8 concluded. The second triggering event will occur eighteen months after either the entry of a final court decision relating to the two patents asserted by Pferck, or a dismissal with or without prejudice of that action.[223] Fortunately, we do not need to calculate the exact date of the second triggering event to conclude that the award of procedurally imperfect market exclusivity is in practice no incentive at all.

For the exclusivity to have any value at all to an FOB applicant, that applicant must have the opportunity to commercialize its product prior to its expiration. The alternative would permit other interchangeable FOBs to compete commercially with the first interchangeable FOB on the first day the latter could be marketed. Thus, under our hypothetical, the procedurally imperfect market exclusivity must not expire prior to January 4, 2023—the earliest opportunity BioSame would have to market its FOB. To prevent the second triggering event from occurring prior to January 4, 2023, the litigation commenced in Step 8 must not end any earlier than eighteen months prior to that date, July 4, 2021. Given that the litigation in Step 8 began on October 9, 2015, the litigation will have to persist for a period of *almost seven years* for the exclusivity period to have any value. The average duration of any patent infringement suit lasts approximately two years, including appeal.[224] An FOB applicant therefore must hope perversely to extend litigation for approximately four years to derive any value from the BPCIA's procedurally imperfect market exclusivity.

Consider also that this calculation ignores completely the possibility that an FOB applicant may be delayed in commercially launching its product on the day it receives FDA approval for a variety of reasons. For instance, in our hypothetical, the litigation of Step 8 involved only two of Pferck's three issued patents. Pferck may assert the third patent, and either or both of the previously pending patent applications if they ultimately and timely issue, as part of a preliminary injunction suit within 180 days of BioSame's intended commercial launch. In this circumstance, BioSame must hope to extend the initial litigation for an even longer period, which

222 § 262(k)(6)(A).

223 § 262(k)(6)(B).

224 Richard D. Margiano, *Cost and Duration of Patent Litigation*, MANAGING INTELL. PROP. (Feb. 1, 2009), http:// http://www.managingip.com/Article/2089405/Cost-and-duration-of-patent-litigation.html.

in turn would result in BioSame litigating two lawsuits simultaneously for at least some period of time.

The triggering events, when considered in light of both the twelve-year procedurally perfect market exclusivity awarded the innovative biologic and the contemplated patent litigation framework of the BPCIA, render the procedurally imperfect market exclusivity awarded to the first interchangeable FOB entirely worthless.[225]

3. Unrealistic and Inefficient Litigation Framework.—The third and final problem inherent in the BPCIA and raised for purposes of this article has to do with the nature of the litigation framework provided in the BPCIA. Specifically, the fact that the BPCIA requires good faith negotiations for months prior to the initiation of any patent litigation suit, and the fact that two litigations are contemplated for every subsection (k) application filed, make the prospects of filing a subsection (k) application perhaps too daunting to consider. As alluded to earlier, the "good faith" negotiations permit far too many opportunities for skilled litigators to participate in gamesmanship. For instance, in considering which patents a reference product sponsor should include in its initial (l)(3) list, the reference product sponsor and its counsel should consider a variety of factors, including the likelihood that a subsection (k) applicant will supplement any omission of a relevant patent by including those in its own (l)(3) list (and thereby eliminate the need to disclose infringement positions on these patents prior to suit);[226] the likelihood of any pending patent applications issuing as patents after exchange of (l)(3) lists (thereby ensuring the possibility of a second litigation for the same predicate act of filing a subsection (k) application); and the likelihood of the subsection (k) applicant disengaging from pre–litigation negotiation at any stage. Similarly, the subsection (k) applicant and its counsel should consider whether to engage in the pre–litigation negotiations at all; whether it should participate only insofar as

225 Underlying this criticism is the question of what it means precisely when an FOB is deemed to be "interchangeable" under the BPCIA, and whether being deemed interchangeable amounts to being "approved" to commercially market an FOB. Assuming that a designation of interchangeability necessarily comes with approval to begin commercial marketing, the criticism provided in the text is sound. If a designation of "interchangeability" can precede FDA approval to commercially market a product, then this serves only to cloud the issue further. No prospective subsection (k) applicant could calculate with any certainty the amount of "interchangeable" exclusivity it could expect, regardless of the outcome of any (l)(6) litigation.

