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[L]aw is order, good law is good order.[1]

A corollary to Aristotle's statement is that bad law is bad order, or, in other words, disorder. When Congress enacts new laws, that body indubitably hopes that such laws will further the goals we, as a society, find desirable and also further the added purpose of avoiding disorder. Occasionally, a statutory scheme is established that leads to an inequitable or undesirable result. Society commonly associates these results as "loop holes" in the laws, or shortcomings that lead to inadvertent and inequitable situations. Society's observations, as is often the case, are right.

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act ("the Hatch-Waxman Act" or "the Act").[2] The amendments altered the Federal Food, Drug, and Cosmetic Act[3] ("FFDCA" or "FDCA") and the patent laws[4] by creating a statutory scheme that sought to strike a balance between "two conflicting policy objectives: to induce brand name pharmaceutical firms to make the investments necessary to research and develop new drug products, while simultaneously enabling competitors to bring cheaper, generic copies of those drugs to market."[5] These amendments have, in part, led to both public benefit and detriment. This article investigates certain litigation involving the Act, evaluates the current statutory and regulatory constructs, including the

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1. ARISTOTLE, THE POLITICS 162 (Stephen Everson ed., Cambridge University Press 1988).

2. Pub. L. No. 98-417, 98 Stat. 1585 (codified at 21 U.S.C. §§ 355, 360cc (2000), and 35 U.S.C. §§ 156, 271, 282 (2000)).

3. 21 U.S.C. §§ 301–397 (2000).

4. 35 U.S.C. §§ 100–376 (2000).

5. Abbott Labs. v. Young, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting on other grounds). A generic drug contains the same active ingredients as its brand-name counterpart, but does not necessarily contain the same inactive ingredients. Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1063 (D.C. Cir. 1998).

government's own opinions, and, in particular, traces the entangled history of one drug, Neurontin®, through both the courts and the media.

I. STATUTORY AND REGULATORY BACKGROUND

The modern profusion of . . . governmental authorities offers almost limitless possibilities for abuse.[6]

The 1984 Hatch-Waxman Act introduced a complex set of rules with the stated purpose to "make available more low cost generic drugs."[7] The amendments brought about by the Act "were designed to simplify and expedite the process by which the generic drugs are brought to market."[8] In passing the Act, Congress was motivated by the concern that the Food and Drug Administration's ("the FDA") lengthy drug approval process was a burden for both the generic manufacturers and the rights and investments of the branded drug manufacturers.[9] This section provides the general framework necessary to fully appreciate the impact of certain judicial decisions discussed herein. This is, unfortunately, a complicated statute; it is described by one court as "cumbersome"[10] and by another as "very confusing and ambiguous."[11] Despite this, or rather because of this, it is worthwhile to investigate the statute and review whether the above-stated goals are being realized, and to what degree. It is also valuable so that the branded drug manufacturer and generic drug manufacturer can clearly discern their rights and avoid needless litigation.

Before the enactment of the Act, both branded[12] and generic[13] drug manufacturers wishing to bring a drug to market were required to file a New

6. ROBERT H. BORK, THE ANTITRUST PARADOX 347 (1978).

7. H.R. REP. NO. 98-857, pt. 1, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2647.

8. Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191, 193 (D.D.C. 2002).

9. The Amendments have been criticized for, *inter alia*, taking a "split-the-baby" approach in an attempt to reach its stated goals. *See* Watson Pharms., Inc. v. Henney, 194 F. Supp. 2d 442, 444 (D. Md. 2001).

10. Mova Pharm. Corp. v. Shalala, 955 F. Supp. 128, 130 (D.D.C. 1997).

11. *Mova*, 140 F.3d at 1069 (quoting Mylan Pharms., Inc. v. Sullivan, No. 89-6-C(K), slip op. at 7 (N.D.W.Va. May 5, 1989)).

12. The term "branded" drug manufacturer refers to those drug manufacturers holding the patent rights to a particular FDA approved drug. The terms "pioneer" and "brand name" manufacturer are used by the courts and various government agencies quoted herein. For purposes of this writing, the terms are used interchangeably unless otherwise indicated.

13. The term "generic" drug manufacturer refers to those drug manufacturers producing drugs having the same active ingredient or ingredients, often in the same formulation, as those found in the products of "branded" drug manufacturers. Generic drugs are often sold at prices considerably lower than branded drugs. *See, e.g.*, Congressional Budget Office, *How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry* (July 1998) (hereinafter "CBO Study"), *available at* http://www.cbo.gov/showdoc.cfm?index=655&sequence=1 (last visited Feb. 22, 2003).

Drug Application, or "NDA."[14] This requirement presented a considerable barrier to generic drug manufacturers because an NDA requires a full battery of safety and efficacy tests, including expensive clinical trials.[15] To further impede a generic manufacturer's entry into the market, and before the Act, the Federal Circuit Court of Appeals[16] interpreted the patent laws in a manner such that a generic manufacturer was liable for infringement for research and clinical trials until patents claiming the branded drugs had expired.[17] This interpretation of the statute resulted in the branded drug manufacturer having a *de facto* extension of its patent monopoly because a generic manufacturer would not only have to begin research and production after the patent's technical expiration, but would have to complete the NDA process as well.

In order to benefit consumers, the Act altered this requirement by allowing a generic drug manufacturer to "piggyback on the original NDA filed by the manufacturer of the brand-name drug."[18] This streamlined process allows a drug manufacturer, generic or branded, to submit an Abbreviated New Drug Application ("ANDA").[19] The ANDA process allows a drug manufacturer to rely on the clinical studies performed by the New Drug Applicant and to forego the safety and effectiveness testing of its new generic drug. The ANDA applicant must prove only that its drug is a "bioequivalent" to the pioneer drug approved in the NDA.[20] This process allows generic manufacturers "to avoid

14. The term "NDA," as used herein, may refer to a "New Drug Application" or a "New Drug Applicant." Its use will be apparent from the context.

15. *See Mova*, 140 F.3d at 1063.

16. The Federal Court of Appeals was created in 1982 by act of Congress. *See* Federal Courts Improvement Act of 1982, Pub. L. No. 97-164, 96 Stat. 25. Congress conferred exclusive appellate jurisdiction over most cases involving patent issues, including: (1) decisions by the Board of Appeals of the Patent and Trademark Office; (2) decisions by District Courts in infringement and other patent suits; (3) decisions by the United States Court of Federal Claims (including reasonable compensation suits against the United States for use of a patented invention); and (4) determinations of the United States International Trade Commission. *See* 28 U.S.C. §§ 1295(a)(4)(A), 1295(a)(1), 1295(a)(3) and 1295(a)(6) (2000) respectively.

17. *See, e.g.*, Roche Prods., Inc. v. Bolar Pharm. Co., Inc., 733 F.2d 858, 861 (Fed. Cir. 1984) (holding that the plain language of § 271(a) made the manufacture and testing (a use) of a patented product before the expiration of the patent an act of infringement unless licensed, even if that manufacture or use was solely for the purpose of conducting tests and developing the necessary information to apply for regulatory approval later on). *See also* Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1356-58 (Fed. Cir. 2003) (recounting history of the Hatch-Waxman Act). For further analysis of Section 271 of Title 35, see Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 679 (1990) ("No interpretation we have been able to imagine can transform § 271(e)(1) into an elegant piece of statutory draftsmanship.").

18. Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191, 193 (D.D.C. 2002).

19. *See* 21 U.S.C. § 355(j) (2000).

