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## You Can Dance if You Want To? Initial Interpretations of the BPCIA's Patent Dance with Sandoz and Amgen

Jenny M. Alsup

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# You Can Dance if You Want To? Initial Interpretations of the BPCIA’s Patent Dance with Sandoz and Amgen

by JENNY M. ALSUP\*

Abstract: As patents covering brand-name biologics begin to expire, biosimilar manufacturers are preparing to enter the market. Since its enactment in 2010, many have speculated on how the Biologics Price Competition and Innovation Act will influence competition and innovation, and whether the provisions struck the right balance. Now for the first time, the judiciary is interpreting the so-called “patent dance,” the Act’s information exchange and litigation provisions, in decisions that will impact the biosimilar landscape in the years to come. Two cases involving the biologic manufacturers Sandoz and Amgen illustrate the Act’s susceptibility to different interpretations.

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## I. Introduction

Biologics are medicinal products comprised of complex protein molecules produced using living cells and recombinant DNA technology.<sup>1</sup> They include a wide range of products such as enzymes, vaccines, and gene therapies.<sup>2</sup> Where conventional pharmaceutical drugs are chemically synthesized and relatively predictable in their interactions, biologics are complex macromolecules whose biological activity can vary due to media, temperature, and other interactions.<sup>3</sup>

Biologics were first developed in the 1980s, and the patents covering a growing number of biologics have already expired or are due to expire soon. They were initially considered so specialized that making generic versions was seen as most likely impossible.<sup>4</sup> However, science has advanced, and drug companies have begun to develop close copies.<sup>5</sup> These generic versions are called biosimilars because by definition they are not likely to be identical to the original biologic; they are highly similar, but not the same.<sup>6</sup>

The Biologics Price Competition and Innovation Act of 2009 (BPCIA or Act) regulates the approval of biosimilars.<sup>7</sup> Borrowing from the Hatch-

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1. Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J., 535, 535 (2010).

2. 42 U.S.C. § 262(i)(1) (2010). The BPCIA defines a biologic as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or other 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.”

3. Trevor Woodage, *Blinded by (a Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-On Biologics and Barriers to Their Approval and Commercialization*, 9 STAN. TECH. L. REV. 1, 13 (2012).

4. Sabrina Tavernise, *For First Time, F.D.A. Panel Approves Generic Copy of Costly Biologic Drug*, N.Y. TIMES, Jan. 7, 2015. Indeed, even if the structure of a biosimilar were completely replicated, additional post-translational modifications may result in minute and undetectable differences that can cause adverse results in patients.

5. *Id.*

6. Woodage, *supra* note 3, at 9.

7. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001-03, 124 Stat. 119, 804-21 (2010) (enacting Biologics Price Competition and Innovation Act of 2009, codified principally at 42 U.S.C. § 262).

Waxman Act,<sup>8</sup> the BPCIA lays out an abbreviated pathway to FDA approval and market entry. Since its passage, scholars have speculated on the BPCIA's impact on accessibility,<sup>9</sup> feasibility,<sup>10</sup> and competition.<sup>11</sup> The first cases interpreting the BPCIA came out in late 2014 and early 2015, and the first biosimilar was approved by the FDA in March 2015 and eventually entered the market in September 2015.

Both of the first cases involve the parties Sandoz and Amgen. Sandoz is the generic pharmaceuticals division of Swiss drug giant Novartis. Sandoz strategically develops and releases products following the loss of the pioneer maker's patent protection.<sup>12</sup> Building on its success in generics, Sandoz was the first company to develop and market biosimilars.<sup>13</sup> Amgen is a pioneer drug maker based in California and is counted among the early innovators of biotechnology.<sup>14</sup> In both cases, Amgen's biologic products serve as the "reference product" that Sandoz's biosimilar seeks to imitate, making Amgen what is known as the reference product sponsor (RPS).

The first case, *Sandoz v. Amgen*,<sup>15</sup> presented a question of whether a biosimilar maker<sup>16</sup> that had not yet filed an application with the FDA could maintain a declaratory judgment action to establish its rights as to newly announced patents. The Northern District of California and the Federal

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8. The Drug Price Competition and Patent Term Restoration Act, also known as the Hatch-Waxman Act, Pub. L. No. 84-417, 98 Stat. 1584 (1984).

9. See, e.g., Jason Kanter & Robin Feldman, *Understanding and Incentivizing Biosimilars*, 64 HASTINGS L.J. 57 (2012); however, Express Scripts, the nation's largest manager of prescription drug benefits, estimates that the introduction of Sandoz's approved biosimilar could save \$5.7 billion in drug costs over the next ten years. EXPRESS SCRIPTS INFOGRAPHIC, available at <http://lab.express-scripts.com/insights/drug-options/infographic-two-biosimilars-to-save-227-billion>.

10. See, e.g., Sara Margolis, Note, *Destined for Failure? An Analysis of the Biologics Price Competition and Innovation Act of 2009*, 2013 COLUM. BUS. L. REV. 209 (2013).

11. See, e.g., Matthew J. Seamon, *Antitrust and the Biopharmaceutical Industry: Lessons from Hatch-Waxman and an Early Evaluation of the Biologics Price Competition and Innovation Act of 2009*, 34 NOVA L. REV. 269 (2010).

12. *Sandoz Biopharmaceutical*, <http://www.sandoz-biosimilars.com> (last visited April 2, 2015).

13. *Id.* Sandoz's biosimilar filgrastim product was approved by the FDA on Mar. 16, 2015.

14. *Amgen Fact Sheet*, available at [http://www.amgen.com/pdfs/misc/Fact\\_Sheet\\_Amgen.pdf](http://www.amgen.com/pdfs/misc/Fact_Sheet_Amgen.pdf).

15. *Sandoz, Inc. v. Amgen, Inc.*, 773 F.3d 1274 (Fed. Cir. 2014).