226 *See* § 262(l)(3).

exchanging (l)(3) lists; or whether there is an optimal point further in the negotiations at which it should disengage entirely.[227]

Additionally, with the costs associated with traditional patent litigations of late,[228] filing a subsection (k) application with the knowledge that potentially either of two lawsuits might prevent the commercial launch of its proposed FOB may be prohibitive.

B. Proposed Solutions

1. The Easy Fixes.—Of the three practical problems noted above, two can be resolved with very little effort. First, with respect to the illusory incentive to be the first to receive an interchangeable determination, the grant of twelve years of procedurally perfect market exclusivity period afforded novel biologics should be replaced with an award of seven to nine years of data exclusivity. Second, the unrealistic and inefficient patent litigation framework of the BPCIA should be replaced with the predecessor model provided for in Hatch–Waxman. These simple fixes would dramatically improve the likelihood that the BPCIA will assist rather than hinder the growth of a domestic biosimilars market.

Reduction of the twelve–year procedurally perfect market exclusivity period to seven to nine years serves at least two purposes. It would impart significance to the now–illusory procedurally imperfect market exclusivity afforded a first interchangeable biologic. It would also render the expectation that parties engage in the entirety of the BPCIA's pre–litigation negotiation a bit more realistic. Subsection (k) applicants could file their FDA applications expecting an immediate patent infringement suit, they could engage in negotiations leading to suit with confidence, and they would know when the suit is filed that their procedurally imperfect market exclusivity will not expire before they had a chance to exploit it. The incentive to avoid immediate litigation by defaulting in the pre–litigation negotiations is eliminated, as is the need to extend any immediate patent litigation for a period of seven to eleven years. This solution has the added attraction of having been discussed previously in Congress, as a seven–year exclusivity period was originally contemplated in at least one of the earlier versions of the bill prior to enactment.[229]

Replacement of the procedurally perfect market exclusivity with data exclusivity also serves two important objectives: it restores value to

227 Indeed, a strict reading of the exclusivity provisions afforded a first interchangeable FOB might incentivize a party to avoid (l)(6) litigation altogether, instead subjecting itself to a declaratory judgment action for failure to comply with pre–litigation negotiation obligations. A final judgment from a declaratory judgment action under (l)(9) would not serve as a "trigger" event like that from an (l)(6) litigation.

228 *See* Margiano, *supra* note 224.

229 *See supra* Part IV.A.2–3

pharmaceutical patents pertaining to biologics, and it balances the need to incentivize innovation with the need to secure the public's well-being. Others have commented upon the fact that, in light of an award of perfect market exclusivity for a new biologic, trade secrecy would replace patent law as the preferred intellectually property protection mechanism in the industry.[230] The conclusion makes perfect sense. With the average pharmaceutical patent enjoying an effective term of 11.7 years,[231] an award of a twelve-year, completely impregnable, guaranteed market exclusivity would eliminate any incentive at all to incur even the monetary cost of obtaining a patent. When one also considers the cost incurred by the obligation to disclose and enable the invention in order to obtain the patent, thereby encouraging potential competitors to make and use the invention upon the patent's expiry, patent protection would serve more harm than good to any biologics innovator. The complexities of biologics render them nearly impossible to reverse engineer, and an incredible expenditure in resources would be required to do so in any event. The disclosure required to obtain a patent is too high a price to pay in this context. Biologic pharmaceutical patents have virtually no value under the current terms of the BPCIA.

Data exclusivity, rather than procedurally perfect market exclusivity, also serves the public's interest. Recall that prior to enactment of the BPCIA, Congress awarded procedurally perfect market exclusivity for new medicines only under the Orphan Drug Act. The ODA awarded such an extreme and valuable incentive only because absent such a grant, the ODA would likely never achieve its intended purpose—to stimulate research and development for the treatment and/or cure of rare conditions or diseases. Without the grant, pharmaceutical companies would have no sound business justification to expend resources to treat rare diseases. The low demand for the drug, coupled with the costs for research and development of that drug, would require innovator companies to set prices prohibitively high in order to recoup costs before generic entry in the market. The ODA alleviated that concern by guaranteeing market exclusivity for seven years, independent of any patent rights that may or may not be held.