20. *See id.* at § 355(j)(2)(A)(iv). *See also Eli Lilly*, 496 U.S. at 676 ("The ANDA applicant can substitute bioequivalence data for the extensive animal and human studies of safety and effectiveness that must accompany a full new drug application.").

the costly and time-consuming process associated with NDAs, thus facilitating the approval and dissemination of low-costs generic drugs."[21] The Act amended the patent laws so that a generic drug manufacturer no longer infringes a patent covering an approved drug by performing those acts necessary to prepare and file an ANDA.[22] The Congressional Budget Office estimates that, by purchasing bioequivalents of brand name drugs, consumers saved $8-10 billion on retail purchases of prescription drugs in 1994 alone.[23] Generic drugs now comprise more than 47 percent of the prescriptions filled for pharmaceutical products.[24] This is up from 19 percent in 1984 when the Hatch-Waxman Act was enacted.[25]

To compensate pioneer drug manufacturers that invest heavily in the clinical trials necessary for the NDA, the Hatch-Waxman Act also amended the patent laws "to protect patent holders whose rights could be threatened by the marketing of generic versions of their patented innovations."[26] To this end, the amendments establish a mechanism for the listing of patents impacted by a generic manufacturer attempting to enter the market through the filing of an ANDA. Each drug company filing an NDA must submit, as part of its application, a list of all the patents that:

> [C]laim[] the drug for which the applicant submitted the application or which claim[] a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.[27]

The FDA, through regulation, has defined the three types of patents that may be submitted with an NDA: (1) drug substance (active ingredient patents) patents; (2) drug product (formulation and composition) patents; and (3) method of use patents.[28] When the FDA approves an NDA, the patent information submitted therewith is published in a publication entitled "Approved Drug Products With Therapeutic Equivalence," known in agency parlance as the "Orange Book."[29] An NDA applicant must list any new patents

21. *Purepac*, 238 F. Supp. 2d at 194 (citing H.R. REP. NO. 98-857, pt. 1, at 14 (1984)).

22. *See* 35 U.S.C. § 271(e)(1) (2000). *See also* aaiPharma Inc. v. Thompson, 296 F.3d 227, 231 (4th Cir. 2002).

23. CBO Study, *supra* note 13.

24. *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, Federal Trade Commission, July 2002, at p. i. (hereinafter "the FTC Study"), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (last visited Feb. 22, 2003).

25. *Id.*

26. *Purepac*, 238 F. Supp. 2d at 194 (citing Am. Bioscience, Inc. v. Thompson, 243 F.3d 579, 580 (D.C. Cir. 2001)).

27. 21 U.S.C. § 355(b)(1) (2000).

28. *See* 21 C.F.R. § 314.53(b) (2002).

29. *See* Am. Bioscience, Inc. v. Thompson, 269 F.3d 1077, 1079 (D.C. Cir. 2001); Terry G. Mahn, *Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process*, 54 FOOD DRUG COSM. L.J. 245, 249-50 (1999).

that issue during the pendency of the NDA application that claims the drug at issue.[30] Further, an NDA applicant also must amend its patent listing to include information about any newly issued patents that claim the drug at issue within thirty days of their issuance if they want to later invoke the statutory mechanisms for excluding generic manufacturers (the 30-month stay, discussed in detail supra).[31] To further complicate matters, because an applicant may not receive original approval for all aspects of the drug as described in the original NDA submission, the applicant must amend the patent submission to list only the patents that meet the listing criteria for the approved drug product.[32] Orange Book listings play an important role in effectuating the dual goals articulated by Congress.

There are four important points to make about Orange Book listings: (1) ANDA applicants are required to make certifications with respect to patents listed in the Orange Book; (2) the NDA holder can use the listed patents to invoke a temporary stay against approval of any ANDAs; (3) the FDA mandates that method of use patents can be listed and remain in the book only if such patents actually claim a use that has been approved by the agency; and (4) the FDA has consistently taken the position that it does not, and will not, police the listings for accuracy. Neither of these positions are statutory directives; rather, they are imposed through FDA regulations.[33]

These first two points are discussed in more detail below. With respect to the third, the listing of use patents, the FDA's obvious goal is to restrict those patents listed to patents that actually claim an *approved* use of the drug. For example, if the drug was aspirin,[34] and its approved use was to treat headaches, a patent claiming the use of aspirin to treat high blood pressure should not be listed. If, at some later time, aspirin is approved for the treatment of high blood pressure, then the patent may be listed. The FDA takes the position that it is the NDA's obligation to verify the propriety of the use patents in the Orange Book.[35]

30. 21 U.S.C. § 355(b)(1) (2000).

31. *Id.* at § 355(b)(2)(B).

32. 21 C.F.R. § 314.53(c)(2)(ii) (2002).

33. *See* 21 C.F.R. § 314.53(b); Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,908 (July 10, 1989) (codified at 21 C.F.R. pts. 10, 310, 314, & 320 ("[I]nformation will be published in the list only on patents that . . . claim approved indications or other conditions of use."); Abbreviated New Drug Application Regulations; Patent & Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,345 (Oct. 3, 1994) (codified at 21 C.F.R. pt. 314).

34. Aspirin is good example of a trademark "gone generic." Aspirin, at one time, was the trade name for salicylic acid, the active ingredient in what we now call aspirin.

35. *See* Abbreviated New Drug Application Regulations; Patent & Exclusivity Provisions, 59 Fed. Reg., *supra* note 33, at 50,345.

That brings the fourth point squarely into focus—the FDA does not assume any responsibility for verifying the patent submissions of an ANDA.[36] The agency views its role as purely ministerial.[37] The agency bases this position on the premise that they do not have the resources or the expertise to determine the validity or scope of patent claims.[38] The FDA's practice is simply to list the patent information it receives from brand manufacturers with the expectation that those parties will understand and abide by the statutory and regulatory mandates.[39]

In formulating the applicable regulations, the FDA explicitly declined to establish a "mechanism for review of submitted patent information to determine, at least on a very general basis, applicability to the particular NDA in question."[40] The duty to verify the correctness of Orange Book listings, at least under the current law, soundly resides with NDA holders.[41] The statute does not mandate the FDA to take any other position. It is, however, the FDA's position that allows manufacturers to "game" the system, which is discussed further in Section II.

The ANDA applicant, when seeking approval for a generic drug, must specify information about the patents listed by the branded drug manufacturer in the Orange Book. The information must include:

> [T]he patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.[42]

There are two means by which an ANDA can satisfy this requirement.[43]

In the first instance, when the Orange Book-listed patent "claims the listed [i.e., FDA-approved] drug . . . or which claims a use for such listed drug for

36. aaiPharma Inc. v. Thompson, 296 F.3d 227, 237 (4th Cir. 2002) ("In short, the FDA's position is that if the NDA holder stands on it Orange Book listing, aggrieved parties are out of luck."). *See also*, Mahn, *supra* note 29, at 250 (noting the FDA's "willingness to list in the Orange Book virtually any patent submitted by an NDA holder").

37. Purepac Pharm. Co. v. Thompson, 238 F. Supp. 2d 191, 196 (D.D.C. 2002).

38. *Id.*

39. *See* Abbreviated New Drug Application Regulations; Patent & Exclusivity Provisions, 59 Fed. Reg., *supra* note 33, at 50,345.

40. *Id.* at 50,343; *see aaiPharma*, 296 F.3d at 243 (upholding the FDA's "purely ministerial approach to the Orange Book listing process" as a reasonable interpretation of its statutory responsibilities).

41. *See* Watson Pharm., Inc. v. Henney, 194 F. Supp. 2d 442, 445-46 (D. Md. 2001) ("In making its decision to list a patent . . . it is entirely appropriate and reasonable for the FDA to rely on the patentee's declaration as to coverage, and to let the patent infringement issues play out in other, proper arenas, as is the clear intent of the Hatch-Waxman Amendments.").

42. 21 U.S.C. § 355(b)(1) (2000).

