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## The Promise and Problem of Biologics

Michael A. Sanzo

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## THE PROMISE AND PROBLEM OF BIOLOGICS

*Michael A. Sanzo*<sup>†</sup>

*Biologics are drugs derived from living organisms and are typically too complex to be fully characterized or chemically synthesized. They represent some of the most promising new therapies in the United States and are already extensively used in the treatment of autoimmune diseases and several types of cancer. Unfortunately, the cost these drugs is often so high that much of the U.S. population cannot afford them.*

*In 2010, Congress enacted the Biologic Price Competition and Innovation Act (“BPCIA”), whose purpose was designed to promote the development of biosimilars. These are drugs that are similar enough to a previously-approved pioneer drug that they can be marketed with less testing. While it is still too early to ascertain how the BPCIA will affect the price of biologics, economic considerations and results from the first-marketed biosimilar suggest that its effect will be modest.*

*This Article argues that part the reason for the unpromising outlook regarding the effect of the BPCIA is that it fails to provide adequate incentives for companies to innovate—particularly methods of producing biologics more reliably and at a lower cost. In the absence of improvement in this area, the effect of biosimilars on the price of biologics is likely to be insufficient to make these drugs more affordable. This Article suggests alternative incentives that may help the BPCIA better achieve its intended purpose.*

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## INTRODUCTION

Many of our most effective therapeutic agents are derived from living organisms and are too large or too complex to be chemically synthesized.<sup>1</sup> These are termed “biologics” and include vaccines, cells, gene therapy agents, tissues, recombinant proteins, monoclonal antibodies, cytokines, and immunomodulators.<sup>2</sup> Current biologics having global sales of five billion dollars or more include Humira<sup>®</sup> for the treatment of rheumatoid arthritis; Rituxan<sup>®</sup> for Non-Hodgkins lymphoma; Avastin<sup>®</sup> for breast, colorectal, and ovarian cancer; Harvoni<sup>®</sup> for hepatitis C and Seretide<sup>®</sup> for asthma.<sup>3</sup>

In addition to being among the most effective therapeutics, biologics are also among the most expensive. In 2013, Express Scripts (the largest third-party manager of prescription drug programs in the U.S.) reported that biologics then on the market typically cost \$1,000 to over \$50,000 per treatment. In some instances, biologics cost patients hundreds of thousands of dollars per year.<sup>4</sup> Healthcare plans do not always fully cover these drugs,<sup>5</sup> and many people diagnosed

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1. *Going Large*, ECONOMIST (Dec. 30, 2014), <http://bit.do/GoingLarge>.

2. U.S. FOOD & DRUG ADMIN., *FDA 101: Regulating Biological Products*, (July 28, 2005), <http://bit.do/FDAWhatBiologicalProducts>.

3. Ann M. Thayer, *Leading Drugs Under Fire In 2015*, CHEMICAL & ENGINEERING NEWS, Dec. 7, 2015, at 19, 19; see also Kathlyn Stone, *The Top 10 Biologic Drugs in the United States*, BALANCE (Oct. 13, 2016), <http://bit.do/Top10BiologicDrugs>.

4. Steve Miller, *The \$250 Billion Potential of Biosimilars*, EXPRESS SCRIPTS (Apr. 23, 2013), [http://bit.do/ExpressScripts\\_Biosimilars](http://bit.do/ExpressScripts_Biosimilars).

5. *How to Get Your Health Plan to Cover Specialty Drugs*, REUTERS (Jan. 19, 2013), [http://bit.do/CNBC\\_SpecialtyDrugs](http://bit.do/CNBC_SpecialtyDrugs).

with chronic, or even lethal, diseases cannot afford the best and in some cases, the only treatment available.<sup>6</sup> Moreover, the strain of these high-priced drugs on total healthcare cost in the U.S. is getting worse as their market share of the pharmaceutical market increases.<sup>7</sup>

Part of the reason for the high cost of biologics is inherent. The complex structure of these drugs makes them much more difficult to produce than chemically-synthesized small molecules and creates a need for more testing.<sup>8</sup> An additional reason is that, because of natural variability in biological organisms and purification procedures, it is essentially impossible to produce a generic version of a pioneer drug.<sup>9</sup> Congress attempted to address this problem in the Biologic Price Competition and Innovation Act (“BPCIA”), which came into law as Title VII of the Patient Protection and Affordable Care Act (sometimes referred to as “Obamacare”).<sup>10</sup> The basic rationale for the BPCIA is that, even if generics in the traditional sense are not available for biologics, it may still be possible to develop compounds that are similar enough to allow them to be used as clinical alternatives without the full degree of testing otherwise required.<sup>11</sup>

Thus far, the BPCIA has had only limited success. The first biosimilar, Zarxio, did not arrive on the market until September of 2015, more than five years after the BPCIA became law, and at a price only 15% lower than its reference product, Neupogen.<sup>12</sup> Part of the reason for the delay may have been that the legislation was so poorly

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6. Lacie Glover, *Why Are Biologic Drugs So Costly?*, U.S. NEWS & WORLD REPORT, (Feb. 6, 2015), [http://bit.do/USNews\\_BiologicDrugsCostly](http://bit.do/USNews_BiologicDrugsCostly).

7. Mari Serebrov, *Biologics' Share of Medicine Chest Grows, and So Do the Pricing Concerns*, BIO WORLD TODAY (Mar. 9, 2015), [http://bit.do/BioWorld\\_ShareofMedicineChest](http://bit.do/BioWorld_ShareofMedicineChest).

8. Glover, *supra* note 6.

9. Brian Palmer, *The \$8,000 Pill*, SLATE (Aug. 16, 2010), [http://bit.do/Slate\\_8000Pill](http://bit.do/Slate_8000Pill); see also JUDITH A. JOHNSON, CONG. RESEARCH SERV., RL34045, FDA REGULATION OF FOLLOW-ON BIOLOGICS 7-5700, at 5-6 (2010). The term “generic,” as used herein, refers to a copy of a proprietary drug that is structurally identical and essentially identical in all other respects to a pioneer drug. The term “pioneer drug” refers to a chemical entity that has been approved or licensed for marketing as a drug in the U.S. for the first time.

10. Ryan Timmis, *The Biologics Price Competition and Innovation Act: Potential Problems in the Biologic-Drug Regulatory Scheme*, 13 NW. J. TECH. & INTELL. PROP. 215, 216 (2015).

11. *Id.* at 215.

12. Ben Hirschler & Michael Shields, *Novartis Launches First U.S. 'Biosimilar' Drug at 15 Percent Discount*, REUTERS HEALTH NEWS (Sept. 3, 2015), [http://bit.do/Reuters\\_Novartis](http://bit.do/Reuters_Novartis). Zarxio had been approved on March 6, 2015. Sabrina Tavernise & Andrew Pollak, *F.D.A. Approves Zarxio, Its First Biosimilar Drug*, N.Y. TIMES (Mar. 6, 2015), <https://nyti.ms/1EvtpC>. Four other biosimilars have been subsequently approved and several other applications are nearing approval. Kiran Panesar, *Biosimilars: Current Approvals and Pipeline Agents*, 41 U.S. PHARMACIST 26, 26-29 (Oct. 14, 2016). The term “reference product” refers to a previously approved drug that the generic attempts to replicate.

drafted and so convoluted that the Federal Circuit, borrowing a quote from Winston Churchill, referred to it as “a riddle wrapped in a mystery inside an enigma.”<sup>13</sup> Unsurprisingly, substantial litigation over various statutory interpretations of the BPCIA, as well as how to resolve those inconsistencies, has occurred, and its case law continues to evolve.<sup>14</sup>

The present paper argues that revisions are needed in this legislation not only to clarify its terms, but also because it fails to provide adequate incentives for the development of innovative production methods that will be crucial to a substantial reduction in the cost of biologics.<sup>15</sup> Amendments are suggested that may better induce biosimilar manufacturers to develop more efficient means of production without compromising the incentives that exist for proprietary drug manufacturers to develop new biological products.

## I. LEGISLATIVE BACKGROUND

### A. *Historical Framework*

Throughout the 1800s, there was a remarkable absence of regulation governing the way in which drugs in the U.S. are approved, manufactured, and sold.<sup>16</sup> The only major regulatory legislation passed by Congress during this period was the Drug Importation Act of 1848.<sup>17</sup> This Act prohibited unsafe or adulterated drugs from being imported but did not have any effect on drug products made in the U.S. The latter

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13. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347, 1351 n.1 (Fed. Cir. 2015). The phrase was taken from Winston Churchill in a speech he gave on Russia on October 1, 1939.

14. *Id.* at 1353. The biosimilar applicant for Zarxio, Sandoz, has been in litigation with the reference drug owner, Amgen, since October of 2014 over contradictory statutory requirements and the case is now slated for consideration by the U.S. Supreme Court. Jason Rantanen, *Supreme Court to Review BPCIA*, PATENTLY-O (Jan. 14, 2017), [http://bit.do/PatentlyO\\_AmgenvSandoz](http://bit.do/PatentlyO_AmgenvSandoz). Close on the heels of this case is a second case, *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052 (Fed. Cir. 2016), which is concerned with the interpretation of essentially the same provisions. See also Kurt R. Karst, *Feeling Dissed, Amgen Sues After Sandoz Abandons the BPCIA Patent Dance Procedures for NEUPOGEN Biosimilar*, FDA LAW BLOG, (Oct. 29, 2014), [http://bit.do/FDALawBlog\\_FeelingDissed](http://bit.do/FDALawBlog_FeelingDissed).