The same concerns are not at issue for biologics. Prior to the BPCIA, biologics had already become a significant part of the pharmaceutical market. Normal market demands have produced expected business responses without need for legislative intervention. The BPCIA admittedly introduces a more efficient means through which competition is introduced into a given biologics market, so some incentive to the innovator is appropriate to offset that effect. But an award that permits the innovator to set prices without fear of competition for over a decade over-

230 *See, e.g.*, Morgan, *supra* note 31, at 111.

231 *See* Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT'L J. TECH. MGMT. 98, 116 (2000).

compensates the innovator at the expense of the public. The potential for innovator abuse is tremendous. Data exclusivity at least provides the public with security in that if the innovator sets prices too exorbitantly, potential competitors will enter the market sooner. So long as the cost to conduct their own clinical trials is less than the profit they might expect to gain by earlier entry into the market, potential competitors will circumvent the data exclusivity to enter the market. Innovators are then free to set prices for their biologics with restraint: set them high enough to recoup costs over a period of time, but not so high as to attract premature competition. This seems a more balanced approach than that currently found in the BPCIA.

Replacing the twelve-year procedurally perfect market exclusivity with a seven to nine year data exclusivity period would also lead to facilitating the implementation of the litigation framework contemplated under Hatch-Waxman, a framework far more practicable than that proposed under the BPCIA. While use of the Orange Book and related litigation under the Hatch-Waxman regime has been far from flawless, it is at least honest. Hatch-Waxman does not contemplate the parties to an ANDA litigation to be anything other than what they are—adversaries. The NDA holder wants to keep any competitors off the market for as long as they can; the ANDA applicants want to be the first to market a generic competitor to that reference product as soon as possible. The interests of each party are in direct conflict with those of the other. This is no less so in the biologics market, yet the BPCIA naïvely expects opposing parties to cooperate in negotiations prior to the inevitable patent litigation. The BPCIA provides a framework of cooperative game theory for players who are by definition non-cooperative.[232] This is destined to fail. At best, the BPCIA as it stands will require years of litigation and volumes of case law to sort those behaviors in pre-litigation negotiations that are acceptable from those that are punishable, and to define the extent that unacceptable practices should be punished. By mirroring the provisions of Hatch-Waxman, at least with respect to listing patents in the Orange Book and requiring subsection (k) applicants to certify as to patent rights as part of their applications, the parties and the courts could benefit from the wisdom accumulated during the years of litigation that have occurred since passage of the Hatch-Waxman Act.

Moreover, returning to the use of data exclusivities, the Orange Book, and the requirement for patent certifications as part of subsection (k) applications will restore value to biologic pharmaceutical patents. By awarding less than an impregnable hold on a given market by way of regulatory forbearance, the Act necessarily promotes the significance of patent rights to maintain market exclusivity. This in turn promotes continued innovation in the industry as a whole. Instead of permitting an innovator to hoard profits

232 Giacomo Bonanno, *Non-Cooperative Game Theory* 2–3 (Univ. Cal. Davis, Working Paper No. 86, 2008), *available at* http://www.econ.ucdavis.edu/working_papers/08-6.pdf.

for an incremental advancement in biomedicine, it permits an innovator to reap reward for its achievement while encouraging future innovation. Just as patents have stimulated innovation in all industries, they could do so in the biologic pharmaceutical industry.

2. The Tough Fix.—There seems to be no simple solution for determining how the FDA should distinguish between "interchangeables" and "biosimilars," which is arguably the most problematic of the three flaws addressed above. The problem is inherent in the nature of biologics—they are exponentially more complex and more expensive than their small molecule counterparts. As such, the need for a streamlined approach to approve FOBs is simultaneously much greater and much more difficult to implement.

