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NOTES

GENERICS AND BIOSIMILARS: MAPPING THE BIOSIMILARS REGULATORY APPROVAL PATHWAY AGAINST THE HATCH-WAXMAN ACT AND PROJECTING FUTURE EFFECTS ON THE BIOLOGICS MARKET AND PATENT PROTECTION

Michael S. Montgomery

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GENERICS AND BIOSIMILARS: MAPPING THE BIOSIMILARS REGULATORY APPROVAL PATHWAY AGAINST THE HATCH-WAXMAN ACT AND PROJECTING FUTURE EFFECTS ON THE BIOLOGICS MARKET AND PATENT PROTECTION

Michael S. Montgomery*

I. INTRODUCTION

This Note discusses in detail the regulatory approval pathways set forth by Congress for gaining approval for the sale of generic pharmaceuticals and biosimilars. Both generic pharmaceuticals and biosimilars are subject to approval by the Food and Drug Administration (FDA) before they are capable of entering interstate commerce.[1] The biosimilars regulatory approval pathway is novel and untested, while the generics regulatory approval pathway is well established. Therefore, this Note initially sets forth the generics pathway, and the biosimilars pathway is later contrasted against the generics pathway. Special attention is paid to the mechanisms and procedures that involve the basis for claims of patent

* Registered U.S. Patent Agent, Reg. No. 70919; University of Pittsburgh School of Law, J.D. Candidate 2015, Certificate in Intellectual Property & Technology Law; Johns Hopkins University, M.S. in Biotechnology 2014, University of Wisconsin-Madison, B.S. in Natural Sciences (Biology) 2011. Special thanks to Professor C. Allen Black for helping me select this topic and for providing feedback during the initial research gathering stage, and to Ben Klaber (J.D. 2013) for giving me stylistic advice on drafting my student note.

[1] 21 U.S.C. § 355(a) (2012) (for pharmaceuticals); 42 U.S.C. § 262(a) (2012) (for biologics).

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http://lawreview.law.pitt.edu

infringement. The analysis portion of the Note separately examines implications that the Biologics Price Competition and Innovation Act of 2009 (BPCI) will have on the biologics market and implications on patent protection related to the underlying biologic "reference product" which forms the basis of the biosimilar application approval. This Note concludes with a series of recommendations based upon the observations that are intended to stimulate innovation, promote competition, and adequately protect consumers. Finally, there is a side-by-side comparison table summarizing and contrasting the regulatory approval pathways and generics/biosimilars markets.

II. REGULATORY PATHWAYS—GENERICS AND BIOSIMILARS

A. Generics: Hatch-Waxman Act

The Hatch-Waxman Act was signed into law in 1984, bearing the official title Drug Price Competition and Patent Term Restoration Act.[2] The Hatch-Waxman Act was intended to represent "compromises reached in negotiations between the brand name drug industry and the generic drug industry" in order to "[assure] consumers of more low-cost generic drugs when a valid patent expires and the drug industry of sufficient incentive to develop innovative pharmaceutical therapies."[3] Generic drugs can be priced lower than brand-name drugs "because their manufacturers do not incur the research, development, and promotional costs normally associated with the creation and marketing of an original product."[4] Novel drug development is notoriously expensive and drawn-out; average costs for developing new pharmaceuticals have been estimated to be about $1.2 billion, and the average time to discover and develop a new drug is ten to fifteen years.[5]

1. Generics Regulatory Approval Pathway

At its most basic, the Hatch-Waxman Act provides means for "expedited marketing approval pathways" for generic pharmaceutical manufacturers to get their product to the marketplace.[6] In order to achieve this goal, the Act established

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[2] Yuki Onoe, *"Pay-for-Delay" Settlements in Pharmaceutical Litigation: Drawing a Fine Line Between Patent Zone and Antitrust Zone*, 9 J. MARSHALL REV. INTELL. PROP. L. 528, 533 (2009).

[3] 130 CONG. REC. H24425 (daily ed. Sept. 6, 1984) (statement of Rep. Henry A. Waxman).

[4] United States v. Generix Drug Corp., 460 U.S. 453, 455 n.1 (1983).

[5] *Key Industry and PhRMA Facts*, PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, http://phrma.org/news-media/related-resources/key-industry-factsabout-phrma (last visited Jan. 19, 2014) [hereinafter PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA].

[6] Onoe, *supra* note 2, at 533.

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http://lawreview.law.pitt.edu

the practice of filing abbreviated new drug applications (ANDAs), a substantially less-costly counterpart to new drug applications (NDAs) filed by innovative name brand entities.[7] Prior to these changes, in order to gain marketing approval by the FDA, generic manufacturers had to face the same rigorous standards required for filing NDAs.[8] Under the Hatch-Waxman Act framework, entities seeking to file ANDAs, unlike NDAs, do not need to undergo the lengthy and costly processes of independently demonstrating the safety and efficacy of their products because they need only to "demonstrate the bioequivalence [of the generic medication] to an already-approved innovator drug."[9]

A name brand entity that files an NDA with the FDA must file with the application the patent number and the expiration date of any patent that claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.[10] These patents are listed, along with the compound sought for approval in the NDA, in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (published by the FDA), which is commonly referred to as the "Orange Book" because of its orange-colored cover.[11]

In contrast, an ANDA filer must file a certification stating that, with respect to each patent listed in the Orange Book which claims the listed drug or which claims a use for such listed drug (sought for approval by the ANDA filer), that 1) such patent information has not been filed, 2) that such patent has expired, 3) the date

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[7] Alyssa L. Brown, *Modest Proposals for a Complex Problem: Patent Misuse and Incremental Changes to the Hatch-Waxman Act as Solutions to the Problem of Reverse Payment Settlements*, 41 U. BALT. L. REV. 583, 585 (2012).