15. By most estimates, it is likely that the ACA will soon be substantially revised and that the section concerned with biosimilars will be either kept or reintroduced. This may give Congress an opportunity to reexamine the BPCIA in light of developments since its passage. Zachary Brennan, *Cassidy Says Obamacare Repeal Will Not Repeal Biosimilars Approval Pathway*, REG. AFF. PROFS. SOC'Y (Dec. 7, 2016), [http://bit.do/RAPS\\_CassidySays](http://bit.do/RAPS_CassidySays).

16. See U.S. FOOD & DRUG ADMIN., *The History of Drug Regulation in the U.S.* (Sept. 24, 2015), [http://bit.do/FDA\\_CDERBrochure](http://bit.do/FDA_CDERBrochure).

17. Angela Walsh, *An In-Depth Look at The Import Drugs Act of 1848* (2002), <http://bit.do/SpuriousSolution>. See also Dennis B. Worthen, *Pharmaceutical Legislation: A Historical Perspective*, 10 INT'L J. PHARMACEUTICAL COMPOUNDING 20, 21 (2006).

could be sold without regard to efficacy or safety and without even disclosing what they contained.<sup>18</sup>

In such an atmosphere, disaster is inevitable, and it arrived in the fall of 1901.<sup>19</sup> At that time, diphtheria patients were routinely treated with an antiserum derived from horses. On September 30, antiserum was collected from a horse in St. Louis who, two days later, died of a tetanus infection.<sup>20</sup> The antiserum was recalled, but not before a fatal dose had been administered to thirteen children.<sup>21</sup> In response to this, and a similar incident in New Jersey that resulted in death of nine children, Congress passed the Biologics Control Act of 1902.<sup>22</sup> This legislation was the first to require pre-market approval of drugs by the federal government.<sup>23</sup> In 1944, the Biologics Act became the Public Health Service Act, and this is currently the legislation under which most biologics are regulated.<sup>24</sup>

A second major health safety act, the Pure Food and Drugs Act, was passed by Congress in 1906. In its initial form, this legislation prohibited the interstate transport or sale of adulterated or misbranded drugs,<sup>25</sup> including all preparations in the United States Pharmacopoeia or National Formulary.<sup>26</sup> Despite its name, however, the Pure Food and

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18. U.S. FOOD & DRUG ADMIN., *supra* note 16; *see also* Walsh, *supra* note 17.

19. Ross E. DeHovitz, *The 1901 St. Louis Incident: The First Modern Medical Disaster*, 133 PEDIATRICS 964, 965 (2014); *see also* Valerie Marshall et al., *Food and Drug Administration Regulation and Evaluation of Vaccines*, 127 PEDIATRICS S23, S24 (May 2011).

20. DeHovitz, *supra* note 19, at 964.

21. *Id.*

22. Biologics Control Act of 1902, Pub. L. No. 57-244, 32 STAT. 728 (1902) (codified as amended at 42 U.S.C. § 262); 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, 682-83 (2010).

23. JUDITH A. JOHNSON, CONG. RESEARCH SERV., RL34045, FDA REGULATION OF FOLLOW-ON BIOLOGICS 7-5700, at 5-6 (2010).

24. *Id.*

25. Section 8 of the Act defined the term “misbranded” as applying to any drugs which are sold in conjunction with false or misleading statements about the drug or its ingredients. The federal government initially used this provision as a basis for acting against drugs with unfounded claims for curative effects. *History of Federal Regulation: 1902–Present*, FDAREVIEW.ORG (2016), [http://bit.do/FDARReview\\_History](http://bit.do/FDARReview_History) [hereinafter *History of Federal Regulation*]. However, in 1911, the Supreme Court held that the statute did not cover all false or misleading statements, but only those concerned with the identity of the article and possibly including its strength, quality, and purity. Claims to cure for cancer, baldness etc., were outside the scope of the Act. *See* United States v. Johnson, 221 U.S. 488, 497 (1911). In response to this decision, Congress passed the Sherley Amendment in 1912. However, this applied only to claims that the seller knew to be false and, like the 1906 legislation, was confined to statements made on labeling and not advertising. *History of Federal Regulation*.

26. *History of Federal Regulation*, *supra* note 25; Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906) (amended 1912). The law appointed the Bureau of Chemistry of the Department of Agriculture to carry out the testing of drugs on the market. This Bureau eventually became the FDA.

Drugs Act did little to actually prevent adulterated drugs from getting to the market. Unlike the Biologics Control Act, it did not require the pre-market testing of drug products.<sup>27</sup>

It was not until 1938 that this deficiency was addressed when the Act of 1906 was replaced with the Federal Food Drug and Cosmetic Act (“FDCA”). This required drug manufacturers to file a new drug application (“NDA”) prior to marketing, in which they demonstrate the safety of their proposed product.<sup>28</sup> Remarkably, however, the FDA had only 60 days from the date of filing to disapprove an application or the applicant was free to begin marketing.<sup>29</sup> Also, there still was no requirement that a drug maker show that its product actually worked.

Finally, in 1962, Congress passed the Kefauver-Harris Drug Amendment, which compelled drug makers to demonstrate that its proposed product is both safe and effective.<sup>30</sup> Drugs that were approved *prior to* 1962 were evaluated by a committee that made a recommendation as to their efficacy.<sup>31</sup> In cases where this review suggested that continued marketing of a drug was warranted, the legislation provided that a generic version could be approved by the filing of an Abbreviated New Drug Application (“ANDA”), which demonstrated chemical identity and bioequivalence.<sup>32</sup> For most drugs approved *after* 1962, a generic only required the filing of a “paper NDA,” in which safety and efficacy could be established based in part on citations to published reports.<sup>33</sup>

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27. *History of Federal Regulation*, *supra* note 25.

28. JOHNSON, *supra* note 23, at 5-6; *see also* Frederick R. Ball et al., *Generic Drugs: ANDAs, Section 505(b)(2) Applications, Patents, and Exclusivities*, in *FOOD AND DRUG LAW AND REGULATION*, 376-78 (David G. Adams et al. eds., 3d ed. 2014). As an alternative to submitting an NDA, a drug could be approved if it was generally recognized as safe (GRAS). In cases where a drug had already been approved and a second manufacturer was attempting to get approval of the same drug, the GRAS option allowed a manufacturer to avoid safety testing and market a generic. *See History of Federal Regulation*, *supra* note 25.

29. *Roche Prods. v. Bolar Pharm. Co.*, 733 F.2d 858, 864 (Fed. Cir. 1984).

30. Ball et al., *supra* note 28, at 376-78. Like in a great deal of FDA legislation, the Kefauver-Harris Amendment was prompted by a disaster—the sale of the morning sickness drug thalidomide in Canada and Europe and the ensuing births of severely-deformed babies. A similar fate was averted in the U.S. largely due to the intransigence of a single FDA Medical Officer, Frances O. Kelsey. *See* Robert D. McFadden, *Frances Oldham Kelsey, Who Saved U.S. Babies From Thalidomide, Dies at 101*, N.Y. TIMES A1 (Aug. 7, 2015).

31. Ball et al., *supra* note 28, at 376-78.

32. *Id.*

33. *Id.* at 377-78. Forty-seven paper NDAs were approved by FDA between January 1979 and June 1983, resulting in generic versions of 19 drugs. Edward Tabor, *Generic Drug Approvals in the U.S. Prior to the Hatch-Waxman Act*, REGULATORY FOCUS 50, 52 (Sept. 2008). A different procedure existed for antibiotics and insulin.

From the viewpoint of the proprietary drug industry, the primary effect of the testing requirements imposed by the Kefauver-Harris Drug Amendment was that it decreased the number of drugs that made it to the market and greatly increased the development cost of the drugs that did.<sup>34</sup> In addition, the Amendment resulted in a reduction in the effective life of any relevant patents that issued before a drug was approved for marketing.<sup>35</sup>

There were also problems for generic manufacturers wanting to replicate drugs approved after 1962. The FDA never extended the ANDA policy that it had established under the Kefauver-Harris Amendment for pre-1962 drugs and the paper NDA procedure was hampered by an absence of adequate publications for many drugs.<sup>36</sup> Even though the FDA possessed studies establishing the safety and efficacy of the products that generic companies were attempting to replicate, these studies were considered to be the confidential property of the proprietary drug sponsor and were not made available to generic applicants.<sup>37</sup>

*B. Roche Products v. Bolar Pharmaceutical Co.*

The state of the drug approval process in the U.S. after 1962 can be seen in *Roche Products v. Bolar Pharmaceutical Co.*, a case decided by the Federal Circuit in 1984.<sup>38</sup> The facts in this case are quite simple. Roche had a patent covering a sedative that it had marketed under the brand name “Dalmane.”<sup>39</sup> Bolar was interested in marketing a generic version of the drug in 1984, as soon as the patent expired.<sup>40</sup> In order to gain access to the market as soon as possible, Bolar began bioequivalency studies needed for FDA approval in mid-1983 and, based on this activity, Roche filed suit for patent infringement in the District Court for the District of New Jersey.<sup>41</sup> The case was then transferred to the District Court for the Eastern District of New York,

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34. Dale H. Geiringer, *The Safety and Efficacy of New Drug Approval*, 5 CATO J. 177, 178 (1985) (citing a 1980 report by the U.S. General Accounting Office). Mr. Geiringer indicates that by 1976, the cost of developing a new drug was ten to twenty times higher than in the early 1960s. See also Jeremy A. Greene et al., *Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Amendments at 50*, 367 NEW ENG. J. MED. 1481 (Oct. 18, 2012).