43. *Purepac*, 238 F. Supp. 2d at 194.

which the applicant is seeking approval," an ANDA applicant must certify that the new drug, i.e., the generic drug, will not infringe the patent and explain that conclusion.[44] The statute provides four grounds on which this certification can be made: (1) that the required patent information has not been filed; (2) that the patent has expired; (3) that the patent will expire on a certain date; or (4) that the patent is invalid or will not be infringed by the drug for which approval is sought.[45] An ANDA applicant must also make additional certifications with respect to any newly listed patents during its application process, so long as the NDA holder submits the patent for listing no later than thirty days after the patent's issuance.[46] The certification date determines the date on which FDA approval of the application can become effective.[47] The ANDA must submit information for all patents listed in the Orange Book "despite any disagreement as to the correctness of the patent information."[48]

An ANDA making a paragraph (I) or paragraph (II) certification may be approved immediately if the FDA finds that all the relevant scientific and regulatory requirements have been met.[49] An application making a paragraph (III) certification becomes effective on the date the patent or patents at issue expire, assuming the other FDA requirements are met.[50] Certifications made under paragraphs (I-III), therefore, do not implicate patent infringement because the generic manufacturer's product will not come to market until any relevant patents have expired. It is this last option, the so-called "Paragraph (IV) certification," however, that gives rise to most litigation involving ANDAs.

The Paragraph (IV) certification is frequently litigated because of the rights created in both an ANDA *and* the NDA when such certification is made. An ANDA applicant making a paragraph (IV) certification must give notice of the filing both to the owner of the patent and to the holder of the NDA for the approved drug (often, but not always, the same party).[51] The applicant must also include a detailed statement providing the factual and legal basis of the applicant's opinion that the patent is not valid or will not be infringed.[52] The Hatch-Waxman Act provides that the act of filing a paragraph (IV) certification with respect to a patent creates a cause of action for patent

44. 21 U.S.C. § 355(j)(2)(A)(vii).
45. *Id.* at (I)-(IV).
46. 21 C.F.R. § 314.94(a)(12)(vi) (2002).
47. 21 U.S.C. § 355(j)(5)(B) (2000).
48. 21 C.F.R. § 314.53(f).
49. 21 U.S.C. § 355(j)(5)(B)(i).
50. *Id.* at § 355(j)(5)(B)(ii).
51. 21 U.S.C. § 355(j)(2)(B)(i).
52. 21 U.S.C. § 355(j)(2)(B)(ii) (2000).

infringement in the patent holder.[53] The patent holder, once it receives notice of the paragraph (IV) certification, has forty-five days in which to file a suit for patent infringement. The patent holder is motivated to bring suit because the FDA will approve, unless such suit is brought, the ANDA's application.[54] If an infringement suit is initiated, the FDA's approval of the ANDA is automatically stayed for 30 months ("the 30-month stay").[55] Precisely speaking, the stay continues until the earliest of: (1) the expiration of the patent; (2) judicial resolution of the patent infringement suit, or (3) thirty months from the patent holder's receipt of notice.[56] In addition, the period of the stay can be lengthened or shortened by the court hearing the infringement action if either party fails to "reasonably cooperate in expediting the action."[57] These provisions allow the patent holder to defend their intellectual property rights before the FDA approves a generic version of a drug.[58] Thus, the listing of a patent in the Orange Book is important for the fact that the patent holder can potentially rely on the 30-month stay. In the alternative, "[i]f a patent is not listed in the Orange Book, ANDA applicants do not have to file a paragraph (IV) certification, and the patent holder is unable to take advantage of the thirty-month stay."[59] Thus, a patent holder would have to wait until a generic sought out and received ANDA approval and began marketing its drug product before bringing suit. The implications of the 30-month stay are of great economic import to a drug company and, as discussed below, the listing of patents in the Orange Book has become the issue in more than one lawsuit.

Facing a patent infringement suit and a 30-month stay on its ANDA, a generic manufacturer may not wish to risk liability in an infringement suit. The Hatch-Waxman Act, however, provides an incentive to generic manufacturers willing to risk defending a patent infringement suit. The first generic manufacturer to gain approval of an ANDA containing a paragraph (IV) certification is entitled to a 180-day period of market exclusivity.[60] During this 180-day period, described by one court as an "edenic moment of freedom from the pressures of the marketplace,"[61] the FDA will not approve applications subsequently filed by other manufacturers. This effectively

53. *See* 35 U.S.C. § 271(e)(2) (2000) ("It shall be an act of infringement to submit . . . [an ANDA] . . . if the purpose of such submission is to obtain [FDA] approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent.").

54. 21 U.S.C. § 355(j)(5)(B)(iii).

55. *Id.*

56. *Id.*

57. *Id. See* Andrx Pharm., Inc. v. Biovail Corp. Int'l, 256 F.3d 799, 802 (D.C. Cir. 2001).

58. *aaiPharma*, 296 F.3d at 232 (citing Bristol-Myers Squibb Co. v. Royce Labs., Inc., 69 F.3d 1130, 1135 (Fed. Cir. 1995)).

59. *aaiPharma*, 296 F.3d at 232.

60. 21 U.S.C. § 355(j)(5)(B)(iv) (2000).

61. Mova v. Shalala, 140 F.3d 1060, 1064 (D.C. Cir. 1998).

allows the generic drug manufacturer to move its drug to market before the other generic manufacturers.[62] From 1992 until 1998, the FDA did not grant the 180-day market exclusivity to any applicants. Since 1998, however, and as a result of a court ruling changing the FDA's regulations, the FDA has granted the 180-day market exclusivity for thirty-one drug products.[63]

As mentioned above, there is an alternative to a paragraph (IV) certification. This alternative is commonly known as a "section (viii) statement."[64] This section applies when the patent in question is a "method of use of patent which *does not claim a use* for which the applicant is seeking approval under this subsection."[65] An applicant is directed, by FDA regulation, to use a section (viii) statement when "the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent" that was submitted by the NDA.[66] When an applicant files a section (viii) statement, no certification is needed under paragraphs I-IV; rather, the ANDA applicant must submit a statement that the method of use patent at issue does not claim the use of the drug for which the applicant is seeking approval.[67] The significant difference between a paragraph (IV) certification and a section (viii) statement is that an ANDA applicant making a section (viii) statement does not have to notify the patent owner of its ANDA nor is the ANDA applicant liable to a patent infringement action.[68] Furthermore, should the patent holder decide to bring an infringement action, the 30-month stay could not be invoked. The FDA, therefore, can immediately approve an ANDA containing a section (viii) statement. This provision obviously provides an attractive route for ANDA applicants, even though it does not provide for a 180-day market exclusivity period. As discussed below, the availability of a section (viii) statement turns on whether the method of use patent covering the approved drug actually claims the use for which the ANDA is applying.

Within this tapestry of laws and regulations, litigants have brought to light many of the shortcomings of this system. For some, the cause of action lies in a patent infringement suit to protect their research and development

62. *See* Mylan Pharm., Inc. v. Shalala, 81 F. Supp. 2d 30, 33 (D.D.C. 2000).

63. Generic Drug Entry Prior to Patent Expiration: An FTC Study, Federal Trade Commission, July 2002, at 57 (hereinafter "FTC Study"), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (citing *Mova*, 140 F.3d at 1074).

64. *See* 21 U.S.C. § 355(j)(2)(A)(viii) (2000).

65. *Id.* (emphasis added).

66. *See* 21 C.F.R. § 314.94(b)(12)(iii)(A) (1998).

67. *Id. See also* Purepac Pharma. Co v. Thompson, 238 F. Supp. 2d 191, 194-95 (D.C. 2002); Mylan Pharm., Inc. v. Thompson, 139 F. Supp. 2d 1, 6 (D.D.C. 2001), *rev'd on other grounds*, 268 F.3d 1323 (Fed. Cir. 2001).