16. This Note uses the term "biosimilar" to refer to generic or follow-on versions of biologic products, and "biosimilar maker" or "biosimilar manufacturer" to refer to the company that develops the biologic product. The Author acknowledges that these terms may not be entirely accurate in cases where the biologic product being developed proves through trials not to be biosimilar to the branded product, or is in fact a biobetter (a new product designed to mimic an existing biological product, that may completely forgo the biosimilar pathway), or where the company has not yet begun making or manufacturing the product, in the ordinary sense of those terms.

Circuit both ruled for Amgen, finding that under the facts of the case, a Phase III clinical trial did not create a justiciable case or controversy. The Federal Circuit did not address the determination made by the district court that the BPCIA precludes a pre-application declaratory judgment action.

The second case, *Amgen v. Sandoz*,<sup>17</sup> asked whether the so-called “patent dance,” the disclosure and negotiation procedures outlined in the BPCIA, was mandatory and the only way for a biosimilar maker, once approved by the FDA, to enter the market and compete with an innovator biologic. The case also required interpretation of the Act’s notice requirements, which impact the length of the innovator’s period of exclusivity. The Northern District of California ruled in favor of Sandoz, finding that the patent dance is optional and that a biosimilar maker may give notice of commercial marketing before gaining FDA approval. The Federal Circuit followed with a fractured decision that leaves neither party completely satisfied, finding that the patent dance is voluntary, but notice of commercial marketing can only be given after FDA approval.

This Note provides an overview of the current state for biosimilar makers getting in the biologics market and analyzes the first judicial interpretations of the BPCIA, as well as the practical consequences of the decisions reached in the two cases. Part II provides background on the BPCIA. Part III describes the facts leading up to *Sandoz v. Amgen* and the decisions reached in the district court and Federal Circuit, and Part IV does the same for *Amgen v. Sandoz*. Part V follows by describing the statutory interpretations offered by the parties and adopted by the courts. The Note concludes in Part VI.

## II. Biologics Price Competition and Innovation Act

### A. Legislative Background

On March 23, 2010, President Obama signed the BPCIA into law as part of the Affordable Care Act (ACA).<sup>18</sup> The BPCIA creates a statutory pathway for biosimilar biological products and lays out a scheme for litigation of related patent issues. By facilitating market entry of generic

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17. *Amgen v. Sandoz*, No. 14-04741, 2015 U.S. Dist. WL 1264756 (N.D. Cal. Mar. 19, 2015).

18. Patient Protection and Affordable Care Act, Pub. L. No. 111-148 §§ 7001-03, 124 Stat. 119, 804-21 (2010). The federal government has been involved in the regulation of biologics since the 1800s (then as vaccines), but the governing statutes were enacted at separate times and were largely administered by separate agencies. For a thorough survey of legislation leading up to the BPCIA, see Krista Hessler Carver et al., *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010).

versions of biologic products, the BPCIA aims to decrease costs and improve access to biologics, and to incentivize innovation.<sup>19</sup>

The BPCIA amended three laws: Section 351 of the Public Health Service Act,<sup>20</sup> the Patent Act,<sup>21</sup> and the Declaratory Judgment Act.<sup>22</sup> The Public Health Service Act (PHSA) governs the approval and regulation of new biologics. The BPCIA amended the PHSA to include subsection (k), which defines the pathway for licensure of biological products as biosimilar or interchangeable, and subsection (l), which lays out the information exchange provisions relating to patent litigation. Section 271 of the Patent Act defines infringement activities. The BPCIA amended § 271 to include subsection (e)(2)(C), which creates an act of infringement upon the submission of an application to the FDA seeking approval of a biosimilar.<sup>23</sup> This act of infringement is considered artificial and like its counterpart under the Hatch-Waxman Act, it enables an earlier adjudication of patent disputes and creates a justiciable case or controversy.<sup>24</sup> The BPCIA amended 28 U.S.C. § 2201 to include a reference to relevant sections of the PHSA on limitations to declaratory judgment actions brought with respect to drug patents.<sup>25</sup>

The BPCIA is a complex statute nestled into the colossal ACA, and the judiciary first interpreted its reach and application nearly four years after its enactment. The two provisions at the heart of these first cases involve the approval pathway under subsection (k), and the information exchange procedures under subsection (l).

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19. Ude Lu, *Biologics Price Competition and Innovation Act: Striking a Delicate Balance Between Innovation and Accessibility*, 15 MINN. J.L. SCI. & TECH. 613, 613–14 (2014).

20. 42 U.S.C. § 262.

21. 35 U.S.C. § 271.

22. 28 U.S.C. § 2201.

23. 35 U.S.C. § 271(e)(2)(C)(i) (“It shall be an act of infringement [of a patent identified in the information exchange procedures under 42 U.S.C. § 262(l)] to submit . . . an application seeking approval of a biological product.”).

24. Carl Minniti, *Sandoz v. Amgen: Why the Biologics Price Competition and Innovation Act of 2009 Allows Biosimilar Makers to Pursue Pre-Application Declaratory Judgment Actions and Will Enhance Competition* (forthcoming), available at <http://ssrn.com/abstract=2519393>. See also the Hatch-Waxman Act, *supra* note 8 which regulates the abbreviated approval of conventional pharmaceuticals. An application for a new generic drug filed under Paragraph iv is an act of infringement. 35 U.S.C. § 271(e)(2)(A).

25. 28 U.S.C. § 2201(b) (“For limitations on actions brought with respect to drug patents see Section 505 or 512 of the Federal Food, Drug, and Cosmetic Act, or Section 351 of the Public Health Service Act.”).