35. At that time, a patent term ran for 17 years from the date of issuance and, as a result, the life of an issued patent eroded during FDA testing.

36. Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28872, 28872-74 (July 10, 1989) (to be codified at 21 C.F.R. pts. 10, 310, 314, & 320).

37. *Id.*

38. *Roche Prods. v. Bolar Pharm. Co.*, 733 F.2d 858 (1984).

39. *Id.* at 860.

40. *Id.*

41. *Id.*

which held that Bolar was not liable because its use of the patented drug was “*de minimis* and experimental.”<sup>42</sup>

On appeal, the Federal Circuit offered an interesting assessment of the effect of the Kefauver Amendment on the drug approval process:

The new drug approval procedure which existed between 1938 and 1962 was relatively innocuous and had little impact on the development of pioneer prescription new drugs. Section 505 of the FDCA required the manufacturer of a pioneer new drug to submit to the FDA a New Drug Application (NDA) containing information concerning the safety of the drug. If the FDA did not disapprove the new drug within 60 days after it received the NDA, marketing could begin.

The provisions of the Drug Amendments of 1962 caused a substantial increase in the time required for development and approval of a pioneer new drug. Beginning in 1962, the amended Section 505 required an NDA to contain proof of efficacy (effectiveness) as well as safety, and required the FDA affirmatively to approve the NDA rather than just to permit marketing by inaction. A recent study indicated that it now can take on average from 7 to 10 years for a pharmaceutical company to satisfy the current regulatory requirements.

Because most FDA-required testing is done after a patent issues, the remaining effective life of patent protection assertedly may be as low as 7 years. Litigation such as this is one example of how research-oriented pharmaceutical companies have sought to regain some of the earning time lost to regulatory entanglements. They gain for themselves, it is asserted, a *de facto* monopoly of upwards of 2 years by enjoining FDA-required testing of a generic drug until the patent on the drug's active ingredient expires.<sup>43</sup>

The Federal Circuit reversed the district court's holdings. It found that Bolar's activities were not covered by the experimental use exception and were not *de minimis*:

Bolar's intended “experimental” use is solely for business reasons and not for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry. Bolar's intended use of flurazepam hcl to derive FDA required test data is thus an infringement of the '053 patent. Bolar may intend to perform “experiments,” but unlicensed experiments conducted with a view to the adaption of the patented invention to the experimenter's business is a violation of the rights of the patentee to exclude others from using his patented invention. It is obvious here that it is a misnomer to call the intended use *de minimis*. It is no trifle in its economic effect on the parties even if

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42. *Id.* at 860-61.

43. *Id.* at 864 (citations have been omitted to improve readability).

the quantity used is small. It is no dilettante affair such as Justice Story envisioned. We cannot construe the experimental use rule so broadly as to allow a violation of the patent laws in the guise of “scientific inquiry,” when that inquiry has definite, cognizable, and not insubstantial commercial purposes.<sup>44</sup>

## II. THE HATCH-WAXMAN ACT

In 1984, Congress passed the Hatch Waxman Act, which legislatively overruled *Roche* and established a clearly-defined and efficient route for generics to enter the market.<sup>45</sup> The Act attempts to balance the interests of generic manufacturers with the need of branded manufacturers to recover the cost of new drug development and realize a profit. The Act’s most important provisions are discussed below.<sup>46</sup>

### A. Provisions of Primary Benefit to Proprietary Manufacturers

#### 1. Market Exclusivity

Under the Hatch-Waxman Act, the sponsor of a drug application directed to a new chemical entity is entitled to five years of data exclusivity from the date of approval.<sup>47</sup> During this time, the FDA will not accept an application directed to the same drug.<sup>48</sup> Due to the time required for approval after an application for a generic is filed, the market exclusivity enjoyed by the sponsor will, as a practical matter, likely be extended for an additional one to three years.<sup>49</sup>

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44. *Id.* at 863. The Court also declined Bolar’s suggestion that public policy favors generic drugs and that it should therefore create an exception to infringement for FDA-required drug testing. *Id.* at 864.

45. Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. §§ 301, 355, 360cc (2012)).

46. The review of the Hatch-Waxman Act and later, the BPCIA, focuses only on those aspects of the legislation pertinent to the present discussion. Certain sections of the legislation have been simplified somewhat and others, such as those dealing with pediatric exclusivity, have been omitted entirely.

47. 21 C.F.R. § 314.108(b)(2) (1984). Exclusivity is reduced to four years if the approved drug becomes the subject of an abbreviated new drug application (ANDA) filed by a generic manufacturer and which contains a paragraph IV certification. *See infra* Part II, Section B.

48. § 314.108(b)(2).

49. Remarkably, it currently takes longer for the FDA to approve most abbreviated new drug applications (ANDAs) for a generic than it takes to approve an application for a new drug. This is due to a large backlog in ANDAs, and the FDA has been trying to rectify this. The FDA aims to eventually complete approval of applications in eight to ten months. The one to three years provided in the text is based on FDA numbers from 2015. Zachary Brennan, *Generic Drug Backlog at FDA: A Dive Into the Confusing Numbers*, REG. AFF. PROFS. SOC’Y: REG. FOCUS, (Nov. 1, 2016), [http://bit.do/RAPS\\_Generic-Drug-Backlog](http://bit.do/RAPS_Generic-Drug-Backlog).

Further, the sponsor of an approved new chemical entity may later file a supplemental application for a new therapeutic indication, formulation, route of administration, or other change.<sup>50</sup> If the supplemental application relies on clinical investigations that are not previously submitted for approval, the FDA will refrain from approving any other application that relies on the same clinical investigations for a period of three years.<sup>51</sup>

## 2. Establishment of the “Orange Book”

The Hatch-Waxman Act requires that an NDA include the number and expiration date of any patents that claim either the new drug or a method of using the new drug.<sup>52</sup> Upon acceptance of the NDA, these patents are included in a list of approved drugs compiled by the FDA (known informally as the “Orange Book”) and may be used as a basis for litigation.<sup>53</sup>

## 3. Litigation Under Hatch-Waxman Act (Automatic 30-Month Stay)

When an ANDA is filed for a generic product, it must include one of several statements regarding patents listed in the Orange Book as covering its reference drug.<sup>54</sup> One of these statements, generally known as a paragraph IV certification, is essentially an assertion that the listed patents may be disregarded because their claims are invalid, unenforceable, or do not include the proposed generic product.<sup>55</sup> In cases where such a certification is made, the generic applicant must, within 20 days of filing its application, give notice to each owner of the patent to which the certification pertains and provide a detailed explanation for the assertions made.<sup>56</sup> The filing of an ANDA with a paragraph IV certification is, in itself, sufficient to constitute an act of infringement for any patent listed in the Orange Book and the recipients of the notice have a period of 45 days to file suit.<sup>57</sup>

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50. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CHANGES TO AN APPROVED NDA OR ANDA (Apr. 2004).

51. § 314.108(5)(2).

52. 21 U.S.C. § 355(b)(1) (2012). The statute is silent regarding patents directed to methods of making drugs.

53. *Id.*

54. § 355(j)(2)(vii). The “reference drug” is the proprietary drug product that has been previously approved and is being duplicated by the generic manufacturer.

55. *Id.* See *infra* Subsection B.1.

56. § 355(j)(2)(B)(i)-(iv). Notice must also be given to the NDA holder if different from the patent owner.

57. § 355(j)(5)(B)(iii).

Importantly, the party that has brought the action then automatically receives a stay under which the ANDA will not be approved for thirty months unless the litigation is completed, a settlement is reached, or the court otherwise intervenes before the expiration of that period.<sup>58</sup> In effect, the party alleging infringement receives a preliminary injunction without the need to actually establish the criteria normally required.<sup>59</sup> The 30-month period assures the proprietary manufacturer that it will have an opportunity to favorably resolve an infringement action *before* a generic enters the market.<sup>60</sup>

#### 4. Patent Term Restoration

In 1984, patents had a term that began running when they issued and lasted for 17 years thereafter.<sup>61</sup> If the patent had claims covering a drug product, the portion of the term from the time of patent issuance to drug approval was irretrievably lost with respect to protection of the marketed drug. This loss however, was partly offset by the fact that, under *Roche*, testing by generic manufacturers in the U.S. could not begin until any patents covering their activities had expired.<sup>62</sup>

Hatch-Waxman upset this rough balance between lost proprietary patent life and delayed generic market entry by introducing a safe harbor provision under which a generic manufacturer is permitted to engage in FDA-related testing before patent expiration.<sup>63</sup> In order to compensate proprietary drug manufacturers, other provisions were included that allowed for recovery of a portion of the effective patent life that they had lost in getting a pioneer drug approved by the FDA.<sup>64</sup> Specifically, under Hatch-Waxman, a patent term may be extended by

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58. The period may be altered either by a court decision or court order. § 355(j)(5)(B)(iii)(I)-(IV). If no such action is filed, the ANDA will become effective immediately upon approval.