[8] *Id.*

[9] *Id.* at 585–86, citing Cong. Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*, at xii (1998), *available at* http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf.

[10] 21 U.S.C. § 355(b)(1)(G) (2012).

[11] Natalie M. Derzko, *The Impact of Recent Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation*, 45 IDEA 165, 167 (2005); *see also* Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of thirty month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, 68 Fed. Reg. 36, 676, 36, 676 (June 18, 2003) ("[W]e publish patent information after approval of an NDA application in our approved drug products list entitled 'Approved Drug Products With Therapeutic Equivalence Evaluations.' This list is known popularly as the 'Orange Book' because of its orange-colored cover.").

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

such patent will expire, or 4) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.[12] ANDA applicants may forgo submitting a certification under Paragraphs I–IV if the NDA holder submits a method-of-use patent, "which does not claim a use for which the applicant is seeking approval."[13]

Of these four possible certifications, the most common are Paragraph III and Paragraph IV certifications.[14] Regarding a Paragraph III certification, the FDA is statutorily prohibited from approving the ANDA until the patent(s) expire.[15] In a Paragraph IV certification, the ANDA applicant certifies that their generic does not infringe any of the Orange Book listed patents or that those patents are unenforceable.[16]

Once the FDA receives an ANDA filing, the FDA has 180 days to accept it.[17] If the accepted application contains a Paragraph IV certification, the applicant has twenty days to notify any patent holder(s) of the approved application, including reasons the applicant believes why the patent(s) is/are not infringed and/or invalid.[18]

2. Practical Benefits Given by Hatch-Waxman Act

i. Benefits to the Generic Competitors

The greatest benefit to generic competitors is that, compared to submitting an NDA, ANDA filers need only submit bioequivalence studies.[19] The second greatest benefit is the relatively passive role the FDA plays in protecting or enforcing the

[12] 21 U.S.C. § 355(j)(2)(A)(vii) (2012).

[13] Brian J. Malkin & Andrew S. Wasson, *Should FDA Undertake More than a "Ministerial" Role with Respect to Patent Information*, FDLI'S FOOD AND DRUG POLICY FORUM, Feb. 23, 2011, at 1, 2; *see* 21 U.S.C. § 355(j)(2)(A)(viii) (2012).

[14] Brown, *supra* note 7, at 587.

[15] 21 U.S.C. § 355(j)(5)(B)(ii) (2012).

[16] 21 U.S.C. § 355(j)(5)(B)(iv) (2012).

[17] 21 U.S.C. § 355(j)(5)(A) (2012).

[18] 21 U.S.C. § 355(j)(2)(B) (2012).

[19] Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 189 (1999) ("In that regard, it is a unique piece of legislation because it actually ties the hands of a regulatory agency—in the area of public health—by providing specifically that FDA can require only bioavailability studies for ANDAs.").

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

patents listed in the Orange Book. The FDA allows ANDA filers to file one of four certifications, and the FDA has explicitly stated its interest in remaining neutral to any underlying patent suits or other enforcement/invalidity issues.[20]

Of the four certifications, Paragraph IV certifications are the most common. Generic pharmaceutical manufacturers are incentivized to submit Paragraph IV certifications because the first ANDA filer to submit a Paragraph IV certification for a particular listed compound, if ultimately approved and successful in any subsequent legal challenge to the certification, obtains a "180-day exclusivity period" in which no other generic manufacturer can receive FDA approval.[21]

Global pharmaceutical sales nearly doubled over the last decade, from $503 billion in 2003 to $956 billion in 2011.[22] A significant portion of this growth is directly traceable to the growth and proliferation of generic pharmaceuticals; generic share of the pharmaceutical market was only 49% in 2000, by 2011 generic pharmaceuticals accounted for 80% of the total market share.[23] Despite the overall growth in pharmaceutical sales, only two out of every ten marketed novel drugs between the years 2001 to 2011 returned revenues that matched or exceeded research and development costs.[24]

ii. Benefits to the Name Brand Patent Holders

The filing of an ANDA application triggers what is known as an "artificial" or "constructive" act of patent infringement.[25] A constructive infringement is a fictional infringement, which in effect states that the act of filing an ANDA amounts to at least *de minimus* patent infringement.[26] The principal benefit the

[20] Malkin & Wasson, *supra* note 13, at 1; *see, e.g.*, Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of thirty month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, 68 Fed. Reg. 36,676, 36,683 (June 18, 2003).

[21] 21 U.S.C. § 355(j)(5)(B)(iv)(I) (2012).

[22] *Total Unaudited and Audited Global Pharmaceutical Market, 2003-2011*, IMS HEALTH, http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-Line%20Market%20Data%20&%20Trends/2011%20Top-line%20Market%20Data/Global_Pharma_Market_by_Spending_2003-2011.pdf (last visited Jan. 19, 2014).