68. *See* 35 U.S.C. § 271(e)(2)(A) (2000) (making it an act of infringement to file a paragraph (IV) certification).

investments. For others, the causes of action are yet to be recognized by the courts, for, as discussed below, the Hatch-Waxman Act failed to supply an enforcement mechanism and, consequently, failed to include a deterrent for over-aggressive use of patents through Orange Book listings. A number of major players in the pharmaceutical drug industry, both branded and generics, have been accused of "gaming" the system.[69] None other than the Chairman of the Federal Trade Commission ("the FTC") has testified to the United States Senate that certain drug companies have used the system to secure greater profits for themselves without creating a corresponding benefit to consumers.[70]

The FTC followed this testimony by preparing a detailed report ("the FTC Study") that investigated whether the 30-month stay and the 180-day market exclusivity provisions of the Hatch-Waxman Act "are susceptible to strategies to delay or deter consumer access to generic alternatives to brand-name drug products."[71] The report notes that an increasing number of generic drug manufacturers are seeking to enter the market before the expiration of patents held by branded manufacturers.[72] The FTC Study reveals that during the 1980s, only two percent of generic applications sought entry through the provisions of the Hatch-Waxman Act.[73] From 1998 to 2000, however, approximately 20 percent of the generic applications sought entry before patent expiration.[74] The FTC Study comprehensively studies the effects the Hatch-Waxman Act has had on generic drugs reaching the market and is also a valuable resource for information regarding antitrust issues.[75]

The study reports that, according to the FDA, "from the time Hatch-Waxman became effective in 1984 through December 31, 2000, 8,019 ANDAs were filed with the FDA."[76] Of these applications, 7,536 (94 percent) raised no patent issues (i.e., they did not contain a paragraph (IV) certification).[77] Six percent, or 483, of the total number of ANDA's did contain paragraph (IV) certifications.[78] These 483 ANDAs represented 130 unique brand name drug products.[79] The share of ANDAs containing paragraph (IV) certifications has

69. Prepared Statement of The Federal Trade Commission, Before the Committee on Commerce, Science, and Transportation, United States Senate, Chairman Timothy J. Muris, April 23, 2002, *available at* http://www.ftc.gov/os/2002/04/pharmtestimony.htm.

70. *Id.*

71. FTC Study, *supra* note 63, at i-ii.

72. *Id.*

73. *Id.* at ii.

74. *Id.*

75. Although antitrust issues are mentioned in this article, those issues warrant separate study and, for the most, are not discussed in detail.

76. FTC Study, *supra* note 63, at 10. FDA staff provided this information to the FTC staff. *See id.* at 10 n.42.

77. *Id.* at 10.

78. *Id.*

79. *Id.*

been increasing since the 1980's, where in the years 1998-2000 20 percent of the ANDAs contained paragraph (IV) certifications.[80]

One criticism the FTC Study makes of current practice is that the 30-month stay provision has unduly delayed entry of generic drugs into the market. The study reports that "[o]n average, the time required for FDA review and approval was twenty-five months and fifteen days from the application filing date in those cases where generic applicants filing a paragraph IV certification were not sued (and thus could begin commercial marketing once they had FDA approval)."[81] The average time between the filing of a patent infringement suit and a district court opinion was twenty-five months and thirteen days.[82] The average time between the filing of a patent infringement suit and a court of appeals decision was thirty-seven months and twenty days.[83] In practice, even if the 30-month stay has expired, a generic manufacturer is not likely to bring their product to market for fear of infringement liability if a suit is still pending. The length of pending litigation, however, will likely increase if the NDA holder asserts one or more patents against the ANDA applicant.[84]

The length of stays has been increasing in recent years. These additional months may be added on to a single 30-month stay when the NDA holder lists an additional patent in the Orange Book after an ANDA has filed a certification.[85] The ANDA is then required to re-certify with respect to this later-listed patent.[86] This scenario allows for the NDA holder to have more than one 30-month stay. These additional 30-month stays have added between 4 and 40 months beyond the original 30-month stay.[87]

The FTC Study recognizes that the 30-month stay is the tool used by NDA holders to prevent generic entry into the market.[88] In fact, the study suggest that "[t]he 30-month stay provision of the Hatch-Waxman Amendments protects brand-name companies beyond their existing intellectual property rights."[89] This conclusion is overly broad in that the stay would only extend

80. FTC Study, *supra* note 63 at 10.

81. *Id.* at iii.

82. *Id.*

83. *Id.*

84. The FTC Study reports that as of June 1, 2002, for 6 out of 7 cases that have been pending for more than 30 months before a decision from a district court, the brand-name company has alleged infringement of three or more patents. *Id.* The FTC study uses the term "brand-name company" too broadly in that the NDA holder may or may not be a "brand-name company." Indeed, many NDA holders are drug manufacturers that make only generic drugs. FTC Study, *supra* note 63, at iii.

85. *Id.*

86. *Id.*

87. *Id.*

88. *Id.* at 39.

89. FTC Study, *supra* note 63, at 39.

existing rights if the patent was to expire during the 30-month stay. The stay, however, can improperly exclude generic manufacturers if a patent is improperly listed in the Orange Book. This improper listing is what has been a source of criticism. The complaint is that these later-listed patents do not meet the FDA requirements for listing in the Orange Book, or, in other words, the patents do not claim the approved drugs or uses thereof. This has clearly happened, and is discussed in the Neurontin® cases below. In these cases, a use patent was later-issued and later-listed, the stay was continued, but the court ultimately determined that the patent did not claim an approved use. Thus, by continuing the stay, the NDA improperly extended their exclusivity with respect to the approved drug and its approved uses.

Generic drug manufacturers, however, have been fairly successful in infringement suits brought under the Hatch-Waxman Act. Of all the patent infringement actions involving both the first ANDA to file a paragraph (IV) certification and the second ANDA to do the same, generic applicants have prevailed in seventy-three percent of the cases as of June 1, 2002.[90] The FTC looked at twenty-five decisions in which the generic manufacturer was successful. In these cases, fourteen were decided on non-infringement and eleven were decided on invalidity.[91] The rate at which the United States Court of Appeals for the Federal Circuit overturned district court opinions involving infringement of drug products was eight percent.[92] Despite the odds favoring generic manufacturers, there still exists the potential for "gaming" the system (improper Orange Book listings). Moreover, avoiding such infringement litigation in the first place would be less taxing on all participants, including the ultimate consumers of the drugs.

What emerges from the FTC Study are a number of recommendations to ameliorate the insufficiencies of the Hatch-Waxman Act. One recommendation is that an NDA should be limited to invoking one 30-month stay per ANDA, regardless if additional patents are listed.[93] This is an interesting proposal, but it penalizes an NDA holder having subsequent patents issue that legitimately cover the approved drug or methods of use thereof. This could potentially penalize an NDA for delays in the prosecution of the patent at the Patent and Trademark Office. The FTC Study does recognize that there is no private right of action to "de-list" patents, thus, focusing on the real problem—the propriety of the Orange Book listings, not the number of 30-month stays.[94]

90. *Id.*
91. *Id.*
92. *Id.*
93. *Id.* at v.
94. FTC Study, *supra* note 63, at v.

The study also suggests that certain classes of patents are not appropriate to invoke the 30-month stay. These include: (1) metabolite patents;[95] (2) drug intermediate patents;[96] (3) polymorph patents;[97] and (4) "product by process patents that claim a drug product produced by a specified process."[98] This suggestion, however, should be taken with caution as it is not the type of patent that causes an improper listing in the Orange Book, but rather the improper overly broad assertion of its claims. The root problem rests with the fact there is no recognized cause of action against an Orange Book listing; an NDA can submit any relevant patent, even if it does not claim the approved drug or approved uses thereof.

A number of cases are discussed below that shed light on the practices that have developed under the Hatch-Waxman Act. In particular, because the use of paragraph (IV) certifications has dramatically increased since 1998, the majority of these cases are more recent. A selection of cases found below involve one particular drug, Neurontin®. This, by no means, is the only drug that has found itself embroiled in litigation due to the complexities of the Hatch-Waxman Act. It is, however, one of the drugs for which there are a number of published opinions and one in which the stays have reached an exceptionally long time (fifty-three months).[99]

II. JUDICIAL INTERPRETATION AND LITIGATION INVOLVING THE HATCH-WAXMAN ACT

Many cases have involved some aspect of the Hatch-Waxman Act. Since its passage in 1984, many courts have opined on its intricacies and nuances, of which there are many. Below is a brief review of opinions that have been selected to paint a broad picture of how various parties have found themselves in litigation that somehow turns on interpretation of the Hatch-Waxman Act. In particular, these cases are demonstrative of how aggrieved parties have been frustrated by the statutory scheme and judicial interpretation thereof. The first two cases show that the generic manufacturers have battled one another just as they have battled brand name manufacturers. These cases affirm the need to clarify the rights of both such parties.