**B. 42 U.S.C. § 262(k)**

Subsection (k) includes provisions on application content and exclusivity periods for the first biosimilar and for the reference product.<sup>26</sup> Four years after approval of a biological product licensed under § 262(a), any person may submit a biosimilar application under § 262(k), using that biological product as its reference product.<sup>27</sup> Each application must show that: first, the biological product that is the subject of the application is biosimilar to a reference product; second, the biosimilar and the reference product use the same mechanism of action; third, the reference product was previously licensed for the use proposed by the biosimilar; fourth, the biosimilar has the same route of administration, dosage form, and strength as the reference product; and lastly the originating facility meets specific standards.<sup>28</sup>

Subsection (k) provides a kind of exclusivity for the first biosimilar to be found interchangeable with a particular reference product.<sup>29</sup> A biological product is interchangeable with a reference product if the FDA determines that the application shows that the product is biosimilar and can be expected to produce the same clinical result as the reference product in any given patient, and when the two products can be used interchangeably without any risk in safety or diminished efficacy.<sup>30</sup> During this period, no other product may be deemed interchangeable to that reference product. This biosimilar gets marketing exclusivity of at least one year after the biosimilar applicant first commercially markets the biosimilar; eighteen months after approval of their biosimilar application; or several other periods based on patent litigation activity surrounding the biosimilar applicant.<sup>31</sup>

The RPS is entitled to a period of market exclusivity independent of its patent term, as well as data exclusivity. The FDA may not accept a biosimilar application until four years after the reference product was first licensed, and the FDA may not approve a biosimilar application until twelve years after the

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26. 42 U.S.C. § 262(k)(2), (6)-(7).

27. 42 U.S.C. § 262(k)(7)(B).

28. 42 U.S.C. § 262(k)(2)(A)(i).

29. 42 U.S.C. § 262(k)(6).

30. 42 U.S.C. § 262(k)(4). Once a biosimilar is found to be interchangeable, it can be substituted for the innovator biologic by a pharmacist and does not require a prescribing doctor's intervention. Some have issues with this; *see, e.g.*, Stacey Worthy & John Kozak, *Follow-On Biologics: Protecting Consumers Through State Pharmacy Law in Light of FDA Actions*, 17 QUINNIPIAC HEALTH L.J. 207 (2014).

31. 42 U.S.C. § 262(k)(6).

reference product was first licensed, whether or not the reference product is covered by a patent, and whether or not that patent has expired.<sup>32</sup>

### C. 42 U.S.C. § 262(l)

Subsection (l) provides what has been called the “patent dance,”<sup>33</sup> a back-and-forth process for exchange of information prior to patent litigation.<sup>34</sup> This process involves several steps. First, the biosimilar applicant must provide a copy of its application and information about the manufacturing process to the RPS within twenty days after the FDA notifies the applicant that the application has been accepted for review.<sup>35</sup> There are limitations on who may review the application, along with confidentiality restrictions.<sup>36</sup> Second, within sixty days of receiving the biosimilar application, the RPS must provide the applicant with a list of patents for which it believes could reasonably assert a claim of infringement and indicate which of those patents it would be prepared to license.<sup>37</sup> Third, within another sixty-day period, the biosimilar applicant must provide to the RPS a detailed statement either that it will not market its product before the patent expires or that asserts on a claim-by-claim basis that the patent is invalid, unenforceable, or not infringed.<sup>38</sup> At this point, the biosimilar applicant may also provide its own list of patents as to which it believes the RPS could assert an infringement claim. Fourth, within a further sixty-day period, the RPS must provide a response to the biosimilar applicant’s statement, consisting of a detailed, claim-by-claim statement as to why the patent will be infringed, or is valid and enforceable.<sup>39</sup>

Paragraphs 4, 5, and 6 of subsection (l) establish a two-phase litigation process that represents a radical departure from traditional patent litigation.<sup>40</sup> After receiving the RPS’s response, the biosimilar applicant and the RPS must negotiate a list of patents that should be the subject of an infringement

32. 42 U.S.C. § 262(k)(7).

33. See, e.g., Kurt R. Karst, *The Federal Circuit is Slated to Consider an Appeal of the First BPCIA Biosimilars “Patent Dance” Decision*, FDA LAW BLOG, (Jan. 6, 2014), [www.fdalawblog.net](http://www.fdalawblog.net).

34. 42 U.S.C. § 262(l).

35. 42 U.S.C. § 262(l)(2)(A).

36. 42 U.S.C. § 262(l)(1)(B).

37. 42 U.S.C. § 262(l)(2)(3)(A).

38. 42 U.S.C. § 262(l)(2)(3)(B).

39. 42 U.S.C. § 262(l)(2)(3)(C).

40. Carver et al., *supra* note 18, at 814.



action.<sup>41</sup> If they agree, the RPS must bring an infringement action within thirty days; if they cannot agree, there is a further back-and-forth exchange described in paragraph five, followed by a thirty-day period for the RPS to bring an infringement action.<sup>42</sup>

In the second phase of patent litigation, the biosimilar applicant must provide notice to the RPS at least one hundred and eighty days before commercially marketing its biosimilar product.<sup>43</sup> At that point, the RPS may seek a preliminary injunction on any patent that was identified in the initial lists but did not make it to the immediate litigation phase.<sup>44</sup>

### III. *Sandoz v. Amgen: Etanercept*

#### A. Facts and Background

Amgen markets Enbrel to treat five long-term inflammatory diseases, including rheumatoid arthritis.<sup>45</sup> Enbrel is a biologic based on the protein etanercept, which reduces levels of a substance that contributes to the inflammatory disease process.<sup>46</sup> The FDA first approved Enbrel in 1998, giving it a twelve-year exclusivity period that expired in 2010.<sup>47</sup> Enbrel was protected by U.S. patents that allowed Amgen to enjoy exclusivity over Enbrel since the mid-1990s.<sup>48</sup> These patents are referred to as the '760 and '690 patents. Sandoz began developing its own etanercept product in 2004, planning to release the product for commercial marketing as Amgen's relevant patents expired in 2012 and 2014.<sup>49</sup> For nearly a decade, at substantial effort and expense, Sandoz has created a cell line of comparable attributes to Enbrel, developed a manufacturing process and formulation of the drug, provided virtual molecular and functional identity with Enbrel,

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41. 42 U.S.C. § 262(l)(4).

42. 42 U.S.C. § 262(l)(4)(a)-(b) and (5).

43. 42 U.S.C. § 262 (l)(8)(A).

44. 42 U.S.C. § 262 (l)(8)(B).