Four high–level FDA officials co–authored a paper recently published in the *New England Journal of Medicine* acknowledging the difficulties that await the FDA in evaluating FOBs.[233] Specifically, the authors concede that "[g]iven the complex nature of biologics, it's unlikely that a 'one size fits all' systematic assessment" of FOBs could be used even to determine the biosimilarity *vel non* of a particular FOB when compared to a reference product.[234] They therefore advocate a "totality–of–the–evidence" approach to evaluate proposed biosimilars, and they expect that each FOB will be evaluated on a case–by–case basis similar to the method employed in Europe.[235] This proposed solution only underscores the dysfunction inherent in the BPCIA. The case–by–case assessment protocol lacks the certainty a potential subsection (k) applicant would require prior to submission of its application. Without knowledge of the costs involved in obtaining even a biosimilarity determination, let alone an interchangeability determination, the potential subsection (k) applicant would be better served in filing an original BLA. Pursuing a BLA would at least give the applicant cost certainty related to the application, and the known reward for obtaining BLA approval would serve to defray any extra expense occurred in opting for the more costly route. Filing an abbreviated application in this instance simply makes no economic sense, particularly when the availability of a reward in the form of a procedurally imperfect market exclusivity would remain unknown during the pendency of the FOB's evaluation.

Perhaps an alternative solution might be to eliminate the distinction between biosimilarity and interchangeability at the legislative level and simply award regulatory exclusivities for the first–filed or first–approved FOB. Interchangeability in the biologics context—where a pharmacist

233 *See* Kozlowski et al., *supra* note 200, at 385.

234 *Id.* at 387.

235 *Id.*

can substitute one biologic for another without doctor approval[236]—seems unrealistic to achieve in any event. Moreover, this would be consistent with the award of regulatory exclusivities in the generic drug context. Hatch–Waxman makes no legislative distinction between Therapeutic and Pharmaceutical Equivalents;[237] the BPCIA should refrain from doing so in the biologics context. Potential subsection (k) applicants also would benefit to know at or around the time they filed their applications whether procedurally imperfect market exclusivity was available. While this solution has at least superficial appeal, however, detractors will readily point out that this does little to remedy the uncertainty a subsection (k) applicant would have with respect to the application's cost. This proposed solution fixes only the uncertainty regarding the potential award awaiting an FOB applicant. Until something more than a case–by–case, totality–of–the–evidence approach is contemplated for evaluating FOBs, the uncertainty surrounding the investment required for an FOB application may well prove sufficient to deter potential applicants from using the BPCIA's abbreviated pathway to obtain FDA approval for any FOBs.

V. Legislative Prudence

A. The BPCIA and Legislative Imprudence

A study of the terms of the BPCIA and its impending consequences reveals the presence of certain idiosyncrasies within the Act itself, all of which reveal a certain imprudence in ultimately ratifying the Act. For example, consider that the Act contains both a data exclusivity provision and procedurally perfect market exclusivity provision. As stated earlier, the former exclusivity is entirely superfluous to the reference product sponsor in light of the latter. Query then why the BPCIA's data exclusivity provision exists. Within Hatch–Waxman, the data exclusivity provision serves as a gatekeeper for any applicant willing to challenge a relevant Orange Book–listed patent as part of its abbreviated application. Such a challenge cannot be submitted to the FDA prior to the expiration of the data exclusivity period. The provision also serves as an implicit reminder that an applicant is free to file an abbreviated "paper NDA" to obtain approval for a product; the applicant simply cannot rely on the data submitted by the reference product sponsor. The BPCIA, however, has no corresponding role for the data exclusivity provision. There is no "paper NDA" version of an abbreviated biologic application in the BPCIA. Patent challenges do not comprise any part of a subsection (k) application. Perhaps the BPCIA's data exclusivity provision serves to minimize the responsibility of the FDA for

236 42 U.S.C.A. § 262(k)(6) (West 2011).

237 *See* 21 U.S.C. § 355(j)(5)(B)(iv)(I) (2006).

storing early-filed applications for later review, but one would think that Congress had some other reason to include that provision. What, then, is that purpose?