[23] PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, *supra* note 5.

[24] *Id.*

[25] Mossinghoff, *supra* note 19, at 190; *see* 35 U.S.C. § 271(e)(2)(A), (B) (2012).

[26] *Id.*

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

"artificial" infringement provides has been come to known as the "thirty-month stay."[27] If an ANDA filer makes a Paragraph IV certification (which, as previously stated, is the most common certification)[28] and the patent holder commences an infringement action against the ANDA filer within forty-five days of receiving notice of the certification, the FDA grants an essentially automatic thirty-month stay on approval of the generic drug.[29] This thirty-month stay is of great consequence, as it provides thirty months of market exclusivity that may otherwise not be present, and as such it provides a seemingly necessary recourse to ward off at least some potential ANDA filers.

The Hatch-Waxman Act also provides a five-year data exclusivity for new compounds. The Act provides for a period of exclusivity such that once a new, non-generic pharmaceutical is approved via an NDA submission, the FDA cannot approve a generic version for five years, and the test data used to support the NDA filing cannot be relied upon by competitors for that same time.[30] This exclusivity is independent of any patent rights.[31]

The Hatch-Waxman Act gave name-brand pharmaceutical manufacturers an additional benefit related to patent term extension. For utility patents, a patent term ordinarily lasts twenty years from its earliest effective filing date.[32] However, the Hatch-Waxman Act provides for a patent term extension equal to one-half of the time of the investigational new drug (IND) period, running from the time in which a manufacturer began human clinical trials, plus the NDA period (the period during the NDA review).[33] The maximum extension is five years and the total market exclusivity time cannot exceed fourteen years.[34]

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[27] Derzko, *supra* note 11, at 176.

[28] Brown, *supra* note 7, at 587.

[29] Mossinghoff, *supra* note 19, at 189–90; *see also* 21 U.S.C. § 355(c)(3)(C) (2012).

[30] Mossinghoff, *supra* note 19, at 189; *see* 21 C.F.R. § 314.108 (2013).

[31] *Id.*

[32] 35 U.S.C. § 154(a)(2) (2012).

[33] Mossinghoff, *supra* note 19, at 190; *see also* 35 U.S.C. § 156 (2012).

[34] 35 U.S.C. § 156.

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

B. *Biosimilars Contrasted: Regulatory Framework Under the Biologics Price Competition and Innovation Act of 2009*[35]

The Biologics Price Competition and Innovation Act of 2009 (BPCI) was signed into law in March 2010 as part of the monumentally larger and controversial bill titled the Patient Protection and Affordable Care Act (PPACA).[36] Biologics are statutorily defined as being

> a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.[37]

Nearly any therapeutic compound that is not chemically synthesized can be considered a biologic.[38] Biologics typically have a relatively high molecular weight, are much more complex than traditional pharmaceuticals, and cover a broad array of products.[39]

The biologics market is nearly $600 billion internationally, with the United States constituting almost half of that market.[40] Nearly half of the top-twenty bestselling medicines in the world in 2011 were biologic compounds.[41] Like pharmaceuticals, the costs associated with innovating new biologics are immense and can be prohibitive; biologic development takes on average between ten and

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[35] *See infra* Table 1 for a side-by-side comparison.

[36] 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 (2011). The PPACA is better known by the colloquial name, "Obamacare."

[37] 42 U.S.C. § 262(i)(1) (2012).

[38] Kyle Barrett, *Implementing the Biologics Price Competition and Innovation Act: Why Legal Principles Justify a Broad Definition of Biosimilarity*, 85 S. CAL. L. REV. 1597, 1600 (2012).

[39] *Id.*

[40] Addison, *supra* note 36, at 554.

[41] Top 20 Global Products, 2011, Total Audited Markets. IMS Health Services, http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press%20Room/Top-Line%20Market%20Data%20&%20Trends/Top_20_Global_Products.pdf (last visited Jan. 19, 2014) (The globally top-selling products in 2011 which are biologics consist of avastin, enbrel, glivec, herceptin, humira, lantus, mabthera, neulasta, and remicade).

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http://lawreview.law.pitt.edu

fifteen years and costs about $1.3 billion, with most biologic companies having negative earnings.[42]

Biosimilarity is statutorily defined to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[43] There are ongoing debates about how broadly the term "biosimilars" should be construed, because Congress did not provide a specific definition of "biosimilarity."[44]

With the rapidly growing world market for biologics in mind, Congress drafted the BPCI in order to create a streamlined process for approval of biosimilars, which can be loosely defined as a generic biologic product. Notably, as of January 2014, despite the passage of the BPCI in March 2010, the FDA has not yet approved a *single* biosimilar molecule, thus lending much speculation as to the future of biosimilars and the biologics market. Recently, the FDA explicitly stated that "[i]t is not yet known when the first biosimilar will be on the U.S. market."[45]

Because biologics are more complex (often containing several million atoms as compared to several dozen in traditional pharmaceuticals), it is virtually impossible to manufacture a biosimilar in a structurally identical way as its reference biologic compound.[46] Therefore, Congress has allowed for approval and subsequent regulatory exclusivity of biosimilar compounds that are not structurally identical to already approved biologic compounds.[47] Significantly, this is in contrast with generics, which must contain the same active ingredient(s) as the NDA reference product listed in the Orange Book.[48]

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[42] Erwin E. Blackstone & Joseph P. Fuhr, Jr., *The Future of Competition in the Biologics Market*, 31 TEMP. J. SCI. TECH & ENVTL. L. 1, 6 (2012).