45. ENBREL HOMEPAGE, [www.enbrel.com](http://www.enbrel.com) (last visited Apr. 2, 2015).

46. *Id.* Enbrel reduces the levels of tumor necrosis factor (TNF), overproduced by the immune systems of people with inflammatory diseases.

47. 42 U.S.C. § 262(k)(7).

48. Corrected Nonconfidential Brief of Plaintiff-Appellant Sandoz, Inc. at 13, *Sandoz, Inc. v. Amgen, Inc.*, No. 14-1693 (Fed. Cir. filed Mar. 14, 2014) (hereinafter *Sandoz Fed. Cir. Brief*). Amgen's predecessor, Immunex received the license, under 42 U.S.C. § 262(a) and 21 C.F.R. pt. 601, and acquired U.S. patents 5,395,760 and 5,605,690.

49. *Sandoz Fed. Cir. Brief*, *supra* note 48, at 10–11. The '760 and '690 patents were listed on the package insert for Enbrel.

developed a prefilled syringe drug product, and transferred its process to large-scale production for clinical trials.<sup>50</sup> Sandoz has what it considers a final etanercept product that it claims is exactly the same as Amgen's product for all practical purposes.<sup>51</sup> Sandoz's etanercept product is in the late stages of a Phase III trial, conducted outside of the U.S., to test the safety and efficacy of the product in a large population of patients, as compared to Enbrel, and intended to support both U.S. approval and European registration.<sup>52</sup> Sandoz characterizes the Phase III trial as a "mere confirmation that Sandoz's etanercept product is essentially identical to Enbrel,"<sup>53</sup> and expects to file an application seeking FDA approval at its conclusion.<sup>54</sup>

Enbrel is, by all accounts, a blockbuster drug.<sup>55</sup> As the expiration dates for the '760 and '690 patents loomed, Amgen procured an exclusive license from Roche<sup>56</sup> to applications claiming specific proteins and related pharmaceutical compositions that ostensibly cover etanercept.<sup>57</sup> In 2005, Amgen took over the prosecution of these applications, which were filed in 1995 and claimed priority back to 1990 and earlier.<sup>58</sup> Since these applications were unpublished and unavailable to the public, no one, including Sandoz, had reason to suspect they even existed, and much less to

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50. *Id.* at 11.

51. *Id.* at 11–12; Sandoz asserts that it has shown that its product has the "same primary amino acid sequence as Enbrel, the same secondary and tertiary protein structures, and that it is essentially indistinguishable in a wide array of molecular and biological tests . . . [and that] Sandoz's etanercept was bioequivalent to Enbrel in its pharmacokinetics and . . . safety profile."

52. *Id.* at 12–13; In Phase III trials, the drug is studied in a group of approximately 1,000–3,000 people who have the targeted disease. This phase further tests the product's effectiveness, monitors side effects and may compare the product's effects to a standard treatment. See *Inside Clinical Trials: Testing Medical Products in People*, USFDA, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm>.

53. *Id.* at 13 (Emphasis in original).

54. *Id.*

55. In 2012, Enbrel accounted for 25% of Amgen's annual revenues and over \$4 billion in U.S. sales as Amgen's second largest product. See *Amgen's 2014 Revenues Increased 7 Percent To \$20.1 Billion and Adjusted Earnings Per Share (EPS) Increased 14 Percent to \$8.70*, AMGEN NEWS RELEASES (Jan. 27, 2015), <https://www.amgen.com/media/news-releases/2015/01/amgens-2014-revenues-increased-7-percent-to-201-billion-and-adjusted-earnings-per-share-eps-increased-14-percent-to-870/>.

56. Sandoz Fed. Cir. Brief, *supra* note 48, at 14.

57. Sandoz, Inc. v. Amgen, Inc., 773 F.3d 1274, 1276 (2014) ("Amgen has identified [these] two patents as among four patents 'for etanercept.'").

58. Sandoz Fed. Cir. Brief, *supra* note 48, at 14.

anticipate the scope of the subject matter claimed.<sup>59</sup> These patents are referred to as the '182 and the '522 patents.

The first of these patents, the '182, issued in November 2011, and expires in 2028.<sup>60</sup> The other, the '522, issued in April 2012, and expires in 2029.<sup>61</sup> Through media and at industry events in 2012 and 2013, Amgen stated numerous times that it, to paraphrase, had the etanercept market on lock, would not abide competition, and would defend against any infringement; however, Amgen did not make any statements directly to Sandoz and did not threaten to bring an infringement suit.<sup>62</sup> Sandoz brought an action for declaratory judgment in the district court for the Northern District of California in June 2013, seeking a determination of its rights under Amgen's '182 and '522 patents.

### B. District Court

Sandoz sought a declaration that its etanercept product does not infringe any claim of either the '182 patent or the '522 patent, and that these patents are invalid and unenforceable.<sup>63</sup> In response, Amgen and Roche moved to dismiss for lack of subject matter jurisdiction, or in the alternative, for the court to decline to exercise declaratory judgment.<sup>64</sup> Specifically, they argued that the court lacked the statutory authority to entertain a patent dispute involving a biosimilar product until after an application for FDA approval was filed, and that as a factual matter, no case or controversy presently existed. On November 12, 2013, District Judge Maxine Chesney granted the motion to dismiss on two grounds: lack of jurisdiction under the Declaratory Judgment Act, and alternatively, failure to establish a case or controversy.<sup>65</sup>

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59. *Id.* Applications like these are known as submarine patents; through a feature of former term practices, they lurk undisclosed and unsuspected during their long pendency, scope unknown, only to surprise and preempt the field upon publication. The patent term of applications filed before June 8, 1995, was measured from the date of publication. The Uruguay Round Agreements Act changed the date from which the term was measured to the filing date for applications filed on or after June 8, 1995. Though mostly a thing of the past, submarine patents' legacy continues.