The entirety of the pre-litigation negotiations required by the BPCIA is another idiosyncrasy of the Act. The process outlined by the BPCIA is unlike anything previously promulgated by Congress, and it reads more like a district court's local rules for "meet and confer" requirements than it does federal legislation.

A third example can be found in the BPCIA's express delineation of a distinction between a "biosimilar" biologic product and an "interchangeable" one. If one exists, currently the FDA is asking where it can be found.

A fourth is the litany of conflicting or irreconcilable terms within the Act itself. The twelve-year procedurally perfect exclusivity period, in addition to rendering pointless the data exclusivity period, also eviscerates the value of the procedurally imperfect market exclusivity awarded to the first interchangeable FOB. The triggering events of the procedurally imperfect market exclusivity period perversely motivate subsection (k) applicants to either extend litigation for prolonged periods or default during the BPCIA's required pre-litigation negotiations so to avoid a premature triggering event.

The author respectfully submits that these examples are indicative of Congressional failure to practice legislative prudence in ratifying the BPCIA.

B. Defining Legislative Prudence

Legislative prudence was first introduced as a concept in Aristotle's Nicomachean Ethics. There, it was identified and discretely distinguished from more general notions of prudence, and it was defined as the "controlling part" of "the wisdom concerned with the city."[238] Additional details were wanting. Instead, a brief taxonomic classification of prudence followed. Prudence was defined generally as the virtue of practical wisdom "concerned with things just and noble and good for man"; "political"

238 INTRODUCTION TO ARISTOTLE 470 (Richard McKeon ed., 2d ed. 1973). Note that the term prudence is not found in the cited text; rather, the term "practical wisdom" or "wisdom" is employed. Centuries earlier, however, Aquinas had understood these passages of Aristotle's to refer to the concept of "prudence" rather than "wisdom." *See infra* notes 237–39 and accompanying text. For this reason, credit is given to Aristotle for first introducing the notion of "legislative prudence."

prudence was not to be confused with "legislative" prudence; and the former was concerned with the "particulars" comprising latter.[239]

Aquinas later provided some clarification concerning Aristotelian ideas of legislative prudence in his Summa Theologiae, but that clarification was minimal.[240] He did take issue with Aristotelian classifications of legislative and political prudence, positing instead, "Prudence is in the reason . . . [a]nd so the more each shares in the responsibilities of ruling and governing so much the more he possesses in the quality of being reasonable and prudent."[241] By definition, then, it seemed that Aquinas viewed legislative prudence simply as prudence exercised by lawmakers in performing legislative functions.[242] After subsequently reasoning that kingly prudence was "of a special and most complete kind," however, he declared that "the ruling [lawmaking] prudence of a polity is set down as a kind of prudence."[243] No further details were provided.

Little else readily appears to have been written on the subject until recently, when Hittinger,[244] later elaborated upon by Strang,[245] reintroduced Aristotelian distinctions: "[Legislative prudence], possessed by legislators, is 'the capacity to make and impose laws.' [It] allows the legislator to issue laws that order society toward the common good. Political prudence, by contrast, is the virtue of directing oneself in accord with the commands of superiors."[246]

For purposes of this article, no definition from this brief etymologic survey will do. While each provides an arguably sufficient conceptual description of legislative prudence, none provide a standard by which one can measure whether legislative prudence was exercised by a legislating body at the time of a law's ratification. Aquinas's definition is limited to whether individual lawmakers exercised prudence individually. Hittinger's is similarly limited, and it is a tautology—legislators by definition have the capacity to make and impose laws; they therefore demonstrate legislative prudence each time they propose and approve new law. Strang's definition also is limited to evaluating the prudence of an individual lawmaker, though arguably the concept could be extended with integrity

239 INTRODUCTION TO ARISTOTLE, *supra* note 238, at 476.

240 36 ST THOMAS AQUINAS, SUMMA THEOLOGIAE: PRUDENCE 39 (Thomas Gilby ed., 1974).