95. "Patents that claim the chemical compound into which a patient's body converts the approved drug product." *Id.* at 55.

96. "Patents that claim a chemical compound used during production of the active ingredient, but not appearing in the final drug product." *Id.*

97. "Patents that claim a crystalline form of the active ingredient that differs from the approved crystalline form." *Id.*

98. *Id.*

99. It should be noted that the lengthy pendency (time the application spends under examination) of the later-listed patent with respect to Neurontin® caused it to be listed after the ANDA holders had filed their initial certifications.

In *Mova Pharmaceutical Corporation v. Shalala*,[100] the plaintiff, Mova Pharmaceutical Corporation ("Mova"), brought an action to compel the FDA to withdraw or change the effective date of the approval of an ANDA submitted by Mylan Pharmaceuticals, Inc. ("Mylan") to market a generic version of micronized glyburide, a drug used to treat diabetes.[101] Mova had filed an earlier application to market the same drug. Thus, they were the second ANDA. Mova's application, however, was delayed because the NDA holder, Pharmacia & Upjohn Company ("Upjohn"), brought a patent infringement action against Mova.[102]

Mova essentially asked the FDA to delay approval of Mylan's application until Mova prevailed in the infringement suit or it began marketing its drug, whichever event came first.[103] The FDA countered, citing regulations that allowed it "to approve Mylan's application immediately because, at the time Mylan submitted its application Mova had not yet 'successfully defended' against (that is prevailed in) Upjohn's patent infringement suit."[104] Mova argued the regulation was inconsistent with the section of Title 21 which governs the 180-day exclusivity period.[105]

The district court entered a preliminary injunction requiring the FDA to delay approval of Mylan's ANDA.[106] The FDA and Mylan appealed.[107] Upjohn moved to intervene after the district court granted the injunction, but their motion was denied. Upjohn appealed that decision.[108] Importantly, for reasons that are unclear (and were unclear to the appellate court as well),[109] Upjohn did not bring suit against Mylan in the 45-day window after they filed their paragraph (IV) certification, thus precluding them from enacting the 30-month stay (really a suspension of FDA approval of Mylan's ANDA), even if suit was subsequently brought.[110]

The Court of Appeals for the District of Columbia held that the FDA has overstepped its authority in enacting and applying the regulation at issue.[111] After an exhaustive analysis of congressional intent, the Court held that the

100. 140 F.3d 1060 (D.C. Cir. 1998).

101. *Id.* at 1062.

102. *Id*.

103. *Id.*

104. *Id.* at 1063 (quoting 21 C.F.R. § 314.107(c)(1)).

105. *Mova*, 140 F.3d at 1063; *see* 21 U.S.C. § 355(j)(5)(B)(iv) (2000).

106. *Mova*, 140 F.3d at 1063.

107. *Id.*

108. *Id.* at 1063. Upjohn moved to intervene to argue against approval of Mylan's application in order to protect its exclusivity in the market. *Id.*

109. *See id.* at 1065.

110. *See* 21 U.S.C. 355(j)(5)(B)(iii). Upjohn did eventually sue Mylan. The court ultimately ruled that Upjohn's patent was invalid and not infringed. *See Mova*, 140 F.3d at 1065 n.5.

111. *Id.* at 1076.

FDA's enforcement of its regulation exceeded its statutory authority.[112] The intervenor, Upjohn, was consequently found to have a right to intervene because, "a firm has constitutional standing to challenge a competitor's entry into its market."[113] This case demonstrates that an aggrieved ANDA, seeking to protect its position, cannot seek redress from the FDA.

In a similar case, *Mylan Pharmaceuticals, Inc. v. Shalala*,[114] Mylan brought a declaratory judgment action challenging the validity of the FDA's regulation governing when the 180-day period of market exclusivity begins.[115] In this case, it was Mylan that succeeded in defending a patent infringement action before its competitor but was second to have filed an ANDA containing a paragraph (IV) certification. At the time Mylan prevailed in the infringement litigation, its competitor was still defending a separate patent infringement action.[116] Mylan argued it was entitled to begin marketing and was entitled to a 180-day market exclusivity period as well.

Interestingly, Mylan took a diametrically opposed position in this litigation as compared to its position in the *Mova* case. This is because Mylan found itself in the position of having filed the second ANDA with a paragraph (IV) certification, unlike in the *Mova* case, where it sought to deny entry of the second filed ANDA holder in to the market. As in *Mova*, the District Court for the District of Columbia held that the FDA once again exceeded its statutory authority in interpreting its regulations.[117] Again, this shows the FDA regulations need clarification and unambiguous statutory direction.

In one of the first cases to directly challenge the propriety of an Orange Book listing of a patent, the FDA was allowed to reasonably rely on the submissions of the NDA holder when determining which patents are properly listed. In *Watson Pharmaceuticals, Inc. v. Henney*,[118] the NDA holder, Bristol-Meyers Squibb ("BMS") claimed that the listed patent at issue claimed "a method of using BuSpar® [the trade name of the drug at issue] for all of its approved uses."[119] A generic drug manufacturer, Danbury Pharmacal, Inc. ("Danbury"), challenged this listing because, according to Danbury, the patent at issue only claimed a metabolite of BuSpar® and not the drug itself.[120] The

112. *Id.*

113. *Id.* at 1074 (citing Ass'n of Data Processing Serv. Org., Inc. v. Camp, 397 U.S. 150, 152 (1970)).

114. 81 F. Supp. 2d 30 (D.D.C. 2000).

115. Mylan sought review of the FDA's interpretation of 21 C.F.R. § 314.107(e). *Mylan*, 81 F. Supp. 2d at 30. This issue centered on interpretation of the phrases "a court" and "the court" and its bearing on when a generic applicant's 180-day exclusivity period begins to run. *Id.* at 38-39.

116. *Id.* at 35.

117. *Id.* at 42.

118. 194 F. Supp. 2d 442 (D. Md. 2001).

119. *Id.* at 444.

120. *Id.*

FDA sought clarification from BMS. BMS responded that the patent covered both a method of using the metabolite and the basic drug itself.[121] So, at least here, there is a basic claim interpretation issue as opposed to the statutory and regulatory interpretation issues in the two previously discussed cases.

The court held that the FDA was justified in relying upon the assertions of BMS in maintaining the listing of the patent, thus avoiding the claim interpretation issue altogether.[122] The court sanctioned the FDA's "very limited, ministerial role" in listing patents in the Orange Book, finding that "patent infringement issues [should] play out in other, proper arenas."[123] This limited role has been subsequently upheld by higher courts.

In *Mylan Pharmaceuticals, Inc. v. Thompson*,[124] another generic manufacturer seeking to de-list the same patent at issue in *Watson* and manufacture a generic version of BuSpar®, filed suit in the District of Columbia. The district court granted relief, holding that Mylan was entitled to declaratory relief because the patent at issue was improperly listed in the Orange Book under the patent laws.[125] The Declaratory Judgment Act was also approved as a defense to the infringement suit BMS could have brought against Mylan under 35 U.S.C. § 271(e)(2).[126] The Federal Circuit, reversing the decision below, held that a private cause of action to de-list patents found in the Orange Book is not recognized under the Patent laws (Title 35) or the Food, Drug, and Cosmetics Act (Title 21).[127]

The Federal Circuit based its opinion on the lack of an explicit provision in the Hatch-Waxman Act either enabling or prohibiting a private cause of action to challenge a patentee's listing of a patent in the Orange Book.[128] The court found such an action to be "an impermissible attempt by a private party to enforce the FFDCA"[129] and further, that the Declaratory Judgment Act did not

121. *Id.*

122. *Id.* at 445.