59. CONG. RESEARCH SERV., R44643, THE HATCH-WAXMAN ACT: A PRIMER 7-8 (Sept. 28, 2016).

60. One potential problem in this regard is the delay of litigation due to a stay ordered by a court for different reasons, for example, to allow the completion of an IPR action at the Patent Trial and Appeal Board.

61. The term changed in 1995 as a result of the Uruguay Round Agreements Act. Currently the unadjusted term of a patent is 20 years from its effective filing date. See Karen Tripp & Linda Stokley, *Changes in U.S. Patent Law Effected by the Uruguay Round Agreements—the GATT Implementation Legislation*, 3 TEX. INTELL. PROP. L.J. 315, 316-17 (1995). Currently, the unadjusted term of a patent is 20 years from its effective filing date. *Id.*

62. *Id.* See also Hasneen Karbalai, *The Hatch-Waxman (Im)Balancing Act*, 4-5 (2003), <http://bit.do/ImbalancingAct> (unpublished J.D. thesis, Harv. Univ.) (on file with Digital Access to Scholarship, Harv. Univ.).

63. 35 U.S.C. § 271(e)(1) (2012). This is discussed below in the section describing advantages that Hatch-Waxman provided to generic drug makers.

64. This is provided in section 202 of the Act, codified in 35 U.S.C. § 156.

the full period of testing taking place from the time that an NDA is filed until the time it is approved (referred to as the “approval phase”) and for one half of the period from the approval of an investigational new drug application<sup>65</sup> until the filing of the NDA (referred to as the “testing phase”).<sup>66</sup> Adjustments are made for the portion of this period that was before the patent issued and for any periods during which the applicant did not act with diligence in completing the process.<sup>67</sup> Taking these factors into account, the calculation is:

$$\text{Period of Extension} = RRP - PGRRP - DD - \frac{(TP - PGTP)}{2},$$

where *RRP* is the sum of the approval phase and testing phase;

*PGRRP* is the number of days of the *RRP* period that pre-dates the patent issuance date;

*DD* is the number of days of the *RRP* that the applicant did not act with due diligence in completing the approval process;

*TP* is the number of days in the testing phase; and

*PGTP* is the number of days of the *TP* period that pre-dates the patent issuance date.<sup>68</sup>

Unfortunately, the terminology used in connection with this statutory provision is somewhat misleading. It is *not* an entire patent (and all of its claims) that is subject to extension; rather it is only those aspects of the patent that relate directly to the subject matter approved by the FDA. Specifically, under 35 U.S.C. § 156(b), rights during the extension period are limited to: (a) in the case of a patent which claims a product, any use approved by the FDA for the product;<sup>69</sup> (b) in the case of a patent which claims a method of using a product, any use claimed by the patent and approved for the product;<sup>70</sup> and c) in the case of a patent which claims a method of manufacturing a product, the method of manufacturing as used to make the approved product.<sup>71</sup> In addition, only one patent can be extended for a given regulatory review period.<sup>72</sup>

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65. An Investigational New Drug Application (“IND”) is a request for authorization from the FDA to administer an investigational drug or biological product to humans and generally precedes the filing of an NDA. See *Investigational New Drug Application*, U.S. FOOD & DRUG ADMIN. (Aug. 1, 2016), [http://bit.do/FDA\\_IND-Application](http://bit.do/FDA_IND-Application).

66. 35 U.S.C. § 156(g); MPEP § 2758 (9th ed. Rev. E9R-07.2015, Nov. 2015).

67. § 156(g); MPEP § 2758.

68. § 156(g); MPEP § 2758.

69. 35 U.S.C. § 156(b)(1).

70. § 156(b)(2).

71. § 156(b)(3).

72. § 156(c)(4).

*B. Provisions of Primary Benefit to Generic Manufacturers*

1. Abbreviated New Drug Applications

Although abbreviated new drug applications and paper NDAs existed after the 1962 amendments to the FDCA, the Hatch-Waxman legislation redefined and expanded these applications in a way that, for the first time, opened up a clear and readily-accessible route to market for generic drugs. Specifically, an ANDA under Hatch-Waxman can be filed for a generic having the same active ingredient or ingredients, route of administration, dosage form and strength as a “reference drug product” listed in the Orange Book.<sup>73</sup> Having established the identity of these factors, an applicant can rely on the safety and efficacy data submitted to get the pioneer drug approved and generally only needs to conduct studies to demonstrate bioequivalence.<sup>74</sup>

The ANDA must include a certification statement with respect to each patent listed in the Orange Book as covering the reference drug.<sup>75</sup> There are four options:

- (i) that patent information has not been filed,
- (ii) that the patent has expired,
- (iii) that the patent will expire on a specified date, or
- (iv) that the patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.<sup>76</sup>

The certification made by the applicant will determine when approval of an application becomes effective. Specifically, approval will be effective as soon as it is made if the certification of paragraph (i) or (ii) is made,<sup>77</sup> and approval will become effective on the expiration date of the patent if an applicant makes the certification of paragraph (iii).<sup>78</sup> However, things get considerably more complicated if a paragraph (iv) certification is made as this may, by itself, trigger an infringement action against the ANDA applicant.<sup>79</sup>

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73. § 355(j)(2)(A)(i)-(v).

74. The FDCA indicates that a generic is bioequivalent to its listed counterpart if: [t]he rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.

21 U.S.C. § 355(j)(8)(b)(i).

75. § 355(j)(2)(vii).

76. *Id.*

77. § 355(j)(5)(B)(i).

78. § 355(j)(5)(B)(ii).

79. § 355(j)(5)(B)(iii); 35 U.S.C. § 271(e)(2).

Apart from a new ANDA procedure, the Hatch-Waxman Act also established a new type of application that is a hybrid between an NDA and an ANDA and is codified in 21 U.S.C. § 505(B)(2).<sup>80</sup> Unlike the NDA of 21 U.S.C. § 505(B)(1), at least a portion of the support provided by the applicant under section (B)(2) may be derived from someone else's NDA data (regardless of whether the applicant has obtained a right of reference) or from a publication.<sup>81</sup> These applications may be directed to a new chemical entity or to a new dosage form, strength, route of administration, or active agent.<sup>82</sup>

## 2. Safe Harbor for Testing

Hatch-Waxman overturned *Roche* and immunized companies from infringement actions for carrying out tests to meet FDA requirements before patents covering such activities have expired.<sup>83</sup> This provision was codified in 35 U.S.C. § 271(e)(1), which reads:

It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

As a result, a manufacturer can be fully ready to market a generic product as soon as approval of an ANDA becomes effective and exclusivity of the reference drug owner has expired.

## 3. Market Exclusivity

As a further incentive for generic manufacturers, Hatch-Waxman provides that the first company to successfully file an ANDA application with a paragraph IV certification will receive 180 days of market exclusivity relative to other generic manufacturers beginning on the first day of commercial marketing.<sup>84</sup> This means that for the 180-

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80. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2), (Oct. 1999). These applications require much more testing than an ANDA but much less than an application under 21 U.S.C. § 355(b)(1)-(2).

81. *Id.*

82. *Id.*

83. 35 U.S.C. § 271(e)(1). The Act also amended patent law by adding 35 U.S.C. § 271(e)(2), which makes the filing of an ANDA an act of infringement if the purpose of such submission is to obtain approval to engage in the commercial manufacture, use, or sale of a drug, veterinary biological product, or biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

84. 21 U.S.C. § 355(j)(5)(B)(iv).

day period, the first ANDA filer would be the only producer, other than the NDA holder, that can market the approved drug.<sup>85</sup>

### III. COMPARING PROVISIONS OF THE BPCIA TO HATCH-WAXMAN

The BPCIA is essentially the biologics corollary of Hatch-Waxman,<sup>86</sup> and there are many similarities in the structuring of the two Acts. Like Hatch-Waxman, the BPCIA has some provisions designed to primarily benefit proprietary drug manufacturers and others that primarily benefit follow-on manufacturers. Most of these have been substantially altered under the BPCIA, with the biggest changes in the area of litigation. In addition, there are a few Hatch-Waxman provisions that were not part of the BPCIA legislation at all but that are available for and benefit biologic drug makers. The sections below consider the provisions of greatest importance to companies working with biologics.

#### A. Provisions of Primary Interest to Proprietary Manufacturers

##### 1. Patent Term Restoration

Arguably, the greatest benefit to proprietary drug manufacturers of the Hatch-Waxman amendment is the recovery of a portion of patent term lost due to FDA testing. This is available regardless of whether the drug undergoing testing is a small, chemically-synthesized compound or a biologic.<sup>87</sup> However, due to factors unique to biological products, the process of choosing which patent to extend may be somewhat different.<sup>88</sup>

Because small molecule drugs regulated under Hatch-Waxman are easily synthesized, purified, and characterized, patent claims directed to methods of manufacturing are generally regarded as being easily circumvented and of relatively little value.<sup>89</sup> It would therefore be unusual for a proprietary drug maker to choose a patent with claims to a method of manufacture as the one to extend.<sup>90</sup>

However, this is not true for biologics. For these drugs, the method of production is crucial in determining their chemical and clinical characteristics.<sup>91</sup> In fact, it may be difficult or impossible to

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85. *Id.*

86. Henry I. Miller, *Still Awaiting the Biosimilars Revolution*, 38 REG. 22, 22 (2015).

87. 35 U.S.C. § 156.