[43] 42 U.S.C. § 262(i)(2) (2012).

[44] Barrett, *supra* note 38, at 1599.

[45] FDA, *Are biosimilars available now?*, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm (last visited Jan. 19, 2014).

[46] Barrett, *supra* note 38, at 1604.

[47] *Id.* at 1598.

[48] 21 U.S.C. § 355(j)(2)(A)(ii)–(v) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

1. The Regulatory Approval Pathway

i. Initial Application Process

Perhaps most the most prominent difference between the biosimilar approval pathway and the generics approval pathway is the degree to which the process occurs in relative secrecy between the FDA, the party which owns the biologic "reference product," and the biosimilar applicant. In contrast, the generics approval pathway takes place in the public forum, with a centralized listing of chemical compounds and associated patents. Indeed, there is no Orange Book equivalent for patents of biologics having approved biologics license applications (BLAs, somewhat equivalent to NDAs).[49]

An application for a biosimilar product must contain *at least*: 1) one (and only one) reference product, 2) information based on data derived from analytical studies that demonstrate that the biological product is highly similar to the reference product, 3) animal studies, 4) clinical studies that are sufficient to demonstrate safety, purity, and potency, 5) that the biological product and reference product utilize the same mechanism or mechanisms of action for the condition(s) of use, 6) the condition(s) of use, 7) route of administration, and 8) that the facility in which the biological product is manufactured, processed, packed, or held meets certain standards.[50]

If an applicant wishes a showing of interchangeability, a standard higher than just biosimilarity, the applicant must prove both that the biologic product "can be expected to produce the same clinical result as the reference product in any given patient" and that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[51] Compare these strict requirements to an ANDA filing, which only

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[49] Henninger S. Bullock & Andrew J. Calica, *BIOSIMILARS The Next Big Thing?*, 54 No. 10 DRI For Def. 22.

[50] 42 U.S.C. § 262(k)(2)(a)(i)–(ii) (2012). The requirements for a BLA are numerous, onerous, and beyond the scope of this note. 42 U.S.C. § 262(a)(2)(A) states that "[t]he Secretary shall establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses," so unlike the requirements for the biosimilar approval pathway, these requirements are basically non-statutory. They are mainly codified at 21 C.F.R. §§ 601–680 as discussed at http://www.fda.gov/BiologicsBlood Vaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/default.htm.

[51] 42 U.S.C. § 262(k)(4) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

requires the generic manufacturer to show "bioequivalence," and the filing can otherwise rely on materials submitted in the reference product's NDA.[52]

ii. Patent List Exchange Process

Seemingly because there is no central repository for approved biologics and their related patents such as the Orange Book, an applicant who seeks approval for a biosimilar must instead go through a fairly private process with the reference product manufacturer (officially designated "reference product sponsor" in the statute) before obtaining approval. Unless otherwise agreed to, not less than twenty days after the Secretary notifies an applicant that their biosimilar application has been accepted for review, the applicant must provide *confidential access* to a copy of the submitted application, and other such information that describes the process or processes used to manufacture the biosimilar that is the subject of the application. The applicant may also provide additional information that is requested.[53] The requirement that the applicant disclose their potentially trade-secret method(s) of manufacturing the biosimilar has no analogue in the Hatch-Waxman Act regulatory framework, and places a considerable burden and risk upon the applicant in disseminating their proprietary and potentially confidential information.

The recipients of the application and associated confidential information are limited to either one or more outside counsel designated by the reference product sponsor and only one in-house counsel who is an employee of the reference product sponsor.[54] No person that receives the application or any of the associated confidential information is permitted to disclose it to any other person or entity.[55] Interestingly enough, both the outside counsel and in-house counsel are expressly forbidden from having engaged, "formally or informally, in patent prosecution relevant or related to the reference product."[56]

Not later than sixty days after receiving the application and confidential information by the applicant, the reference product sponsor must provide to the applicant a list of patents "for which the reference product sponsor believes a claim

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[52] Brown, *supra* note 7, at 585.

[53] 42 U.S.C. § 262(l)(1), (2) (2012).

[54] 42 U.S.C. § 262(l)(1)(B)(ii) (2012).

[55] 42 U.S.C. § 262(l)(1)(C) (2012).

[56] 42 U.S.C. § 262(l)(1)(B)(ii) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

of patent infringement could reasonably be asserted by the reference product sponsor" against the applicant, as well as "an identification of the patents on such list that the reference product sponsor would be prepared to license" to the applicant.[57] This language almost exactly mirrors the requirements for listing patents on the Orange Book by an NDA filer.[58]

After the applicant receives the list of patents by the reference product sponsor, and within sixty days, the applicant *may* provide to the reference product sponsor a list of patents to which the applicant believes that the reference product sponsor could reasonably assert a claim of patent infringement, and *shall* provide "a detailed statement that describes, on a claim by claim basis, the factual and legal basis of the opinion of the . . . applicant that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the biological product that is the subject of the . . . application."[59] While the first part of this disclosure has no counterpart in the Hatch-Waxman Act regulatory scheme, the "detailed statement" is almost identical to a Paragraph IV certification.[60]