123. *Watson*, 194 F. Supp. 2d at 445.

124. 268 F.3d 1323 (Fed. Cir. 2002).

125. *Id.* at 1325.

126. Mylan Pharm., Inc. v. Thompson, 139 F. Supp. 2d 1, 12-13. In this case, the facts are especially drastic. On the day BMS's one patent was set to expire, a day on which Mylan had manufactured and was prepared to ship its product, BMS listed the patent at issue, thereby triggering the duty of Mylan to make further certifications with respect to the newly listed patent. *Mylan*, 268 F.3d at 1327. This prompted Mylan to seek injunctive relief regarding this second patent. *See id.*

127. *Id.* at 1332-33.

128. *Id.*

129. *Id.* at 1330 (citing 21 U.S.C. § 337(a) and stating "[e]xcept as provided in subsection (b) of this section [regarding suits by states in their own names], all such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States.").

provide grounds to bring such suit either.[130] This case clearly closes the door on private causes of action to correct improper Orange Book listings.

BMS, although insulated from de-listing its patents, has been subject to antitrust lawsuits for its patent listing practice.[131] The plaintiffs in the antitrust action comprised, among others, generic drug manufacturers. Resolving improper listings by an antitrust cause of action is obviously costly for both the plaintiffs and certainly maintains the high cost of the drug at issue until the suit is resolved. Such antitrust cases clearly indicate the need for a private cause of action regarding Orange Book listings.

One other possible route that an aggrieved party could take, by utilizing the Administrative Procedure Act, has also been foreclosed. In *aaiPharma Inc. v. Thompson*, the Fourth Circuit held that the FDA does not violate that Administrative Procedure Act by taking a "purely ministerial" role in Orange Book listings.[132] In an interesting twist, the plaintiff, aaiPharma, sought to have its patent listed in the Orange Book along with the NDA holder's patents.[133] After approaching the NDA holder with such a request, and being rebuffed, aaiPharma approached the FDA, which also refused to list the patent.[134] aaiPharma wanted such patent listed to prevent other generic manufacturers from entering the market.

The cases discussed above demonstrate that there are many aggrieved parties with respect to Orange Book listings. The cases also reveal that these parties have been met with resistance in attempting to correct what they feel is an inequitable wrong. The courts, on the one hand, seem to have sided with the branded drug manufacturers, but on the other hand, they have articulated that that they are bound by the clear language Congress used in the Hatch-Waxman Act. Patentees should always be able to extract the entirety of their legal monopoly from a patent. They should not, however, have unchecked abilities that allow for inequitable extension of the rights conferred under the patent laws. The story of one drug, gabapentin hydrochloride, set forth below, is particularly helpful in exposing some of the shortcomings of the Hatch-Waxman Act.

130. *Mylan*, 268 F.3d at 1330. *See also* Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368 (Fed. Cir. 2002) (holding that a generic drug manufacturer cannot bring a declaratory judgment action or an injunctive action against a NDA holder under the Hatch-Waxman provisions of the FDCA or the patent laws requiring it to de-list a patent from the Orange Book).

131. *See In re* Buspirone Patent Litigation, 185 F. Supp. 2d 363 (S.D.N.Y. 2002) (holding that BMS was not entitled to *Noerr-Pennington* immunity against claims arising out of its allegedly fraudulent listing of its patents in the Orange Book).

132. 296 F.3d 227, 230 (4th Cir. 2002).

133. *Id.* at 233.

134. *Id.*

III. THE SAGA OF GABAPENTIN HYDROCHLORIDE

The saga of Neurontin® began some time ago. Before diving into this history, it is helpful to review some practices common in the medical and pharmaceutical industries that underscore the deficiencies of the Act. In particular, the ability of doctors to prescribe "off-label" use for prescription medication is what drives the story behind Neurontin®.

Under the FDCA,[135] new pharmaceutical drugs cannot be distributed in interstate commerce unless the manufacturer of the drug demonstrates to the FDA that the drug is safe and effective for a particular and intended use.[136] When a drug is approved for a single use, however, the FDA will not prevent a doctor from prescribing that drug for uses other than the FDA-approved use.[137] Allowing physicians "to prescribe drugs for such 'off-label' usage 'is an accepted and necessary corollary of the FDA's mission to regulate [pharmaceuticals] without directly interfering with the practice of medicine."[138]

The difficulty arises because, although the FDA allows physicians to prescribe drugs for off-label uses, it does not allow manufacturers, generic or branded, *to market or promote* drugs for off-label uses.[139] The governing statute expressly prohibits distribution of a drug for non-approved uses[140] and distribution of "misbranded" drug.[141] A "misbranded" drug is a drug for which the manufacturer has included on the label non-FDA-approved uses. For example, if the drug Neurontin® is only approved for the treatment of epilepsy (which it was for a long while), the label cannot suggest or instruct that it may be used to treat bi-polar disorder. Simply including information on a drug's label about an "off-label" use will result in "misbranding."[142] A manufacturer wishing to promote a drug for an "off label" use must submit materials to the FDA where they undergo rigorous review. If the manufacturer wants the drug to be labeled for this new usage, then the manufacturer must submit the safety and efficacy tests that were required for the first use.[143]

Drug companies may seek wide-spread use of a drug for all purposes, both labeled and "off-label." A labeled use is valuable because FDA approval largely determines whether a prescription for that drug will be reimbursed

135. See *supra* note 3, at § 301-397.

136. *See* 21 U.S.C. § 355(a) & (d) (2000).

137. United States *ex rel.* Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 44 (D. Mass. 2001) (citing Buckman Co. v. Plaintiff's Legal Comm., 531 U.S. 341, 350 (2001)).

138. *Id.*

139. 21 U.S.C. § 355(d).

140. *Id.*

141. 21 U.S.C. § 355(a).

142. *See* Washington Legal Found. v. Henney, 202 F.3d 331, 333 (D.C. Cir. 2000).

143. *See id.* at 334 (setting forth the requirements of the Food and Drug Administration Modernization Act of 1997, 21 U.S.C. § 360aaa, *et seq.*).

under the federal Medicaid program.[144] However, as seen in the case of Neurontin®, off-label sales may form the bulk of a drug's sale.

A. Background of Neurontin®

Neurontin® is the brand name for a drug having gabapentin as the active ingredient. The drug was first approved for use in 1993 as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy in doses from 900 to 1,800 mg per day. Since its introduction and first approval, Neurontin® has been prescribed for many off-label uses. The approved usage, however, remained solely for the treatment of epilepsy until mid-2002 when the FDA approved Neurontin® for postherpetic neuralgia.[145] These uses range from pain control, as mono-therapy for epilepsy, for control of bipolar disorder, and as a treatment for attention deficit disorder. The drug was brought to market by the pharmaceutical company Parke-Davis. Parke-Davis later became the pharmaceutical products division of the Warner-Lambert Company. To complete the large-fish-eat-smaller-fish trend, Warner-Lambert, including the Parke-Davis division, was acquired by Pfizer, Inc., another pharmaceutical manufacturer. Pfizer, however, has stayed above the fray and has taken the position that it is only cleaning up the mess, if any, that its predecessors-in-interest wrought.

B. Opinions Involving Neurontin®

There are now more than twenty reported cases that mention the drug Neurontin®. Not all of these involve Orange Book listings. Many involve long lists of medications that litigants were taking with such causes of action sounding in personal injury torts or denial of governmental assistance with the purchase of medication. The remainder of the suits, the focus of this section, are exemplary of the problems inherent in the Hatch-Waxman Act. As an overview, it is helpful to know that Neurontin® has received two "30-month stays" for a total length of fifty-three months, with the second stay beginning at the twenty-third month of the first stay.[146] It is important to note is that generic manufacturers did not immediately attempt to enter the market, i.e., challenge

144. Medicaid is, in most circumstances, available only for "covered outpatient drugs." 42 U.S.C. § 1396b(i)(10) (2000). Covered outpatient drugs do not include drugs that are "used for a medical indication which is not a medically accepted indication." 42 U.S.C. § 1396r-8(k)(3). A medically accepted indication, in turn, includes a use "which is approved under the Federal Food Drug and Cosmetic Act" or which is included in specified drug compendia. 42 U.S.C. § 1396r-8(k)(6). *See also* 42 U.S.C. § 1396r-8(g)(1)(B)(i) (identifying compendia to be consulted).