88. See Brian Coggio & Peter Ludwig, *Process Patents Are Vital In Biotech—Why Not Extend Them?*, LAW360 (Aug. 10, 2015, 10:19 AM EST), [http://bit.do/Law360\\_ProcessPatents](http://bit.do/Law360_ProcessPatents).

89. *Id.*

90. *Id.*

91. W. Nicholson Price & Arti V. Rai, *Manufacturing Barriers to Biologics Competition*

define these compounds except in terms of the way they are made and the way that they behave.<sup>92</sup> Claims to methods of manufacture are therefore on par with claims to the compounds *per se*, and increasing the term of patents with such claims makes a good deal of sense.<sup>93</sup>

## 2. Market Exclusivity

The BPCIA grants to the first party that successfully obtains a license for a biologic four years of data exclusivity (during which a biosimilar application cannot be filed)<sup>94</sup> and twelve years of market exclusivity (during which approval of a biosimilar application will not be made effective).<sup>95</sup> However, these restrictions do not apply to the sponsor of the reference product itself.<sup>96</sup> The sponsor may, at any time, file a supplement to its approved biologics license application (BLA) or a subsequent BLA for either: (a) “a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength,” or (b) “a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.”<sup>97</sup>

### B. Provisions of Primary Benefit to Follow-On Manufacturers

#### 1. Safe Harbor for Testing

One of the main incentives for enacting Hatch-Waxman was to reverse *Roche* and provide drug manufacturers with the ability to perform the experiments needed to ready generics for market as soon as possible.<sup>98</sup> This was done through the portion of the Act that is codified as 35 U.S.C. § 271(e)(1). However, the safe harbor is not confined to generics and has been held to cover a broad array of activities.<sup>99</sup> Thus, it is of substantial value to companies involved in producing biosimilars.

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*and Innovation*, 101 IOWA L. REV. 1023, 1033-35 (2016).

92. *See id.* at 1036-37 (discussing how production methods of biologics can alter their therapeutic effects).

93. Coggio & Ludwig, *supra* note 88.

94. 42 U.S.C. § 262(k)(7)(B) (2015).

95. § 262(k)(7)(A).

96. § 262(k)(7)(C).

97. *Id.*

98. CONG. RESEARCH SERV., *supra* note 59, at 5.

99. *See Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 206-07 (2005); *Momenta Pharm. v. Amphastar Pharm.*, 686 F.3d 1348, 1357-58 (Fed. Cir. 2012) (discussing the scope of 35 U.S.C. § 271(e)(1)).

## 2. Abbreviated Path to Licensing

As with the ANDA procedure for generics, applications for follow-on biologics are based on a comparison between the new follow-on product and a reference product that has already been evaluated and approved.<sup>100</sup> The process is abbreviated in the sense that an applicant can rely on the safety and efficacy data of the reference product.<sup>101</sup> However, meeting the other criteria required for approval is much more difficult for biosimilars than establishing that a generic has identical chemical characteristics and bioequivalence.

In order to establish biosimilarity, an applicant must show that the proposed product is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that it exhibits “no clinically meaningful differences” in terms of safety, purity, and potency.<sup>102</sup> The statute indicates that this is to be accomplished using: (a) analytical studies; (b) animal studies (which include an assessment of toxicity); and (c) clinical studies demonstrating safety, purity, and potency for a use that has been approved for the reference product.<sup>103</sup> The Act further indicates that clinical studies should include an assessment of the immunogenicity and pharmacokinetics or pharmacodynamics of the proposed product.<sup>104</sup>

Beyond these requirements, a biosimilar applicant must show that: a) the labeling proposed recommends conditions of use that have been approved for the reference product; b) the route of administration, dosage form, and strength of the proposed product are the same as the reference product; and c) the facility in which the biological product is manufactured meets standards set by the FDA.<sup>105</sup> Finally, if the mechanism of action of the reference product is known with respect to the approved use, an applicant must show that the proposed biosimilar utilizes the same mechanism.

An applicant for a biosimilar has the option of trying to establish that the proposed product qualifies as an “interchangeable.”<sup>106</sup> This is defined as a drug that meets the criteria for being a biosimilar and

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100. WENDY H. SCHACT & JOHN R. THOMAS, CONG. RESEARCH SERV., R41270, P.L. 111-148: INTELLECTUAL PROPERTY PROVISIONS FOR FOLLOW-ON BIOLOGICS (May 25, 2010) at 1-3.

101. 42 U.S.C. § 262(k)(2)(A)(i)(I).

102. § 262(i)(2).

103. § 262(k)(2)(A)(i)(I)(aa)-(cc).

104. § 262(k)(2)(A)(i)(I)(cc).

105. § 262(k)(2)(A)(i)(II)-(IV).

106. §§ 262(k)(2)(A)(i), (5)(A) (stating an application for a biosimilar may only have a single reference product).

which, in addition, “can be expected to produce the same clinical result as the reference product in any given patient.”<sup>107</sup> If the drug is to be administered more than once to an individual, the statute requires 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.”<sup>108</sup>

A primary difference between a biosimilar and an interchangeable is that the latter may be substituted for its reference product at the pharmacy without the intervention of a health care provider whereas the former cannot.<sup>109</sup> Thus, interchangeables have market characteristics closer to those of a generic than do biosimilars.<sup>110</sup>

### 3. Market Exclusivity

The BPCIA does not provide any exclusivity for a biosimilar. However, if a biosimilar applicant is the first to establish interchangeability, the FDA will not approve a second interchangeable for a period that is the earliest of several options. Specifically, if the drug is approved and marketed without litigation, then exclusivity will end one year after commercialization.<sup>111</sup> However, if the interchangeable applicant is sued for patent infringement under provisions relating to the first phase of the BPCIA process,<sup>112</sup> then exclusivity ends on the earliest of: (a) 18 months from the time of a final court decision or dismissal,<sup>113</sup> or (b) 42 months after *approval* of the interchangeable if litigation is ongoing within the 42-month period.<sup>114</sup> Finally, the statute indicates that exclusivity will end 18 months after the date of *approval* if the applicant is not sued.<sup>115</sup> By measuring the length of time from approval rather than

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107. See §§ 262(i)(2), (k)(4).

108. § 262(k)(4).

109. § 262(i)(3).

110. Approximately 40 states in the U.S. allow pharmacists to substitute a generic for a branded pharmaceutical without consulting with the prescribing physician. See Jeffrey J. Masters, Note, *Not Exactly the Same: An Examination of How Generic Substitution Laws Inadequately Protect Consumers' Needs if Taking Generic Drugs Results in Injuries*, 8 DREXEL L. REV. 233, 240 (2015). A smaller number allow such substitution for an interchangeable. *Id.* at 240-41.

111. § 262(k)(6)(A).

112. See *infra* Part III, Section C. Patent infringement actions under the BPCIA proceed in two distinct phases. The first phase begins when an application for a biosimilar is accepted by the FDA and the second phase occurs after an application is approved and is initiated by the biosimilar applicant giving notice to the reference product sponsor of its intent to commercialize the product.

113. § 262(k)(6)(B).

114. § 262(k)(6)(C)(i).

115. § 262(k)(6)(C)(ii).

commercialization, the BPCIA sets a limit on how long it will withhold the licensing of a second interchangeable. This prevents a situation in which the first interchangeable applicant approved fails to market the interchangeable within a reasonable period of time, e.g., due to an agreement with the reference product sponsor under which they conspire to maintain high prices by keeping additional interchangeables off of the market.

### C. *Litigation Under the BPCIA (The “Patent Dance”)*

Some of the most complex portions of the BPCIA are concerned with the way in which patent disputes arising between proprietary drug sponsors and biosimilar applicants should be handled. The legislation sets forth a series of convoluted interactions that have often been referred to in the literature as the “patent dance,”<sup>116</sup> which progresses in two distinct phases as described below.<sup>117</sup>

#### 1. Phase 1: Negotiation and Early Litigation

The first phase is initiated by the FDA’s acceptance of an application for a biosimilar license and is designed to encourage parties to negotiate.<sup>118</sup> Under current law, this phase is optional.<sup>119</sup> If the biosimilar applicant chooses to enter into phase 1, it must provide the reference product sponsor with a copy of its application and disclose the process that will be used to manufacture the product no later than 20 days after acceptance of the application by the FDA.<sup>120</sup> The reference product sponsor then has 60 days to provide the applicant with a list of patents that could reasonably be used in an infringement action and indicate which patents, if any, it would be willing to license.<sup>121</sup>

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116. Jon Tanaka, “*Shall We Dance? Interpreting the BPCIA’s Patent Provisions*,” 31 BERKELEY TECH. L.J. 659, 659 (2016).

117. See *Amgen Inc. v. Sandoz Inc.*, 794 F.3d at 1363 (Newman, J., dissenting).

118. The steps in the first and second stages of this process are summarized in *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052, 1055-58 (Fed. Cir. 2016).

119. *Amgen Inc. v. Sandoz Inc.*, 794 F.3d at 1356-57. However, this may change. The U.S. Supreme Court granted a petition for a writ of certiorari for this case on January 13, 2017. See *Amgen Inc. v. Sandoz Inc.*, SCOTUSBLOG (last visited June 4, 2017), [http://bit.do/SCOTUSBlog\\_AmgenvSandoz](http://bit.do/SCOTUSBlog_AmgenvSandoz).