Once the product sponsor receives the "detailed statement" and optional list, the product sponsor must provide a counterpart statement that describes "on a claim-by-claim basis, the factual and legal basis of the opinion of the reference product sponsor that such patent will be infringed by the commercial marketing of the biological product that is the subject of the . . . application and a response to the statement concerning validity and enforceability."[61] There is no counterpart to this in the Hatch-Waxman Act regulatory scheme for generics, instead once an ANDA is filed for a generic drug and certification is made, the patent holder may sue for infringement.[62]

The biologics applicant and reference product sponsor must then undergo "good faith negotiations" on which, if any, patents shall be the subject of an action for patent infringement.[63] Regardless of whether or not an agreement is reached between the applicant and reference product sponsor over the patents list, the

[57] 42 U.S.C. § 262(l)(3)(A) (2012).

[58] *See* 21 C.F.R. § 314.53(c) (2013).

[59] 42 U.S.C. § 262(l)(3)(B) (2012).

[60] *See* 21 U.S.C. § 355(j)(2)(B)(iv) (2012).

[61] 42 U.S.C. § 262(l)(3)(C) (2012).

[62] Mossinghoff, *supra* note 19, at 190.

[63] 42 U.S.C. § 262(l)(4)(A) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

reference product sponsor may bring action not less than thirty days from agreement or the most recent exchange of patent lists.[64] This drawn-out back and forth exchange of patent lists and confidential information can last up to eight months.[65]

An interesting result of this exchange occurs in the scenario where the applicant and the reference product sponsor do not reach an agreement on the list of patents that shall by subject of an action for patent infringement. The Act states the number of patents that are listed by the reference product sponsor *may not* exceed the number of patents listed by the applicant.[66] The Act states that if an applicant does not list any patents, the reference product sponsor may list only one patent.[67] This restriction has a very powerful implication, as it essentially allows the biosimilars applicant, a prospective defendant, to be the ultimate arbiter of the underlying patent infringement suit, rather than the patent holder. This is in stark contrast with the long-standing legal principal that plaintiff(s) are "masters of the complaint."[68]

III. PRACTICAL EFFECTS ON THE BIOLOGICS MARKET

A. Costs and Barriers to Market Entry

The Federal Trade Commission (FTC) has estimated biosimilar products are likely to require eight to ten years to develop, and development of a biosimilar product will likely cost between $100 and $200 million.[69] These statistics differ quite significantly from the product development costs for pharmaceutical generic drugs, which typically require three to five years to develop and cost between $1 and $5 million.[70] Considering that a novel biologic compound costs on average $1.3 billion and takes between ten and fifteen years to develop,[71] a competitor who

[64] 42 U.S.C. § 262(l)(6) (2012).

[65] Bullock & Calica, *supra* note 49, at 27.

[66] 42 U.S.C. § 262(l)(5)(B)(ii)(I) (2012).

[67] 42 U.S.C. § 262(l)(5)(B)(ii)(II) (2012).

[68] Caterpillar Inc. v. Williams, 482 U.S. 386, 387 (1987).

[69] F.T.C., *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, F.T.C. REP., June 2009, at 1, 14, *available at* http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.

[70] *Id.*

[71] Blackstone & Fuhr, *supra* note 42, at 6.

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
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wishes to obtain an approved biosimilar must spend roughly one-half the time and one-tenth the capital before obtaining a biosimilar that is fit for regulatory approval. Novel pharmaceutical drugs have a similar entry cost, on average costing $1.2 billion and taking between ten and fifteen years to develop. However, a competitor who wishes to obtain an approved generic spends, on average, one-half to one-third of the time, but only spend between about one-one thousandth (1/1,000) and one-two hundredth (1/200) of the capital to create a suitable generic pharmaceutical.

Furthermore, a biosimilar applicant must provide extensive and time-consuming data to the FDA along with their application.[72] Additionally, if the applicant desires to show interchangeability, they must show even further information that goes above and beyond simple biosimilarity.[73] These extensive requirements are a stark contrast to the generics requirements in Hatch-Waxman Act. In fact, the original intent behind Hatch-Waxman Act was to create a system wherein ANDA filers could avoid having to show all the tests and safety studies filed with the NDA; as generic manufacturers would not spend the time and money doing the clinical trials to get to the market if there was already a suitable name brand pharmaceutical on the market.[74]

B. Greater Regulatory Exclusivity for Biologics, Including Biosimilars

The FDA may not approve an application for a biosimilar product until *twelve* years after the date on which the reference product was first approved as a BLA.[75] This provides a considerable length of time for exclusivity, particularly when the patent term lasts only twenty years from earliest (non-provisional) effective filing date[76] and that many patents are filed before a working model has actually been developed (actual reduction to practice is not required).[77] Comparing this to the shorter five years of exclusivity given to an NDA filer,[78] it is particularly profound

[72] 42 U.S.C. § 262(k)(2)(A)(i)–(ii) (2012).

[73] 42 U.S.C. § 262(k)(4) (2012).

[74] Mossinghoff, *supra* note 19, at 187.

[75] 42 U.S.C. § 262(k)(7)(A) (2012).

[76] 35 U.S.C. § 154(a)(2) (2012).

[77] Barrett, *supra* note 38, at 1623.