60. U.S. Patent 8,063,182, the '182 patent. *Id.* at 14.

61. U.S. Patent 8,163,522, the '522 patent, with expiry over thirty years after Enbrel was first approved. *Id.* at 15.

62. *Id.* at 15–16.; Corrected Nonconfidential Opposition Brief of Defendant-Appellees Amgen Inc. and Hoffmann-La Roche Inc. at 78–79, *Sandoz, Inc. v. Amgen, Inc.*, 773 F.3d 1274 (2014) (No. 14-1693), 2014 WL 2586827 [hereinafter *Amgen Fed. Cir. Brief*].

63. *Sandoz, Inc. v. Amgen, Inc.*, No. C-13-2904 MMC, 2013 WL 6000069, at \*1 (N.D. Cal. Nov. 12, 2013).

64. *Id.*

65. *Id.* at 2–3.

In the short decision, Judge Chesney focused on the fact that Sandoz had yet to file an application with the FDA, and relied on the BPCIA's limitations on declaratory judgment<sup>66</sup> and the timing of exchanges and filings outlined in the Act itself.<sup>67</sup> This brief analysis, the judiciary's first interpretation of the BPCIA, found a jurisdictional bar to all declaratory judgment actions where the biosimilar maker has not yet filed an application with the FDA: "Specifically, with limited exceptions not applicable here, neither a reference product sponsor, such as Amgen, nor an applicant, such as Sandoz, may file a lawsuit unless and until they have engaged in a series of statutorily-mandated exchanges of information."<sup>68</sup> Nor was the court persuaded by Sandoz's assertion that the Act allows either the biosimilar manufacturer or the reference product sponsor to file a declaratory judgment action upon the former's notice of commercial marketing, regardless of whether or not that biosimilar manufacturer had submitted an application to the FDA.<sup>69</sup> The court found that Sandoz misinterpreted the relevant portion of the Act, which it concluded required a biosimilar manufacturer to both submit an application to the FDA, and thus become, in its view, a subsection (k) applicant,<sup>70</sup> and comply with the back-and-forth obligations under subsection (l) before it could bring an action for declaratory relief.<sup>71</sup>

Sandoz appealed.

### C. Federal Circuit

On December 5, 2014, the Federal Circuit reached its decision. However, it did so on the basis of the justiciability question, and did not address the propriety of the district court's interpretation of the BPCIA. Circuit Judge Taranto, writing for the court, cited the Declaratory Judgment Act<sup>72</sup> and *MedImmune's* "all the circumstances" standard,<sup>73</sup> and concluded

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66. 28 U.S.C. § 2201(b).

67. *Sandoz Inc.*, 2013 WL 6000069, at \*2; 42 U.S.C. § 262(l), setting specific limitations on the timing of any litigation arising from the filing of an application for such license.

68. *Sandoz Inc.*, 2013 WL 6000069, at \*2.

69. *Id.* Sandoz asserted that it had at this time given a notice of commercial marketing.

70. 42 U.S.C. § 262(k). For a cogent argument that the N.D. Cal. misinterpreted this portion of the BPCIA, see Carl Minniti's article, *supra* note 24, finding that the BPCIA's declaratory judgment limitations do not apply to Sandoz precisely because it had not submitted an application to the FDA, and was therefore not a subsection (k) applicant.

71. *Sandoz Inc.*, 2013 WL 6000069, at \*2.

72. 28 U.S.C. § 2201.

73. *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007): In the patent context, ask "whether the facts alleged, under all the circumstances, show that there is a substantial

that Sandoz's complaint did not present a case or controversy.<sup>74</sup> The court explicitly declined to address Sandoz's ability to seek a declaratory judgment if and when it files an FDA application under the BPCIA.<sup>75</sup>

When weighing the immediacy and reality of Sandoz's perceived harm, the court disregarded some facts and dwelled on others. For example, Judge Taranto stated "Amgen has not suggested that anything Sandoz is currently doing exposes it to infringement liability,"<sup>76</sup> and indeed, it could not have for at least three reasons: Sandoz is conducting its clinical trial abroad, and Amgen's U.S. patents cannot reach activity outside the U.S.; even if it were in the U.S., the trial is likely exempt from infringement under the safe harbor provided by § 271(e)(1), as interpreted by *Merck*;<sup>77</sup> and Sandoz did not publicly announce its etanercept Phase III trial until the day before it brought this suit.<sup>78</sup> Judge Taranto stated in a similar manner that "Sandoz cannot engage in the only liability-exposing conduct at issue without FDA approval of an application precisely defining the products it may market. Sandoz has not even filed such an application."<sup>79</sup>

Instead of leaving the case-or-controversy analysis there, however, the court went on at length characterizing the finality of Sandoz's etanercept product as highly uncertain, conjecturing that the patent dispute may simply disappear if Sandoz's Phase III trial fails in material ways and Sandoz decides to modify its product, or even abandon it.<sup>80</sup>

In reaching its decision on the justiciability question, the Federal Circuit did not adopt a categorical rule. The court did not hold that all biosimilar makers that have not yet submitted an application to the FDA would be unsuccessful in a declaratory judgment action. Nor did it hold that a Phase

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controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment."

74. *Sandoz Inc.*, 773 F.3d at 1281.

75. *Id.*

76. *Id.* at 1279.

77. 35 U.S.C. § 271(e)(1) provides a safe harbor that "exempt[s] from infringement all uses of patented compounds 'reasonably related' to the process of developing information for submission under any federal law regulating the manufacture, use, or distribution of drugs." *Merck LGAA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 206 (2005) (emphasis in original).

78. Amgen Fed. Cir. Brief, *supra* note 62, at 12.

79. *Sandoz*, 773 F.3d at 1279.

80. *Id.* at 1280.