241 *Id.*

242 *See id.* at 87 (eliminating distinctions between political prudence and general prudence).

243 *Id.* at 85.

244 RUSSELL HITTINGER, THE FIRST GRACE: REDISCOVERING THE NATURAL LAW IN A POST-CHRISTIAN WORLD (2003).

245 Lee J. Strang, *The Clash of Rival and Incompatible Philosophical Traditions within Constitutional Interpretation: Originalism Grounded in the Central Western Philosophical Tradition*, 28 HARV. J.L. & PUB. POL'Y 909 (2005).

246 *Id.* at 919 (quoting HITTINGER, *supra* note 244).

to encompass whether a legislative body issued laws for the common good. The shortcoming with this definition, as well as Aristotle's, however, is that it is result–oriented and therefore temporally imprecise. At the very least, it begs the question of when a particular piece of legislation has achieved a common good.

A process–oriented definition of legislative prudence is required. A return to first principles suggests that prudence is learned from experience and deliberation.[247] Logically it follows that prudence is exercised when actions are made based on experience and deliberation. Legislative experience therefore is exercised when a legislature makes and imposes laws based on experience and deliberation. An examination of the terms of the BPCIA reveals that the Act was not ratified on those bases.

C. Applying Legislative Prudence

The notion that the BPCIA was not deliberated prior to its enactment, nor drafted based on experience, may seem far–fetched. After all, various versions of the legislation had been circulated and debated in Congress for nearly three years prior to its enactment,[248] and as discussed, *supra*, Hatch–Waxman served as the template for at least portions of the Act. True experience, though, means more than borrowing from previous legislation. And deliberation requires more than debate. More accurately, prudential deliberation is a type of inquiry that requires the employment of reason in the proper way at the proper time to achieve a commendable end.[249] Establishment of an abbreviated approval pathway for FOBs is certainly a commendable end. But the flaws of the BPCIA call into question whether the Act was deliberated in the proper way, at the proper time, with experience guiding the discussions.

For example, the apparently superfluous data exclusivity provision of the BPCIA can only be a remnant of the Hatch–Waxman Act itself, indicating that Congress leaned heavily on the Act as a template to fashion legislation of similar kind. The practice itself is not to be admonished, as it is a function of experience. When consequences of certain borrowed provisions are misunderstood or overlooked, however, Congress acts imprudently. Proper deliberation is rightness in thinking.[250] Misunderstanding or overlooking provisions from a predecessor act and incorporating them into new legislation simply is contrary to that principle. So, too, is misunderstanding or overlooking the effect that one provision of new legislation may have on another, as with the twelve–year procedurally perfect market exclusivity period that renders illusory other necessary incentives within the BPCIA.

247 *See* INTRODUCTION TO ARISTOTLE, *supra* note 238, at 474.

248 *See* Carver et al., *supra* note 14, at 716–17.

249 *See* INTRODUCTION TO ARISTOTLE, *supra* note 238, at 472–74.

250 *See id.* at 473.

Proper deliberation would have identified such an effect. The decision to include the regulatory market exclusivities that exist in the current BPCIA was not reached through the exercise of experience and proper deliberation The same can be said for provisions of the BPCIA that are more properly within the province of other government branches. With respect to the required pre–litigation good–faith negotiations, for instance, no government entity is better suited than our federal courts to anticipate and govern the actions of potential litigants of a pharmaceutical patent infringement action. If Congress wanted to impose certain standards of pre–litigation conduct upon potential litigants, it at least should have enlisted the courts' assistance. Courts already impose pre–litigation obligations on future litigants through Federal Rule of Civil Procedure 11. Through similar means, courts could impose obligations sufficient to achieve the purpose of identifying patents for litigation while at the same time honoring its jurisdictional limitations. Further, courts could fashion pre–litigation obligations to minimize opportunities for legal maneuvering. Congressional failure to enlist the courts' assistance in crafting these provisions is another example of imprudent deliberation.