[78] 21 C.F.R. § 314.108(b)(2) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

when one considers that the costs associated with developing a novel biologic and a novel pharmaceutical compound is quite similar to one another.

There is currently heated debate as to whether the twelve years of exclusivity is market exclusivity or data exclusivity, as data exclusivity is found in the Hatch-Waxman Act exclusivity period.[79] If the exclusivity period is data exclusivity, then it could take at least three or four additional years for a biosimilar applicant to develop the drug and an additional one to two years to obtain FDA approval.[80] Healthcare providers like Aetna maintain that the BPCI allows for four years data exclusivity and 12 years market exclusivity, while developers such as Amgen maintain that the BPCI allows for twelve years of data exclusivity.[81] In the latter case, there would be an extraordinary sixteen to eighteen years before a biosimilar is capable of being placed on the market.[82] Several Congressman and biologic manufacturing entities submitted their comments to the FDA's notice and comment asking for input on how to define the exclusionary period.[83]

Biosimilars that are proven to be "interchangeable" are also eligible for exclusivity, though nowhere near the realm of an approved BLA. To be eligible, a biosimilar that is "interchangeable" must be the *first* approved as an interchangeable biosimilar with respect to a particular reference product.[84] The period of exclusivity ranges from the *earlier* of one year after the first commercial marketing of the biosimilar, eighteen months after a final court decision (or dismissal) on all patents in suit, eighteen months after approval if the applicant has not been sued, or forty-two months after approval if the litigation is still ongoing at the forty-second month mark.[85]

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[79] Blackstone & Fuhr, *supra* note 42, at 16.

[80] *Id.*

[81] John Carroll, *Data vs. market "exclusivity" in blockbuster scrap over biosimilars*, FIERCE BIOTECH (Jan. 26, 2011), http://www.fiercebiotech.com/story/data-vs-market-exclusivity-blockbuster-scrap-over-biosimilars/2011-01-26.

[82] Blackstone & Fuhr, *supra* note 42, at 16.

[83] Approval Pathway for Biosimilar and Interchangeable Biological Products, 75 Fed. Reg. 61497, 61500 (Oct. 5, 2010) (notice of public hearing and request for comments); Kurt R. Karst, *Tussle Over BPCIA "Market" Versus "Data" Exclusivity Continues*, FDA LAW BLOG (Jan. 21, 2011, 6:38 AM), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2011/01/tussle-over-bpcia-market-versus-data-exclusivity-continues-this-time-the-generics-side-chimes-in.html.

[84] 42 U.S.C. § 262(k)(6) (2012).

[85] *Id.*

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

IV. PATENT PROTECTION AND INFRINGEMENT

A. Problems Inherent to the BPCI Regulatory Scheme

Regarding patent protection and infringement, the most notable departure for biosimilars from the Hatch-Waxman Act regulatory framework is the total lack of an automatic thirty-month stay on a biosimilar application, where an applicant submits the equivalent of a Paragraph IV certification.[86] As previously mentioned, the automatic thirty-month stay is one of the most significant recourse mechanisms a name-brand pharmaceutical manufacturer can take against an ANDA filer. Removing it takes much of the bite out of bringing suit under 35 U.S.C. § 271(e)(2)(C), which makes filing a biosimilars application an act of "artificial" or "constructive" infringement, much like the act of filing an ANDA.[87] This lack of an automatic thirty-month stay virtually obliterates any advantage of bringing suit under 271(e)(2)(C) over a traditional infringement suit under 35 U.S.C. § 271(a), as the patent holder will not have the arguably necessary prophylactic ability to stay the regulatory approval process.[88]

Further compounding this issue is the confusing and drawn-out mechanism by which patent lists are exchanged. Putting a burden on both the patent holder and the applicant seeking approval to create lists either asserting infringement or non-infringement/invalidity on a "claim-by-claim" basis wherein the final list may consist of a single patent is a potentially large waste of resources on both sides.

There also remains the unusual requirement that the applicant must submit the application and associated confidential information to the reference product holder and that the information must not be sent to any outside or in-house counsel that was engaged, "formally or informally, in patent prosecution relevant or related to the reference product."[89] Legislative history on this peculiar inclusion proves to be challenging because the amendment incorporating the change was introduced without a written report.[90] Nevertheless, this particular inclusion will probably increase costs to the reference product patent holder, as the patent holder will have

[86] Bullock & Calica, *supra* note 49, at 27.

[87] 35 U.S.C. § 271(e)(2)(C) (2012).

[88] 35 U.S.C. § 271(a) (2012).

[89] 42 U.S.C. § 262(l)(1)(B)(ii) (2012).

[90] S. Res. 1695, 110th Cong. (2008) ("Reported by Senator Kennedy with an amendment in the nature of a substitute. Without written report.").

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

the burden of finding additional counsel who will most likely be unfamiliar with the reference compound as well as the patent(s) covering the compound.