III clinical trial would never create a case or controversy. The court held only that here, Sandoz had not established a case or controversy.<sup>81</sup>

#### IV. *Amgen v. Sandoz: Filgrastim*

##### A. Facts and Background

Amgen markets the biologic filgrastim, under the brand name Neupogen, to reduce the risk of infection in certain cancer patients who are receiving strong chemotherapy.<sup>82</sup> Neupogen is a biologic based on a natural protein called G-CSF.<sup>83</sup> Both G-CSF and Neupogen act in the bone marrow to boost the production of white blood cells.<sup>84</sup> The FDA approved Neupogen in 1991<sup>85</sup> and Amgen has enjoyed exclusivity in the U.S. market since then. Neupogen is also protected by a patent (the '427 patent) that issued in 2000 and expired in December 2015.<sup>86</sup> Sandoz developed its own filgrastim product, a close copy of Neupogen called EP2006, under the brand names Zarzio and Zarxio.<sup>87</sup> Sandoz began marketing Zarzio outside the U.S. in 2009, and launched Zarxio in September 2015.<sup>88</sup>

On July 7, 2014, Sandoz received notice that the FDA accepted its application for its filgrastim product, making it the first ever application for a biosimilar biological product to be accepted by the FDA.<sup>89</sup> Amgen

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81. *Id.* at 1282. The court held that preapplication declaratory judgment actions are not allowed under the BPCIA. Mechanisms to challenge patent validity through the U.S. Patent and Trademark Office may be an option for those in Sandoz's position. However, the availability of these mechanisms is limited in scope and time. Here, Sandoz is left without a remedy because the only review mechanism for challenging on the basis of 35 U.S.C. § 101 is only available in the first nine months after a patent is issued. The other mechanisms, including *inter partes* review, are only available on the basis of 35 U.S.C. §§ 102 and 103.

82. NEUPOGEN, [www.neupogen.com](http://www.neupogen.com) (last visited Apr. 2, 2015). Neupogen treats neutropenia, a condition where the body does not make enough neutrophils, a type of white blood cell that fights infection.

83. *Id.*

84. *Id.*

85. *Id.*

86. U.S. Patent No. 6,162,427 (filed Dec. 19, 2000).

87. Sreejit Mohan, *Zarzio Overtakes Neupogen and Granocyte to Become Most Prescribed Daily G-CSF in Europe.*, [http://www.sandoz-biosimilars.com/media\\_center2/press\\_releases/2013\\_07\\_22\\_zarzio.shtml](http://www.sandoz-biosimilars.com/media_center2/press_releases/2013_07_22_zarzio.shtml) (Jul. 22, 2013).

88. *Id.*; see also Leslie Pott, *Sandoz Launches Zarzio TM (filgrastim-sndz), the First Biosimilar in the United States.*, <https://www.novartis.com/news/media-releases/sandoz-launches-zarziotm-filgrastim-sndz-first-biosimilar-united-states> (Sept. 3, 2015).

89. *Amgen Inc. v. Sandoz Inc.*, No. 14-CV-04741-RS, 2015 WL 1264756, at \*1, \*3 (N.D. Cal. Mar. 19, 2015) *aff'd in part, vacated in part, remanded*, 794 F.3d 1347 (Fed. Cir. 2015).

anticipated that the filing would trigger a cascade of events, the patent dance, under the BPCIA; however, Sandoz chose not to comply with the BPCIA's disclosure and negotiation procedures, taking the position that they are optional.<sup>90</sup> Sandoz proposed an alternative arrangement, namely, that Amgen could procure information via an infringement action, and considered that its letter of July 8, 2014, constituted notice of intent to market its product on or after one hundred and eighty days.<sup>91</sup>

Amgen brought suit in the Northern District of California on October 24, 2014.<sup>92</sup> On March 6, 2015, the FDA approved the first biosimilar under the BPCIA, Sandoz's filgrastim, which became the first biosimilar marketed in the U.S.<sup>93</sup>

### **B. District Court**

Amgen asserted claims of unlawful competition based on violations of the BPCIA, conversion, and infringement of Amgen's '427 patent. According to Amgen, Sandoz's failure to comply with the disclosure and negotiation procedures outlined in §§ 262(1)(1)-(8) comprise unlawful business practices actionable under California's Unfair Competition Law,<sup>94</sup> and Sandoz's use of Neupogen as a reference product without abiding by the procedures in subsection (1) amounted to an act of conversion.<sup>95</sup>

Sandoz submitted an answer contending that its actions comported with the letter and spirit of the BPCIA, and asserted seven counterclaims seeking declaratory judgment that, first the '427 patent was invalid and not infringed, and second, its interpretation of the BPCIA is correct.<sup>96</sup> Amgen later asserted that these counterclaims were barred because the BPCIA mandates that only Amgen, not Sandoz, may file a declaratory judgment action at this stage in the process.

On March 19, 2015, the district court reached a determination. Writing for the court in a thorough decision, District Judge Richard Seeborg delivered a victory for Sandoz and held that the patent dance outlined by the BPCIA is discretionary and that marketing can occur immediately upon

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90. *Id.*

91. *Id.* at 3.

92. *Id.*

93. Mohan, *supra* note 87.

94. CAL. BUS. & PROF. CODE § 17200.

95. *Amgen Inc.*, 2015 WL 1264756, at \*4.

96. *Id.*

receiving FDA approval, rather than waiting at least one hundred and eighty days thereafter.<sup>97</sup>

Amgen appealed.

### C. Federal Circuit

The Federal Circuit issued a fractured decision on July 21, 2015.<sup>98</sup> In the initial footnote, Judge Lourie, writing for the court, likened the BPCIA to the manner in which Winston Churchill described Russia, that is, as “a riddle wrapped in a mystery inside an enigma” (citations omitted). Although Lourie said the judges “do [their] best to unravel the riddle, solve the mystery, and comprehend the enigma[,]” the panel was not able to come to a consensus on either of the issues presented, and the lower court’s decision was affirmed in part, vacated in part, and remanded.<sup>99</sup>

Judges Lourie and Chen found that the patent dance procedures were optional, affirming the district court and siding with Sandoz.<sup>100</sup> Judges Lourie and Newman found that in order to effectively start the one-hundred-and-eighty-day countdown to market entry, notice of commercial marketing could be given only after licensure by the FDA, contrary to the district court’s interpretation and in favor of that taken by Amgen.<sup>101</sup>

In his partial dissent, Judge Chen cogently argued that the court’s adoption of Amgen’s interpretation of the notice of commercial marketing and preliminary injunction sections seffectively gives the RPS an “extra-statutory exclusivity windfall.”<sup>102</sup> Under Sandoz’s interpretation supported by the district court, a biosimilar applicant could give the RPS notice about six months prior to gaining a license from the FDA, which then allowed them to enter the market upon FDA approval. The interpretation that the Federal Circuit endorsed pushes this timeline back, so that the biosimilar applicant cannot give notice until after FDA approval. According to this interpretation, the soonest a biosimilar can enter the market is one hundred and eighty days after it has been approved. This, Judge Chen argues, is not correct; “[i]f Congress intended to create a one hundred and eighty-day

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97. *Id.* at 6–7.