Congress also exceeded its prudential limits by legislating into existence the "interchangeable biologic," distinguishing the interchangeable biologic from a biosimilar, and then formulating an abbreviated FOB approval pathway based in part on that distinction. Recall that the Hatch–Waxman Act contains no corresponding language.[251] Hatch–Waxman provides only that an FDA applicant may submit either a "paper NDA" or an ANDA to expedite approval of a follow–on drug.[252] Hatch–Waxman makes no qualitative distinction between follow–on drugs, nor does it award any incentives based on such a qualitative distinction. Hatch–Waxman simply awards an incentive to the first ANDA applicant who files a patent challenge as part of the application.[253] It is the FDA, the government agency with sufficient expertise in the relevant field, which first recognized and then promulgated the distinction between Pharmaceutical Equivalents and Therapeutic Equivalents.[254]

Congress disregarded, or at least mistook, the experience gained from enacting and imposing Hatch–Waxman to assume that qualitative, measurable differences between FOBs exist simply because they exist between follow–on drugs. This assumption now appears premature. As a result, the FDA continues to solicit comments as to how best to implement an Act that is predicated upon premature suppositions. Until the FDA can provide guidance to future subsection (k) applicants as to what data will be required to differentiate a biosimilar from an interchangeable, and unless

251 *See supra* Part I.C.

252 *Id.*

253 *Id.*

254 *See supra* Part III.A.

that data will be less costly to accumulate than the data needed for a BLA application, the BPCIA will serve no purpose. Together, the timing and terms of BPCIA indicate that imprudent deliberation led to its ratification. In formulating the current terms of the BPCIA, Congress admittedly experienced inordinate pressures to propose an abbreviated FOB approval pathway at its earliest opportunity. Currently commercially available biologic therapies were too expensive for many patients to afford and costs for such therapies were projected to soar even higher; few will contest that legislative intervention was necessary.[255] In addition, passage of the Act was projected to facilitate a new, robust biosimilar pharmaceutical industry, and many were eager to participate in the market. Under these circumstances, a less than perfect BPCIA is arguably understandable. Less so, however, is the apparent failure of Congress to employ legislative prudence while enacting this legislation.

D. Deducing Characteristics of Legislative Prudence

The flaws of the BPCIA indicate that Congress acted too hastily in response to growing demands and pressure for an abbreviated regulatory approval pathway for FOBs. Specifically, it failed to deliberate properly prior to the Act's proposal and enactment in order to identify inconsistent or superfluous provisions. It legislated beyond its technological understanding when it created the "interchangeable biologic." It ignored the benefits of experience in abandoning the litigation framework under Hatch–Waxman and creating a new regime without consultation of the courts. Despite these examples, though, the contours of exactly what constitutes legislative prudence remain nebulous. At least an analysis of the BPCIA informs the issue.

First, we now know that legislative prudence is not exercised when legislation contains irreconcilable provisions within the same act. The result is violative of proper deliberation. Second, legislative prudence requires an understanding of the limitations of the legislative body itself, particularly with respect to its knowledge of the governed activities, its familiarity with the governed actors, and its appreciation of the resources needed and costs necessary to implement the legislation. Understanding legislative limitations is something achieved over time with legislative experience. Third, legislative prudence requires the ability to withstand extra–legislative pressures. This is a combination of relying on lessons

255 *See Hearings*, *supra* note 14, at 34 (Nov. 3, 2010 testimony of Dr. James Roach); *see also id.* at 77 (Nov. 3, 2010 testimony of Dr. Anshuman Patwardhan) (concluding the BPCIA will "cause a reduction in monopoly pricing of biologics and a break to the runaway cost of health").

learned from experience and understanding the proper time and manner for deliberation and action.

Additional components of legislative prudence surely exist; these characteristics are not submitted as an exhaustive list. Analyses of past failed acts and the circumstances under which they were enacted may reveal more. Perhaps upon reading this article others may be motivated to engage in such study. For now, however, the shortcomings of the BPCIA suggest at least three characteristics of legislative prudence that should be minded in future legislative endeavors. Heeding as much will lessen the likelihood that future legislation might paradoxically undermine the very objective for which it was enacted.