120. 42 U.S.C. § 262(l)(2)(A). If the applicant does not comply with these requirements, then the submission of its application is deemed to constitute an act of infringement with respect to any patent that could have been listed. 35 U.S.C. § 271(e)(2)(C).

121. 42 U.S.C. § 262(l)(3)(A). The reference product sponsor may later supplement the list with newly-issued or licensed patents that it reasonably believes might be infringed by the marketing of the proposed biosimilar. § 262(l)(3)(C).

Once the applicant receives the patent list from the reference product sponsor, the applicant has 60 days to provide a reply in which it must explain why the proposed product would not infringe the claims in each patent, why the claims are not valid, or why the claims are unenforceable.<sup>122</sup> It can also, optionally, list any additional patents that it believes could potentially be asserted in an infringement action due to the marketing of the proposed product.<sup>123</sup> As an alternative, the applicant may provide the reference product sponsor with a statement that it does not intend to begin commercial marketing of the biological product before the date that a listed patent expires.<sup>124</sup>

In the next step, the reference product sponsor has 60 days to reply with a statement refuting the arguments of the applicant and explaining why the patents would, in fact, be infringed.<sup>125</sup> Once this is received, the parties then will have a period of 15 days to try to come to an agreement on which patents on the lists should be the subject of an infringement action.<sup>126</sup> If they reach an agreement, then the reference product sponsor has a period of 30 days to file suit.<sup>127</sup>

If instead, the parties cannot come to an agreement within the 15 day negotiation period, they then exchange lists of patents a final time, but before doing so, the biosimilar applicant must inform the reference product sponsor of the number of patents that it, *i.e.*, the biosimilar applicant, intends to list.<sup>128</sup> The number of patents that the reference product sponsor lists can be no greater than the number listed by the biosimilar applicant except that, if the applicant chooses not to list any patents, the reference product sponsor can still list one.<sup>129</sup>

Once this exchange is completed, the reference product sponsor has 30 days to bring a suit for infringement but can only do so with respect to a patent on one of the lists. Because of this, the reference product sponsor may have patents potentially infringed by the marketing of the proposed biosimilar, but which cannot be enforced during the first phase of the process.<sup>130</sup>

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122. § 262(l)(3)(B). The newly added patents may be enforced in phase 2 of the process but not in phase 1.

123. *Id.*

124. *Id.*

125. § 262(l)(3)(C).

126. § 262(l)(4)(A).

127. § 262(l)(6)(A). In this regard, the BPCA made it an act of infringement to submit an application for a biosimilar that is covered by a patent and which appears on the negotiated list. This is codified in 35 U.S.C. § 271(e)(2)(C).

128. 42 U.S.C. § 262(l)(5)(A).

129. § 262(l)(5)(B)(ii).

130. *See Amgen Inc. v. Apotex Inc.*, 827 F.3d at 1056 (“But the Biologics Act—having provided for a narrowing of the scope of the [§ 262(l)(6)] litigation, including by allowing the

## 2. Phase 2: Pre-Commercialization Litigation

The second phase of the patent dance begins after the FDA approves a biosimilar for marketing and is much simpler than the first.<sup>131</sup> It is triggered by the biosimilar applicant notifying the reference product sponsor of the approved license, which must occur at least 180 days before the first date of commercial marketing.<sup>132</sup> This notification requirement is mandatory regardless of whether a biosimilar applicant has chosen to exchange information under the first phase of the patent dance or not.<sup>133</sup> Once the reference product sponsor has received notice, it has until the time of commercialization to request a preliminary injunction based on any patent included in the original lists of patents exchanged in phase 1, but not litigated, or with respect to any subsequently issued or licensed patent which had been provided to the biosimilar applicant within 30 days of issuance or licensing.<sup>134</sup>

## 3. Limitations on Relief

There is no legal requirement that a patent owner bring an infringement action against a biosimilar applicant under the provisions of the BPCIA. A reference drug sponsor that does not exchange patent lists under phase 1 of the patent dance, that omits relevant patents from the lists exchanged in phase 1, or that does not bring an action within the time limits required in 42 U.S.C. § 262(l) can still file an action under a different section of 35 U.S.C. § 271. However, under these circumstances, the only remedy available will generally be a reasonable royalty.<sup>135</sup> In contrast, a sponsor that works within the framework of the BPCIA and fully complies with its requirements may be able to recover damages and obtain an injunction.<sup>136</sup>

## IV. THE RELATIONSHIP OF HATCH-WAXMAN TO THE BPCIA

In the early 1900s Congress established two primary frameworks for regulating drugs, the Biologics Act of 1902 (currently part of the Public Health Service Act (“PHS”)) and the Pure Food and Drug Act

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applicant to exclude potentially meritorious patents from that litigation—provides, in [§ 262(l)(8)], for a second stage of patent litigation.”).

131. See *Amgen Inc. v. Sandoz Inc.*, 794 F.3d at 1363 (Newman, J., dissenting).

132. 42 U.S.C. § 262(l)(8)(A).

133. *Amgen Inc. v. Apotex Inc.*, 827 F.3d at 1056.

134. § 262(l)(7)-(8). See also Tanaka, *supra* note 116, at 664. It appears that patents not falling into one of these two groups cannot be enforced by the reference product owner under 42 U.S.C. § 262(l).

135. 35 U.S.C. § 271(e)(6).

136. *Id.*

of 1906 (currently the Federal Food Drug and Cosmetic Act (“FDCA”)).<sup>137</sup> Although these legislative lines of these Acts are distinct, there has historically been a good deal of overlap and confusion regarding their authority.<sup>138</sup> For largely arbitrary reasons, there are some biologics, e.g., insulin and human growth hormone, that are regulated under the FDCA<sup>139</sup> and biosimilars that have been approved under Section 505(b)(2).<sup>140</sup> In addition, provisions that are enacted in connection with one Act sometimes extend to products regulated by another.<sup>141</sup>

The overlap and confusion between the authority of the FDCA and PHS with regard to biologics should be substantially reduced in the future. Section 7002(b) of the BPCIA defines the term “biological product” as follows:

The term “biological product” means 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.<sup>142</sup>

Significantly the above definition includes the phrase, “protein (except any chemically synthesized polypeptide).” Thus, the BPCIA encompasses recombinant and natural proteins that had been previously categorized as falling under the FDCA.<sup>143</sup> After March of 2020, all biologics, including these proteins, will be marketed through a biologic licensing application and, thereafter, the BPCIA pathway will be the sole one used for follow-on biologic products.<sup>144</sup>

## V. THE IMPORTANCE OF METHODS OF PRODUCTION

Because of their size and complexity, biologics and biosimilars require a level of testing that is substantially greater than that needed

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137. JOHNSON, *supra* note 23, at 5.

138. This is discussed in considerable detail in Carver et al., *supra* note 22, at 682-88.

139. *Id.* at 684.

140. *Id.* at 685-86.

141. *See, e.g.*, 35 U.S.C. §§ 156, 271(e)(2). *See also* SCHAFF & THOMAS, *supra* note 100, at 4-5.

142. 42 U.S.C. § 262(i)(1).

143. Carver et al., *supra* note 22, at 807.

144. *Id.*; Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(e), 124 Stat. 119, 817 (2010).

for a small molecule drug or generic in order to be approved.<sup>145</sup> For the same reasons, biologics and biosimilars are more expensive to produce once they are on the market.<sup>146</sup> Since manufacturers must recover the costs incurred in obtaining approval and the ongoing costs of making the products that they market, it follows that an effective plan for reducing the price of biologics must include a strategy for improving methods by which these drugs are made and tested.

#### VI. FINDING THE RIGHT MIX OF INCENTIVES

Recent analysis suggests that, relative to generics, biosimilars may have little impact on the cost of prescription medications in the U.S.<sup>147</sup> After six months on the market, the biosimilar Zarxio was priced only 15% lower than its reference product and had been able to capture only about 10% of sales.<sup>148</sup> By way of comparison, at six months, a generic would be expected to be priced more than 40% lower than its reference product and to have captured about 75% of sales.<sup>149</sup>

Part of the reason why biosimilars may not be as effective at reducing drug prices as generics may be that the incentives provided under the BPCIA do not adequately take into account the differences between these drugs and generics.<sup>150</sup> A biosimilar will essentially never be an exact duplicate of its reference drug and may occupy a market position between being a lower cost replacement and a product offering other characteristics.<sup>151</sup> In addition, the unpredictability inherent in biological systems means that companies developing biosimilars face a much greater risk of failing to produce a product that can compete effectively in the marketplace. Finally, methods of manufacturing biosimilars are of crucial importance in determining the extent to which

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145. Price & Rai, *supra* note 91, at 1032; Tanaka, *supra* note 116, at 661-62. Unlike small, chemically-synthesized drugs, the method by which a biologic is made must be approved by the FDA. 21 C.F.R. § 601.20(c) (2017).

146. Erwin A. Blackstone & Joseph P. Fuhr, Jr., *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS: BUS. 469, 469-71 (2013); Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 MANAGERIAL & DECISION ECON. 439, 439-40 (2007).

147. Paul E. Greenberg et al., *The Biosimilar Revolution Is Just Beginning in the U.S.*, ANALYSIS GROUP: HEALTH CARE BULL., (Fall 2016/Winter 2017), [http://bit.do/AnalysisGroup\\_BiosimilarRevolution](http://bit.do/AnalysisGroup_BiosimilarRevolution).