145. This particular use is protected by a three-year, non-patent market exclusivity conferred by a provision of the Hatch-Waxman Act. Those provisions are not relevant to this article. *See* Purepac Pharms., Inc. v. Thompson, 238 F. Supp. 2d 191 (D.D.C. 2002).

146. *See* FTC Study, *supra* note 63, at 49.

the composition and approved use patents, the first listed patents. It was only when a later-issued patent was listed in the Orange Book did litigation ensue.

In an attempt to make sense of the tangled web Neurontin® has weaved in both the courts and the FDA, the cases are discussed below to provide a broad picture of the system and its failures, for both branded and generic drug manufacturers and the public.

1. Purepac and Apotex - The Generic's Perspective

On January 16, 2003, the United States Court of Appeals for the Federal Circuit held that it is not an act of infringement for a drug manufacturer to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved by the FDA under an NDA.[147] This is a mouthful, but the upshot is that a new drug applicant, having received approval for a particular use of a drug, cannot use the rights conferred under 35 U.S.C. § 271(e)(2)(A) to subject an abbreviated new drug applicant to infringement liability or to extend their exclusivity afforded by their patents when the new drug applicant's listed patents claim a use *different* from the use for which the abbreviated new drug applicant seeks approval. Surprisingly, this simple concept wound up before the Federal Circuit.

In *Warner-Lambert Company v. Apotex Corporation*,[148] the assignee of United States Patent 5,084,479 ("the '479 patent" or "the neurodegenerative patent"),[149] entitled "Novel Methods for Treating Neurodegenerative Diseases," the Warner-Lambert Company ("Warner-Lambert") filed an infringement action against Apotex Corporation, Apotex, Inc., and TorPharm, Inc. (collectively "Apotex"). The '479 patent claims the use of certain cyclic amino acid compounds, as well as the salts and esters derived from them, for the treatment of neurodegenerative diseases such as stroke, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, and Parkinson's disease.[150] One of these cyclic amino acid compounds, 1-aminomethyl-1-

147. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348 (Fed. Cir. 2003).

148. 316 F.3d 1348 (Fed. Cir. 2003).

149. The "'479 patent" is set to expire in January of 2010. *Id.* at 1361.

150. Claim 1, the only independent claim in the "'479 patent", defines the invention as follows:

> 1. A method for treating neurodegenerative diseases which comprises administering a therapeutically effective amount of a compound of formula
>
> $$H_2N—CH_2—\underset{(CH_2)}{C}—CH_2—COOR_1$$
>
> wherein R_1 is hydrogen or a lower alkyl and n is 4, 5, or 6 or pharmaceutically acceptable salt thereof, in unit dosage form, to a mammal in need of said treatment.

Id. at 1351.

cyclohexane acetic acid is commonly known as "gabapentin." Gabapentin is what this, and the subsequently discussed cases, concern.

Warner-Lambert is also the assignee of expired U.S. Patent 4,024,175, expired U.S Patent 4,087,544, and U.S. Patent 4,894,476. The '175 patent (the "product patent"), entitled "Cyclic Amino Acids," disclosed and claimed the actual compounds that are used in the methods claimed in the neurodegenerative method patent; claim 2 specifically claimed 1-aminomethyl-1-cyclohexane acetic acid (i.e., gabapentin). The '544 patent ("the epilepsy method"), entitled "Treatments of Cranial Dysfunctions using Novel Cyclic Amino Acids," disclosed and claimed a method of treating certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas using the cyclic amino acid compounds claimed in the product patent and used in the methods of the neurodegenerative method patent, again including gabapentin. The '476 patent (the "monohydrate patent"), entitled "Gabapentin Monohydrate and a Process for Producing the Same," claims a specific crystalline form of gabapentin monohydrate. [151] It is the listing of these patents, and in particular the '479 neurodegenerative patent, in the Orange Book that gives rise to the suits discussed herein.

On April 17, 1998 Apotex filed an Abbreviated New Drug Application under the Hatch-Waxman Act seeking approval for a generic formulation to treat epilepsy upon the expiration of the epilepsy method patent on January 16, 2000. Apotex sought FDA approval to market gabapentin only for the same use or "indication" for which it was approved under Warner-Lambert's NDA, i.e., for "adjunctive therapy in the treatment of partial seizures without secondary generalization in adults with epilepsy." Under the Act, Apotex could seek approval only for previously approved uses.[152]

With its ANDA, Apotex submitted the required bioavailability/bioequivalence test data and a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("the paragraph (IV) certification") declaring that its proposed manufacture, use, and sale of gabapentin would not infringe either the monohydrate patent or the neurodegenerative method patent.[153] Apotex stated that its formulation would be anhydrous (i.e., would not contain water), and would, "accordingly, be outside the scope of the monohydrate patent."[154] Importantly, Apotex declared that its "pharmaceutical product's labeling does not include any indication for use in the treatment of either neurodegenerative method patent."[155] Apotex argued that because all of the claims of the neurodegenerative method patent "are directed to a use of gabapentin in the

151. *Id.* at 1352 (recounting the coverage of Warner-Lambert's related patents).

152. 21 U.S.C. § 355(j)(2)(A)(i) (2000).

153. *Warner-Lambert*, 316 F.3d at 1352.

154. *Id.*

155. *Id.*

treatment of neurodegenerative diseases," Apotex's manufacture, use, or sale of its gabapentin products for the treatment of epilepsy would not infringe the neurodegenerative method patent.[156] It is important to note that the treatment of epilepsy is not the treatment of neurodegenerative diseases.

An ANDA who files a paragraph (IV) certification must, under 21 U.S.C. § 355(j)(2)(B)(i), include in its application a statement that it will give notice of that filing to the owner of the patent to which the certification pertains[157] and to the holder of the approved NDA for that drug.[158] Pursuant to this duty, Apotex notified Warner-Lambert that it had filed the ANDA and paragraph (IV) certification.[159] In addition, and as required by statute, Apotex included in its notice letter a detailed statement of the factual and legal basis for its opinion of non-infringement of the neurodegenerative method patent.[160] This letter explained that the use for which Apotex sought approval is for the treatment of partial seizure and the '479 neurodegenerative patent does not claim a method of using gabapentin and its derivatives for partial seizure.[161] Apotex's argument was simple, because the '479 patent claims are directed to "a method of using gabapentin and its derivatives in the treatment of neurodegenerative disease," the product marketed by Apotex would "not fall within the scope of any of the claims of the . . . '479 patent."[162]

In response to Apotex's ANDA filing, Warner-Lambert filed an infringement action on July 14, 1998, alleging that Apotex's submission of its ANDA was an act of infringement of the neurodegenerative method patent under 35 U.S.C. § 271(e)(2)(A).[163] Despite the fact that the FDA had not approved gabapentin for any of the indications claimed in the neurodegenerative method patent, and FDA regulations forbid the promotion of unapproved uses by NDA or ANDA holders,[164] Warner-Lambert argued that "patients will use the Apotex Defendants' gabapentin for all purposes for which Neurontin® product has been and customarily is used, and doctors will prescribe the Apotex Defendants' gabapentin product for such uses, including the treatment of neurodegenerative diseases."[165]

156. *Id.*

157. 21 U.S.C. § 355(j)(2)(B)(i)(I) (2000).

158. 21 U.S.C. § 355(j)(2)(B)(i)(II) (2000).

159. *Warner-Lambert*, 316 F.3d at 1352-53.

160. *Id.* at 1353.