B. Problems Inherent to the Biologics Field

Problems inherent to biologics abound for two main reasons. First, biologic patents on both products and processes are inherently more complex than chemical drug patents because they require more claim limitations than chemical drugs given their larger sizes, more complex structures, and more complicated production mechanisms.[91] Second, current science cannot accurately predict what effects slight modifications in a protein's structure will have on its clinical effects in a patient.[92] Relating to the first problem, having more claim limitations makes infringement of biologic patents harder to determine and also offers more ways for competitors to design around these patents by changing any part of a biologic's amino acid sequence or conformation.[93] Relating to the second problem, patent practitioners often must draft more numerous and broader patent claims due to the scientific uncertainties in predicting functional changes from slight structural modifications. These claims are more likely to end up being invalid for reasons of anticipation or obviousness.[94]

Finally, because patent protection for biologics is not as strong in comparison to small molecule pharmaceuticals, there remains the basic principle that patents directed towards "compositions of matter" are, when determining anticipation and infringement, analyzed from a structural standpoint rather than a functional standpoint (notwithstanding the "doctrine of equivalents").[95] Therefore, patent protection is not as strong for biologic drugs as compared to chemical drugs at the level of individual claim-drafting as well as overall scope.[96] There remain other issues beyond claim scope, such as the level of enablement and written description required for biologics, which are inherently unpredictable.[97] This creates an obvious problem for biologics patent holders that admittedly goes beyond the BPCI, as Congress is incentivizing potential biosimilars manufacturers to create

[91] Barrett, *supra* note 38, at 1621.

[92] *Id.*

[93] *Id.*

[94] *Id.*

[95] Astra-Sjuco, A. B. v. U.S. Int'l Trade Comm'n, 629 F.2d 682, 686 (C.C.P.A. 1980).

[96] Barrett, *supra* note 38, at 1621.

[97] *See* Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1352 (Fed. Cir. 2010).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

compounds that are functionally similar, but not structurally identical, to (presumably patented) reference products.[98]

V. CONCLUSION

Combining the market entry barriers as well as the weaknesses in patent protection of biologics, innovation in the biologics/biosimilars field likely faces some challenges heading forward, particularly with respect to the role of which patents may have in the system. The weakened role of patents in the BPCI has some distressing implications on the drug industry, as the patent system has historically been the primary driver of biotechnology innovation in the United States.[99] One can hypothesize that the reasoning behind the relatively long exclusivity period of twelve years for a novel biologic compound is to compensate biologics manufacturers for the weakened patent protection both inherent to the biologics field and explicitly found in the BPCI. Perhaps in the future, if the problems inherent to the biotechnological fields do not self-correct, then the incentives to innovate will lie primarily in limited monopolies via regulatory approval by administrative agencies such as the FDA rather than in exclusive rights granted via patents. This may, in fact, have been the intention of Congress in drafting the BPCI. Certainly it would seem that novel biologics manufacturers will receive greater economic benefits from regulatory exclusivity than patent exclusivity if the twelve years of exclusivity is "data exclusivity" as opposed to "market exclusivity."[100]

Based purely upon market economics, it currently remains a more lucrative prospect to file an ANDA application than a biosimilars application, as the cost is orders of magnitudes less ($100–200 million for a biosimilar compared to $1–5 million for a generic)[101] and the overall market is larger for pharmaceuticals than for biologics; although branded biologics are taking over a larger part of the overall market share and the price of branded biologics is increasing faster than current inflation rates.[102] Since the FDA has not yet approved a biosimilar despite the law being passed in 2010, whether or not eventual market forces prove strong enough

[98] Barrett, *supra* note 38, at 1598.

[99] *Id.* at 1620.

[100] Blackstone & Fuhr, *supra* note 42, at 16.

[101] F.T.C., *Emerging Health Care Issues: Follow-on Biologic Drug Competition*, F.T.C. REPORT, June 2009, at 1, 30, *available at* http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf.

[102] Blackstone & Fuhr, *supra* note 42, at 23–24.

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

to overcome weakened patent rights for innovative biologics manufacturers in addition to overcoming the greater entry costs for biosimilars applicants still remains to be seen.[103] Notably, in September 2013, the European Commission approved the first biosimilar antibody drug in Europe, using Remicade as the reference product.[104]

VI. RECOMMENDATIONS

Below is a list of policy recommendations to help stimulate innovation in the biologics field while simultaneously promoting the development of biosimilars and protecting consumers' interests.

A first recommendation would be to create an Orange Book equivalent style listing for approved biologics and patents associated with them, as that information is already part of the public record, as opposed to the current "closed-door" exchange of patents.[105] There may still be a requirement for exchanging confidential information that stays internal to the parties involved in the dispute, but the patents and related non-confidential information should be made public and easily accessible.

A second recommendation is to implement a temporary stay provision, which does not necessarily need to be as long as the thirty-month stay found in ANDA litigation. A reasonable recommendation would be eighteen months, which was the proposed stay when the Hatch-Waxman Act was pending before Congress.[106] Still, a full thirty-month stay would both protect the patent-holders and prevent the applicants from paying a significantly larger royalty, if they are ultimately found to have infringed, as the applicants would not have had any commercial use during the proposed stay.

A third recommendation, in light of the remarkably high costs associated with manufacturing a biosimilar compared to a generic, is to grant a longer period of exclusivity for an approved interchangeable biosimilar than the current regime.[107]

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[103] *Information for Consumers (Biosimilars)*, U.S. FOOD & DRUG ADMIN. (Nov. 3, 2011), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718.htm.

[104] Jonathan D. Rockoff, *European Commission Approves Biosimilar of J&J and Merck's Remicade*, WALL ST. J., Sept. 11, 2013, at B7.

[105] 37 C.F.R. § 1.11(a)–(e) (2012).