148. *Id.*

149. *Id.*

150. For a discussion of barriers to market entry for biosimilars, see Blackstone & Fuhr, *supra* note 146, at 469-78.

151. Henry Grabowski et al., *Pharmaceutical Patent Challenges: Company Strategies and Litigation Outcomes*, 3 AM. J. HEALTH ECON. 33 (2017); Henry Grabowski et al., *Recent Trends in Brand-Name and Generic Drug Competition*, 17 J. MED. ECON. 207 (2014) [hereinafter Grabowski et al., *Recent Trends*].

these drugs can be marketed at lower prices than their reference products.

The sections below describe several possible modifications to the present system that are envisioned as being used together but that, with some revision, could be used separately. The overall objectives are to: (a) promote the marketing of drug products that compete for customers both vertically (*i.e.*, based primarily on price) as well as horizontally (*i.e.*, based primarily on different clinical characteristics); (b) allow both new drug applicants and biosimilar applicants to benefit from innovations that they make, including innovations related to manufacturing; and (c) minimize the use of litigation as a tool for resolving differences.<sup>152</sup> The modifications suggested are designed to illustrate approaches that might be taken. They are not intended to be complete or comprehensive.<sup>153</sup>

#### A. *Expanding the Use of the Purple Book*

Although not required by the BPCIA, the FDA began publishing the “Purple Book” in 2014 in which it lists all licensed biologics and biosimilars.<sup>154</sup> The name suggests that this is the biologics counterpart of the Orange Book that was established by the Hatch-Waxman Act for drugs approved under the FDCA. However, this is not the case. The Purple Book currently plays no role in patent litigation and does not even list patents covering a licensed product.<sup>155</sup>

This would need to change in order to meet the objectives discussed herein. Patents in effect at the time of approval of a biologic or biosimilar would need to be listed by the drug sponsor. These patents could be used to provide a basis for infringement actions in a way similar to Orange Book patents. Unlike the Orange Book,<sup>156</sup> however, the Purple Book should include not only patents claiming compositions and methods of use but also patents claiming methods of manufacture.

Biosimilar manufacturers should also have an opportunity to list patents and use them in a similar manner to proprietary companies. For

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152. See generally JOHN R. THOMAS, CONG. RESEARCH SERV., R41483, FOLLOW-ON BIOLOGICS: THE LAW AND INTELLECTUAL PROPERTY ISSUES, (Jan. 15, 2014) (the Summary section discusses the objectives of the BPCIA); Blackstone & Fuhr, Jr., *supra* note 146, at 470-71 (discussing the economics of the BPCIA).

153. But see Ude Lu, Note, *Biologics Price Competition and Innovation Act: Striking a Delicate Balance Between Innovation and Accessibility*, 15 MINN. J.L. SCI. & TECH. 613, 613-51 (2014).

154. Kurt R. Karst, *The “Purple Book” Makes Its Debut!*, FDA L. BLOG (Sept. 9, 2014), [http://bit.do/FDALawBlog\\_ThePurpleBook](http://bit.do/FDALawBlog_ThePurpleBook).

155. Mari Serebrov, *Purple Will be the New Orange for Biosimilar Makers*, BIO WORLD (Apr. 14, 2015), [http://bit.do/BioWorld\\_Purple-will-be-New-Orange](http://bit.do/BioWorld_Purple-will-be-New-Orange).

156. 21 U.S.C. § 355(b)(1).

example, if the biosimilar producer patented a new method for producing a reference product, it could list the patent in the Purple Book and then use it as a basis for exclusivity both against the owner of the reference product and against other biosimilar applicants.

*B. Using Total and Partial Exclusivity Periods*

A biologic producer is currently given 12 years of exclusivity from the time that a drug is approved, during which the FDA will not license a biosimilar.<sup>157</sup> Interestingly, in a study of the top-selling 437 drugs in the U.S., the study found that total market exclusivity, *i.e.*, exclusivity due both to patents and FDA regulations from the time of FDA approval of a pioneer drug to the availability of the first generic, is about 12.4 years.<sup>158</sup> Thus, if FDA-based market exclusivity were to be extended much beyond this, the importance of patents in maintaining exclusivity would be greatly diminished and litigation challenges to patents should decrease accordingly.<sup>159</sup> A longer term would also have the effect of giving drug makers an extended period to recover production costs and potentially encourage them to reduce prices somewhat. However, extending exclusivity also means that the benefits of biosimilar entry on price reduction and innovation would be lost.

One way to balance these factors is to divide an approved product's exclusivity term into a relatively short period of total exclusivity, *e.g.*, seven years, and a much longer period of partial exclusivity, *e.g.*, an additional 15 years. During the initial period, the FDA would not approve a biosimilar application and during the latter period of partial exclusivity, the reference product owner would receive royalty payments from biosimilar producers.

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157. 42 U.S.C. § 262(k)(7)(A).

158. Bo Wang et al., *Variations in Time of Market Exclusivity Among Top-Selling Prescription Drugs in the United States*, 175 JAMA INTERNAL MED. 635, 635 (Apr. 2015) (For the purposes of the study, market exclusivity included regulatory exclusivity periods, the life left on the original patent covering the drug, secondary patents covering peripheral aspects of drugs such as metabolites or alternative formulations and other factors determining generic market entry. The authors report a median market exclusivity of 12.5 years.). An earlier study had reported an average market exclusivity of between 12.4 and 13.7 years. Henry G. Grabowski et al., *Evolving Brand-Name And Generic Drug Competition May Warrant A Revision Of The Hatch-Waxman Act*, 30 HEALTH AFF. 2157, 2160 (2011).

159. Regulatory exclusivity, being based solely on the FDA's evaluation of clinical data (as opposed to a myriad of factors affecting the validity of patents) is much less susceptible to court challenge.

*C. Promoting Innovation and Competition*

From the perspective of proprietary drug manufacturers, the main problem with the exclusivity provided by the FDA is that it is of very narrow scope.<sup>160</sup> It is confined to a drug with specific clinical characteristics used in the treatment of a specific condition.<sup>161</sup> This protects the manufacturer from the untimely entry of biosimilars on to the market but does not stop the entry of closely-related products that compete as an alternative.<sup>162</sup> This problem may be offset through the use of patents, which have the potential of providing broader protection. However, patents must be enforced by litigation and are highly susceptible to invalidation in post-grant review proceedings at the U.S. Patent and Trademark Office.<sup>163</sup> What is desired is a system that allows a manufacturer to recover for the innovations it has made (not just for bringing a product to market), that discourages litigation, and that provides a reasonable assurance of recovery of drug development and marketing costs.

One way to address this would be to fix the term of exclusivity based on FDA provisions but determine the scope of exclusivity based on patents covering the licensed product. Specifically, a pioneer drug producer might be granted exclusivity based on FDA approval and this would cover, as it does now, the approved drug product and use. Beyond this, however, the obligation to compensate the drug sponsor would be determined by the scope of any patents identified in the FDA Purple Book as covering the product, the use of the product, and the method of making the product.

Continuing the example suggested above, there might be a period of seven years where a proprietary manufacturer is given total exclusivity based on FDA approval alone and 15 years of partial exclusivity during which it has FDA exclusivity and patent exclusivity. FDA exclusivity would apply to products granted as biosimilars and would not depend at all on patent protection. Therefore, a biosimilar sponsor would be required to pay the statutory royalty unless it had some basis for alleging that the reference product should not have been listed by the FDA. The scope, validity, and enforceability of patents would be irrelevant.

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160. Vincent J. Roth, *Will FDA Data Exclusivity Make Biologic Patents Passé?*, 29 SANTA CLARA HIGH TECH. L.J. 249, 279-80 (2013).

161. *Id.*

162. *Id.*

163. Joanna Shepherd, *Disrupting the Balance: the Conflict Between Hatch-Waxman and Inter Partes Review*, 6 N.Y.U. J. INTELL. PROP. & ENT. L. 14, 28-32 (2016); Peggy P. Ni, *Rethinking Finality in the PTAB Age*, 31 BERKELEY TECH. L.J. 557, 562-69 (2016).

Patent exclusivity would apply to new biologics that do not qualify as biosimilars but are so closely related to a listed drug that they fall within the scope of one or more patents listed in the Purple Book. In one possible scenario, notifications of all approvals would be published by the FDA and would be followed by a period of delay, e.g., 90 days, before the approved product could be marketed. During this time, any party with a patent listed in the Purple Book could seek an injunction, if their period of total exclusivity had not yet expired, or demand the payment of a statutorily set royalty, if their product was in the period of partial exclusivity and the newly-approved product infringed one or more claims in a listed patent. If the party with the newly-approved product agreed to make payments, it would be immune from litigation by the patent owner. If instead it refused, it would be subject to an action for infringement.<sup>164</sup>

This scenario has a number of benefits that do not exist under the current BPCIA framework. When combined with the provisions discussed below, it provides a path for infringing drug products to enter the market that would not otherwise be possible. Specifically, the sponsor of the newly-approved product could avoid an infringement action by respecting the patentee's period of total exclusivity and agreeing to pay royalties for the period of partial exclusivity. The patent owner, gets a guarantee of seven years of complete exclusivity and 15 years of royalty payments for biosimilars which cannot be lost due to patents being invalidated. In addition, the patent owner gets an opportunity to be compensated for other innovations that it has made and patented.