98. *See* *Amgen Inc. v. Sandoz Inc.*, 794 F.3d 1347 (Fed. Cir. 2015).

99. *Id.* at 1371.

100. *Id.* at 1357.

101. *Id.* at 1358.

102. *Id.* at 1367.



automatic stay it understood how to do so[.]” referring to the provisions that accomplish this type of stay in the Hatch-Waxman Act.<sup>103</sup>

Amgen and Sandoz both petitioned the court for a rehearing en banc. Those petitions were denied.

## V. Statutory Interpretation

Sandoz and Amgen built their arguments around the same statutory language, but interpreted its meaning differently. The cases highlight the extent of the ambiguity, with support on both sides, of the reach and application of the BPCIA.

### A. Who is the subsection (k) Applicant?

In the first case, *Sandoz v. Amgen*, Sandoz pointed to the text of the declaratory judgment limitations and asserted that they do not apply to a biosimilar manufacturer that has not yet filed a biosimilar application, and even if they could apply, Sandoz’s notice of commercial marketing precluded their application.<sup>104</sup> Finally, Sandoz asserted that the district court’s finding that a notice of commercial marketing could be given only after the biosimilar had been approved rests entirely on a misinterpretation. In contrast, Sandoz’s interpretation asserts that a biosimilar manufacturer does not have to wait for approval, and can provide notice at any point one hundred and eighty days prior to commercial marketing.<sup>105</sup>

Amgen argued on appeal that Sandoz’s interpretation of the BPCIA creates internal inconsistencies, asserting that Congress did not intend to allow biosimilar makers to avoid the information exchange provisions and litigation obligations simply by filing a declaratory judgment action before filing with the FDA,<sup>106</sup> and that the BPCIA does not distinguish between artificial infringement under § 271(e)(2) and actual infringement under § 271(a).<sup>107</sup> Amgen’s argument characterized subsection (k) as the abbreviated approval pathway created by the BPCIA, rather than a mere piece of the pathway.<sup>108</sup> Thus, as long as a biosimilar manufacturer develops its product as a biosimilar to a reference product and intends to submit it as

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103. *Id.* at 1371.

104. *Amgen Inc.*, 2015 WL1264756 at \*4.

105. *Id.* at \*22–23.

106. *Id.* at \*45.

107. *Id.* at \*48.

108. *Amgen Fed. Cir. Brief*, *supra* note 62, at 30.

such for FDA approval, it does so pursuant to this pathway and is automatically a subsection (k) applicant, whether or not it has yet submitted an application to the FDA.<sup>109</sup> According to this interpretation, all the declaratory judgment limitations apply to any maker of a biologic that purports to be biosimilar to a reference product. In order to bring a declaratory judgment action, a biosimilar manufacturer must comply with all the requirements in § 262(l), including exchange information with the reference product sponsor, secure FDA approval for its product, and provide notice of commercial marketing.<sup>110</sup>

### **B. Does the Applicant Have to Dance?**

The decision in *Amgen v. Sandoz* hinged on the interpretation of two portions of Section 262(l). According to Amgen, Sandoz acted unlawfully when it failed to comply with the disclosure and negotiation procedures, and because it intended to market its biosimilar immediately upon receiving FDA approval, rather than waiting at least one hundred and eighty days thereafter.<sup>111</sup> Regarding whether a biosimilar maker must enter the dance, Sections 262(l)(2)-(8) lay out procedures that “shall” and “may” be carried out. Amgen asserts that the presence of “may” in certain paragraphs suggests that the use of “shall” in others implies an action is required.<sup>112</sup> Sandoz and the courts look to countervailing factors and conclude that the word “shall” does not imply that an action is mandatory in all contexts. The district court says it is fair to read subsection (l) as a series of steps that must be followed, but only after the parties agree to engage in the procedure.<sup>113</sup> That is, once the parties are on the dance floor, that have to follow the steps; but the decision to get on the dance floor in the first place is discretionary.

The district court finds that this reading is supported by the broader intention of the Act as well, in that “compliance allows an applicant to enjoy a temporary safe harbor from litigation and, potentially, to resolve or narrow patent disputes outside court proceedings.”<sup>114</sup> Under this reading, the actions available to reference product sponsor under subparagraphs (l)(9)(B)-(C) are only options where the biosimilar maker gets on the dance floor and does the wrong dance, or quits mid-sequence; they are not

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109. *Id.*

110. *Id.* at 40.

111. *Amgen Inc.*, 2015 WL 1264756, at \*5.

112. *Id.* at 5–6.

113. *Id.* at 6.

114. *Id.*

available where the biosimilar maker never got on the floor. These subparagraphs allow the reference product sponsor to commence patent litigation immediately following the wrong move, removing availability to the applicant of a litigation safe harbor. The court finds further support in that Congress took the additional step to amend 35 U.S.C. § 271(e), adding that an applicant's failure to disclose information regarding a potentially infringed patent under subsection (l)'s requirements is immediately actionable.<sup>115</sup>

Looking to the statute's broader intent to accelerate resolution of patent disputes, the district court finds that there are benefits to compliance with the disclosure process to applicants with a high or unknown risk of liability for infringement. On the other hand, the process outlined in subsection (l) could take several months just to commence patent litigation, and an applicant who is seeking a quick resolution over risk mitigation may choose not to engage in the disclosure and negotiation process because it would introduce needless communications and delay.