[106] Mossinghoff, *supra* note 19, at 190.

[107] 42 U.S.C. § 262(k)(6) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

Furthermore, the period of exclusivity should not be limited to only the "first" interchangeable biological product with respect to the reference product, as doing so unnecessarily disincentives future biosimilar applicants with respect to that reference product.

A fourth recommendation is to allow counsel that was "engaged, formally or informally, in patent prosecution relevant or related to the reference product"[108] to participate in the action, but to limit their involvement to only those patents listed by either the applicant or the reference product sponsor. While there may be legitimate concerns about the possibility of confidential information relating to the process/methods of making the biosimilar to a third party, the potential disadvantage to the patent holder in being unable to contact the individual(s) who were involved in the drafting and prosecution of the patent(s) should outweigh any concerns about the confidentiality of materials involved, particularly if all parties involved are forced to sign an enforceable confidentiality agreement.

A final recommendation is to eliminate the mechanism wherein if no agreement on the patents list is reached between the applicant and the reference product sponsor that the total number of patents cannot exceed those listed by the applicant.[109] This particular law is wasteful, serves little purpose, and in certain circumstances renders the whole act of bringing suit under the "artificial infringement" mechanism practically meaningless. Unless the original intent was to deter patent enforcement by the patent holder through inconvenience and hassle, in which case Congress could have seemingly found less-tedious means, this particular law does not serve much purpose.

[108] 42 U.S.C. § 262(l)(1)(B)(ii) (2012).

[109] 42 U.S.C. § 262(l)(5)(B)(ii) (2012).

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

Table 1. A side-by-side comparison between the regulatory approval pathways and the generics/biosimilars markets.

Regulatory Approval Pathways	
Generics	Biosimilars
Central repository-"Orange Book"	No central repository
Submitting ANDA = "constructive infringement" ← 271(e)(2)(A),(B)	Submitting biosimilar application = "constructive infringement" ← 271(e)(2)(C)
No method patents listed in Orange Book, litigation under 271(e) limited to Orange Book listings	Method patents may be litigated
ANDA need only show "bioequivalence"	Must submit all of the following: - Reference product (approved biologic) - Information based on data derived from analytical studies that demonstrate that the biological product is highly similar to the reference product - Animal studies - Clinical studies that are sufficient to demonstrate safety, purity, and potency - Evidence showing biosimilar and reference product utilize the same mechanism or mechanisms of action for the condition(s) of use - The condition(s) of use - Route of administration - Evidence showing that the facility in which the biological product is manufactured, processed, packed, or held meets certain standards
ANDA filer must make a certification (Paragraph I-Paragraph IV)	Biosimilar sponsor must make the equivalent of a Paragraph IV certification

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

Generics	Biosimilars
Patent holder may bring suit on patents listed in Orange Book	"Patent list exchange process" - Done in confidence/secret - *Must* include method of making biosimilar - Biosimilar sponsor is the ultimate arbiter of how many (number, not which) patents the patent holder can bring suit (patent holder can always bring suit on at least one patent) - Attorneys involved in patent prosecution are statutorily prohibited from participation
Automatic 30-month stay	No automatic stay - *Possible* preliminary injunction until court decision regarding patents asserted by the patent holder
Generics: 180-day regulatory exclusivity, but must be the first to make a Paragraph IV certification.	Biosimilars: - Exclusivity only for "interchangeable" biosimilar, a higher standard than just biosimilarity - Only for *first* interchangeable biosimilar with respect to a particular reference compound - Non-interchangeable can still be approved but no exclusivity will be granted Time period: the *earliest* of: - 1 year after the first commercial marketing of the biosimilar - 18 months after final court decision in infringement case - 18 months after dismissal with/without prejudice - 42 months after approval, if still ongoing litigation - 18 months if no suit is brought
NDAs: 5 year "data" regulatory exclusivity	BLAs: 12 years regulatory exclusivity - FDA has not come forth definitively with whether the exclusivity is "data" or "market" - FTC has estimated 16-18 years before a competitor can enter market if data exclusivity.

ISSN 0041-9915 (print) 1942-8405 (online) ● DOI 10.5195/lawreview.2014.339
http://lawreview.law.pitt.edu

Market Comparisons	
Generics	Biosimilars
Small molecules: $940 billion worldwide, up from $500 billion in 2003 - Compositions and structures known precisely - Dozens of atoms - Typically can be administered orally	Biologics: $600 billion worldwide (no 2003 data) - Compositions much more complex, thousands to millions of atoms typically - Harvested from cell cultures, no two cell cultures produce identical biologics (hence "similar") - Typically cannot be administered orally - Many consider it to be the "fastest growing sector"
Generics constitute 80% of the small molecule pharmaceutical market	No generic biologics, no biosimilars approved yet by FDA (check this before publication)
Cost of manufacturing a generic: $1-5 million	Cost of manufacturing a biosimilar: $100-200 million (estimated)
11/20 Top selling drugs in 2011 (worldwide) were small molecules: lipitor, plavix, seritide, crestor, nexium, seroquel, abilify, singulair, zyprexa, cymbalta, and spiriva.	9/20 Top drugs in 2011 (worldwide) were biologics: avastin, enbrel, glivec, herceptin, humira, lantus, mabthera, neulasta, and remicade.

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http://lawreview.law.pitt.edu