Provisions designed to discourage litigation could also be incorporated into the system. For example, if the owner of a newly-approved application refused to pay royalties and subsequently lost in an action for infringement, it might be subject to an injunction keeping its product off of the market until the period of exclusivity for the patent owner has completely expired. Similarly, if the proprietary manufacturer brought an action and lost, it might be required to forfeit any right to receive royalties (either FDA-based or patent-based) from the applicant and, in cases where the litigation was clearly unwarranted, be required to pay some or all of the applicant's litigation costs.

If patent claims were found to be invalid in reexamination, *inter partes* review or litigation in actions that do not arise from the events related to drug approval, the patents would be removed from the Purple Book's list.

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164. The parties could, of course, agree to resolve issues in some other way.

#### *D. Expanding Patent Term Restoration*

To better suit them for the roles discussed above, all patents listed in the Purple Book, as covering some aspect of a biologic or biosimilar, would need to receive an automatic extension of term to be coextensive with the exclusivity granted as a result of FDA approval. The scope of patent protection for the extended term would be limited to enforcement in actions arising from the filing of an application for a new biologic or biosimilar or the marketing of a biologic or biosimilar. Unlike the current requirements for term extension, more than one patent would need to be subject to extension for a given period of exclusivity and the extension would apply to all existing claims.

#### *E. Expanding the Safe Harbor*

The exemption from infringement that the Hatch-Waxman Act provides to companies making, using, or offering to sell patented subject matter for the purpose of fulfilling federal regulatory requirements already extends to biologics licensed under the Public Health Service Act.<sup>165</sup> This safe harbor from infringement was originally designed to allow generic manufacturers to make copies of reference drugs and conduct tests necessary to get approval of an ANDA.<sup>166</sup> However, the statute has been broadly interpreted by courts to allow for many activities, including testing for the purpose of new product development.<sup>167</sup>

Because true copies of reference products are usually not possible when one is dealing with biologics,<sup>168</sup> the safe harbor takes on an additional role for companies making these types of drugs. It provides them with an opportunity to explore how changes in production methods result in products with different clinical characteristics and an opportunity to collect data that can either be used to file an application for a biosimilar or, in cases where the products are found to have benefits that the reference product does not, to file an application for an entirely new biologic.<sup>169</sup> Thus, testing may result in products that compete with the reference product primarily on the basis of price as well as products that compete based on their distinct characteristics.

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165. 35 U.S.C. § 271(e)(1).

166. Jessica Chao, *Examining the § 271(e)(1) Safe Harbor of the Hatch-Waxman Act: A Legislative Proposal Granting Mandatory Post-Marketing Exceptions*, 32 *CARDOZO ARTS & ENT.* 651, 659-61 (2014).

167. *Merck KGaA v. Integra Lifesciences I, Ltd.* 545 U.S. 193, 193 (2005); *Momenta Pharm., Inc. v. Teva Pharm. USA Inc.*, 809 F.3d 610, 619 (Fed. Cir. 2015).

168. Roth, *supra* note 160, at 257.

169. *Id.*

In the regulatory scheme proposed above, the safe harbor would be expanded to provide that it shall not be an act of infringement to file an application for a biosimilar license or to market a biosimilar provided that commercial sales do not begin during the first seven years after the reference product was approved and provided that the applicant complies with statutory licensing requirements, including paying the sponsor of the reference product the statutory royalty fee. Similarly, it should not be an act of infringement to file an application for, or market, a new biologic product that is covered by a patent listed in the Purple Book for a pioneer drug, provided that commercial sales do not begin during the first seven years from the approval date of the pioneer drug and provided that the applicant complies with statutory licensing requirements, including paying the sponsor of the pioneer drug the statutory royalty fee.

*F. Promoting Improvements in Methods of Manufacturing Biologics*

What a biologic is depends on the way that it is made, and it is very difficult to predict the effect that changes in methods of production will have on the clinical characteristics of a biological product.<sup>170</sup> Although this means that biosimilar development carries risks that the development of a generic drug does not,<sup>171</sup> it also means that there is an increased chance of discovering products with improved characteristics and for the introduction innovative procedures. In this sense, a company attempting to make a biosimilar is much closer to being in the position of a new drug developer than a company making a generic version of a small molecule drug.

Biosimilar development efforts have the potential of producing three different results: (a) a product with essentially the same clinical characteristics as the reference drug; (b) a product that has different and beneficial characteristics compared to the reference drug; and (c) a product that is either nonfunctional or inferior to the reference product. If, as a result of efforts to make a biosimilar, a company finds a drug with substantially improved characteristics compared to the reference product, FDA regulations provide an incentive for the filing of an application for a new biologic license.<sup>172</sup>

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170. Price & Rai, *supra* note 91, at 1033-36.

171. Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 523 (2011); Tanaka, *supra* note 116, at 661-62.

172. Costs associated with this are discussed in Jon Entine, *FDA Balances Costs, Patient Safety in the Biologics and Personalized Medicine Revolution*, FORBES (July 23, 2012), [http://bit.do/Forbes\\_FDA-Balances-Cost](http://bit.do/Forbes_FDA-Balances-Cost).

Unfortunately, there is relatively little incentive given to a biosimilar developer for finding a method of producing a biosimilar that is essentially the same as its reference product but where the cost of production is much lower.<sup>173</sup> Currently, a follow-on developer gets no exclusivity unless they conduct further tests and establish interchangeability. However, it is not generally clear whether the benefit that this provides justifies the additional testing and expense.<sup>174</sup> This may be remedied by granting a biosimilar producer exclusivity similar to that provided to a new product. Specifically, the sponsor would get a short period of complete exclusivity for their method of production (e.g., one year) and a period of partial exclusivity matching the remaining term of the reference product. During the latter, the biosimilar producer would receive a statutorily-fixed royalty from other companies making the reference product by the method developed. As with a new biologic, the biosimilar maker could expand the scope of their exclusivity by listing patents.

### *G. Litigation*

Although one of the objectives of the BPCIA may have been to avoid the need for litigation, it does not appear to be successful in this regard, at least in part due to the convoluted nature of the patent dance and inconsistencies in the text of the statute.<sup>175</sup> Likely the best way to improve this is to eliminate the patent dance and to rewrite the statute entirely. Litigation could then be performed in accordance with the various suggestions made above.

If an application for a biologic was judged by the applicant to fall within the scope of the claims of a product listed in the Purple Book, or if the applicant simply wanted to avoid potential litigation, a certification statement could be included as part of the licensing application identifying the relevant product and stating that the applicant would not market the drug until the initial period of total exclusivity had elapsed and thereafter would pay a statutory royalty for the remaining term of exclusivity. In cases where such statement was made, the applicant would not be subject to an infringement action.

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173. See 42 U.S.C. § 262(k)(6)(A).

174. Jill Wechsler, *Does Interchangeability Really Matter for Biosimilars?*, PHARMEXEC.COM (Nov. 3, 2015), [http://bit.do/PharmExec\\_Does-Interchangeability-Really-Matter](http://bit.do/PharmExec_Does-Interchangeability-Really-Matter).

175. Randi Hernandez, *Biosimilars: The Litigation and Patent Challenges to Come*, PHARMEXEC.COM (May 4, 2015), [http://bit.do/PharmExec\\_Litigation-and-Patent-Challenges](http://bit.do/PharmExec_Litigation-and-Patent-Challenges); Courtenay C. Brinckerhoff & Kristel Schorr, *Have the Biosimilar Floodgates been Opened in the United States?*, 14 NATURE REVIEWS: DRUG DISCOVERY 303, 303-04 (2015).

## CONCLUSION

In 1983, prior to the passage of the Hatch-Waxman Act, only about 13% of prescriptions were for generics.<sup>176</sup> Ten years after enactment, the percentage had risen to 36% and, by 2012, to 84%.<sup>177</sup> The BPCIA was modeled on the Hatch-Waxman Act in the hope that it would have a similar effect on the marketing of biosimilars and ultimately lead to a dramatic decrease in the price of biologics. However, factors affecting the market for biosimilars are substantially different from those for generics and there are good reasons to think that the effect will be much smaller.<sup>178</sup>

Part of the reason for the limited prospects for biosimilars regulated under the BPCIA is that the structural complexity and nature of biologics makes it much more expensive to develop and produce these drugs.<sup>179</sup> Unless incentives are present that encourage innovation in general, and particularly innovations in the methods by which these molecules are made, it is difficult to see how biologics will become affordable to the great majority of people that need them.<sup>180</sup> Although the BPCIA, in its present state, does little in this regard, it may be possible to amend its provisions to encourage innovation more effectively. This is something that should not be overlooked by Congress as they consider replacing portions of the ACA.

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176. Garth Boehm et al., *Development of the Generic Drug Industry in the U.S. After the Hatch-Waxman Act of 1984*, 3 ACTA PHARMACEUTICA SINICA B 297, 298 (2013). There is some discrepancy regarding these numbers. For example, Joanna Shepherd puts the pre-1984 number at about 19%. Joanna M. Shepherd, *Biologic Drugs, Biosimilars, and Barriers to Entry*, 25 HEALTH MATRIX 139, 144 (2015).

177. Grabowski et al., *Recent Trends*, *supra* note 151, at 208.

178. Greenberg et al., *supra* note 147; Blackstone & Fuhr, *supra* note 146, at 470-71; Shepherd, *supra* note 176, at 155-60; Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57, 61 (2012).

179. Price & Rai, *supra* note 91, at 1033-36.

180. *Id.* at 1062-63.