The fractured Federal Circuit affirmed this result, if not all of the reasoning. Judge Lourie wrote the decision and drew a concurrence from Judge Chen on the patent dance issue. Regarding the "mays" and "shalls," the court finds that the relevant language in subsection (l)(2)(A), when read in isolation, indicates the patent dance is mandatory, and that a subsection (k) applicant would be required to disclose its application to the RPS.<sup>116</sup> However, when viewed in the context of other provisions in the statute, participation in the dance must be read as optional.<sup>117</sup> Judge Lourie wrote that:

... read in isolation, the "shall" provision in paragraph (l)(2)(A) appears to mean that a subsection (k) applicant is required to disclose its [application] and manufacturing information to the RPS by the deadline specified in the statute. Indeed, the BPCIA refers to such information as 'required in other provisions. See 42 U.S.C. § 262(l)(1)(B)(i), (l)(9)(A)), (l)(9)(C); 35 U.S.C. § 271(e)(2)(C)(ii). Particularly, paragraph (l)(1)(B)(i) provides that '[w]hen' a subsection (k) applicant submits an [abbreviated application] to the FDA, "such applicant *shall* provide . . . confidential access to the information *required* to be produced pursuant to paragraph (2) and any other information that the subsection (k) applicant determines, in

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115. *Id.*

116. *Amgen Inc.*, 794 F.3d at 1355.

117. *Id.*

its sole discretion, to be appropriate” (emphasis in opinion). Thus under the plain language of paragraph (1)(1)(B)(i), *when* an applicant chooses the abbreviated pathway for regulatory approval of its biosimilar product, it is required to disclose its [abbreviated application] and manufacturing information to the RPS no later than 20 days after the FDA’s notification of acceptance, but not when the “when” criterion is not met . . .<sup>118</sup>

Thus, the court ultimately concludes that the BPCIA expressly contemplated that an applicant may choose not to disclose to the RPS, and that the remedies for an applicant’s failure to disclose are provided for in paragraph (1)(9)(C) and the infringement provisions under § 271(e). “Because Sandoz took a path expressly contemplated by the BPCIA, it did not violate the BPCIA by not disclosing its [application] and the manufacturing information by the statutory deadline.”<sup>119</sup>

Regarding the second question, whether the one-hundred-and-eighty-day period from notice to marketing must take place after FDA approval, the district court again sided with Sandoz’s interpretation.<sup>120</sup> This provision says that an applicant “shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product licensed under subsection (k).”<sup>121</sup> The reference product sponsor may then seek an injunction from such market entry until a court decides issues of patent validity or infringement,<sup>122</sup> or it may initiate a declaratory judgment.<sup>123</sup>

In the district court and on appeal, Amgen argues that the past tense of the word “licensed” indicates that an applicant may not give the required one-hundred-and-eighty-day notice to the reference product sponsor until after the FDA has approved the biosimilar product, resulting in an additional waiting period before the biosimilar may enter the market.<sup>124</sup> The district court found Amgen’s interpretation would have a problematic effect on the overall statutory scheme, as it would append an additional six months on the carefully considered exclusivity periods that the reference product sponsor already enjoys, stating, “[h]ad Congress intended to make the exclusivity

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118. *Id.*

119. *Id.* at 1357.

120. *Amgen Inc.*, 2015 WL 1264756 at \*7.

121. 42 U.S.C. § 262(l)(8)(A).

122. 42 U.S.C. § 262(l)(8)(B).

123. 42 U.S.C. § 262(l)(9)(B).

124. *Amgen Inc.*, 2015 WL 1264756 at \*7.

period twelve and one-half years, it could not have chosen a more convoluted method of doing so.”<sup>125</sup>

The Federal Circuit sided with Amgen on the notice issue. Judge Lourie, this time drawing concurrence from Judge Newman, found that an applicant must be granted a license before it may give an “operative notice” of commercial marketing.<sup>126</sup> Judge Lourie found that the statute’s silence regarding what happens if notice is not given indicates that the notice is mandatory. Judge Lourie reasoned that an applicant could not effectively give notice of commercial marketing before it is granted a license because a subsection (k) applicant cannot be certain if or when it will get FDA licensure, or that the product that is licensed is the same as the product described in the application. “Giving notice after FDA licensure, once the scope of the approved license is known and the marketing of the proposed biosimilar product is imminent,” he says, “allows the RPS to effectively determine whether, and on which patents, to seek a preliminary injunction from the court . . .”<sup>127</sup>

## VI. Practical Consequences and Conclusions

The decisions in these first cases are important because they will influence interpretations of the statute in future litigation. But the practical consequences go beyond a courtroom victory for one billion-dollar company or another. The consequences extend to the lives and pocketbooks of the millions of Americans who stand to benefit from improved access to the most innovative drugs.

Patent protection is limited and calculated to increase innovation. The competition introduced by biosimilars would drive down the cost of these specialty treatments to patients,<sup>128</sup> and innovators would innovate further to hold on to their lead. U.S. consumers spend many billions each year on biologics, and this amount is likely only to increase as more biologic medicines are approved.<sup>129</sup> Denying a remedy and prolonging the monopoly

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125. *Id.* at 8.

126. *Amgen Inc.*, 794 F.3d 1347, 1358 (Fed. Cir. 2015).

127. *Id.*

128. Express Scripts, the nation’s largest manager of prescription drug benefits, estimated that the introduction of Sandoz’s filgrastim product could save \$5.7 billion in drug costs over the next ten years. They estimated that the country would save \$250 billion in drug costs over the next decade if ten other biosimilars in development were approved. *See* EXPRESS SCRIPTS INFOGRAPHIC, *supra* note 9.

129. For example, \$92 billion was spent on biologics in 2013, as part of a trend of steady increases for each of the previous three years. ALEX BRILL, MATRIX GLOBAL ADVISORS, THE

imposes significant additional costs on patients and the healthcare system. When interpreting the statutory “enigma,” courts would do well to remember these broader goals and intentions, and the very real consequences for the consuming public.