161. *Id.*

162. *Id.*

163. Warner-Lambert also included a claim under the monohydrate patent. The district court granted summary judgment of non-infringement with respect to the patent on March 2, 2001. Warner-Lambert Co. v. Apotex Corp., No. 98 C 4293, Doc. No. 67 (N.D. Ill. Mar. 2, 2001). Warner-Lambert did not appeal this judgment.

164. *See* 21 C.F.R. § 202.1(e)(4) (1998).

165. *Warner-Lambert*, 316 F.3d at 1353.

Apotex moved for summary judgment. Warner-Lambert countered by arguing that (1) the FDA does not regulate the uses for which doctors prescribe drugs once they are approved, (2) "more than three-quarters of the prescriptions written by doctors for Warner-Lambert's Neurontin® are for indications other than epilepsy, including the treatment of neurodegenerative diseases," and (3) "doctors, managed care organizations, and other institutions commonly and routinely substitute generic drugs for all indications for which the brand name drug is used."[166] Warner-Lambert further argued that Apotex knows, and even expects, that its generic gabapentin, if approved by the FDA, "will be prescribed by doctors for all the same reasons they prescribe Neurontin®," including "the treatment of . . . neurodegenerative diseases."[167] The district court denied Apotex's motion.[168] At the close of discovery, Apotex again moved for summary judgment. The district court granted this second motion.[169] Warner-Lambert appealed this decision.

On appeal, the Federal Circuit framed the issue as whether it is an act of infringement under the applicable statute, 35 U.S.C. § 271(e)(2),[170] "to submit an ANDA seeking approval to make, use, or sell a drug for an approved use if any other use of the drug is claimed in a patent, or if it is only an act of infringement to submit an ANDA seeking approval to make, use, or sell a drug if the drug or the use *for which FDA approval is sought* is claimed in a patent."[171] The issue was recognized as one of first impression for the court.[172] The court held that "it is not an act of infringement to submit an ANDA for approval to market a drug for a use when neither the drug nor that use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA."[173]

166. *Id.* (citing Warner-Lambert's "Memorandum in Opposition to Aptoex's Motion for Summary Judgment" at 20 (filed December 10, 1998)).

167. *Id.*

168. Warner-Lambert Co. v. Apotex Corp., No. 98 C 4293, 1999 WL 259946 (N.D. Ill. Apr. 8, 1999).

169. Warner-Lambert Co. v. Apotex Corp., No. 98 C 4293, 2001 WL 1104618 (N.D. Ill. Sept. 14, 2001).

170. 35 U.S.C. § 271(e)(2) (2000) provides:

> It shall be an act of infringement to submit – (A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act [codified at 21 U.S.C. §355(j); i.e., and ANDA] . . . for a drug claimed in a patent, . . . if the purpose of such submission is to obtain approval under such Act [i.e., Title 21 of the United States Code] to engage in the commercial manufacturer, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

35 U.S.C. § 271(e)(2) (2000).

171. *Warner-Lambert Co.*, 316 F.3d at 1354.

172. *Id.*

173. *Id.*

The court accepted Apotex's argument that because an ANDA may not seek approval for an unapproved or off-label use of a drug under 21 U.S.C. § 355(j)(2)(A)(i), "it necessarily follows that 35 U.S.C. [§] 271(e)(2)(A) does not apply to a use patent claiming only such a use."[174] The court emphasized that the infringement mechanisms provided by 35 U.S.C. 271(e)(2) may only be used against an ANDA when the NDA's listed patents claim "*the* use" for which the NDA is seeking approval.[175] In addition, the court noted that "[t]he FDA does not grant across-the-board approval to market a drug."[176] Rather, the agency grants approval to make, use, and sell a drug for a specific purpose for which that drug has been demonstrated to be safe and efficacious.[177]

Warner-Lambert argued that Apotex was required to submit a certification under one of the paragraphs of 21 U.S.C. § 355(j)(2)(A)(vii)[178] with respect to the '479 neurodegenerative patent because that patent was listed in the Orange Book.[179] The court noted that such certification need only be made when the listed patent "claims a use for such listed drugs for which the applicant is seeking approval . . . ."[180] Apotex did, in fact, file such certification, labeled as a paragraph (IV) certification, stating that it is not applying for approval to market the drug for a non-approved use.[181] Indeed, Apotex's action is consistent with the statute because an ANDA may not obtain approval to market the drug for a non-approved use without filing its own NDA with full safety and efficacy data. The Federal Circuit, however, noted that Apotex's paragraph (IV) certification was essentially a statement of non-applicable use pursuant to 21 U.S.C. § 355(j)(2)(A)(viii), a "section (viii) statement."[182] This is remarkable because Apotex's competitor, Purepac, did just that and met with considerably less success than Apotex. In fact, Purepac's decision to make such a statement cost it its priority and rights as the first to file an ANDA, discussed below.[183] Despite the removal of the '479 patent from the thicket of

174. *Id.* at 1356.

175. *Id.*

176. *Warner-Lambert*, 316 F.3d at 1356.

177. *Id.*

178. *See supra* note 39, at 28,908.

179. *Warner-Lambert*, 316 F.3d at 1360.

180. *Id.* at 1360 (emphasis removed) (quoting 21 U.S.C. § 355(j)(2)(A)(vii)).

181. *Id.* at 1352.

182. *Id.* at 1362. *See supra* note 65, at § 355(j)(2)(A)(viii) for a discussion of a "section (viii) statement."

183. The Federal Circuit also held that Apotex would not induce infringement of the '479 patent under 35 U.S.C. § 271(b). *Warner-Lambert*, 316 F.3d at 1363. Warner-Lambert argued that because by 1998 only 22% of the Neurontin® prescriptions were for the treatment of epilepsy, the remaining 78% were being prescribed for off-label uses, including the infringing use of treating neurodegenerative diseases. *Id.* Warner-Lambert added that by 1999, the percentage of uses other than to treat epilepsy had risen to 89%. *Id.* Additionally, Warner-Lambert argued that:

potential protection, Pfizer stated that the introduction of generic gabapentin would not change.[184]

About a month before Federal Circuit rendered its decision in *Warner-Lambert, Inc. v. Apotex, Inc.*, the United States District Court, District of Columbia, dealt a fatal blow to the ANDA of Apotex's competitor, Purepac Pharmaceutical ("Purepac"), and its effort to obtain FDA approval to market gabapentin. In *Purepac Pharmaceuticals Co. v. Thompson*,[185] the Court rebuffed Purepac's motion for a preliminary injunction seeking to require the FDA to accept, and thus approve, Purepac's ANDA seeking to market a generic version of gabapentin "for the treatment of epilepsy."[186] Purepac also

> (1) it is common knowledge to many in and out of the pharmaceutical field that physicians routinely prescribe approved drugs for purposes other than those listed on the drugs' labels; indeed, such off-label use is supported by both the FDA and the American Medical Association, (2) information regarding both on- and off-label prescriptions is readily available to the public from publications and databases to which most pharmaceutical companies subscribe, (3) "pharmacists and other drug dispensing organizations . . . commonly substitute generic drugs for name brand drugs wherever possible – unless specifically instructed otherwise by the physician writing the prescription," and, "in many states, substitution is mandatory," and (4) Apotex expects to get an "A-B rating" for its gabapentin, which would allow physicians and pharmacists to substitute generic gabapentin for Neurontin® regardless of the indication for which it is to be used, and (5) Apotex should be assumed to have considered the market size and growth potential of gabapentin when it made the strategic decision to file an ANDA and enter the gabapentin market.

See id. at 1364. Essentially, Warner-Lambert is arguing that Apotex is going for the "off-label" market and not the epilepsy treatment market. *Id.* The Court rejected Warner-Lambert's arguments, reasoning that even if Apotex knew that doctors could prescribe gabapentin for possibly infringing uses, the "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must be proven." *Warner-Lambert*, 316 F.3d at 1364 (citing Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 554 (Fed. Cir. 1990)). Apparently Warner-Lambert did not present the requisite evidence. *Id.*

184. Pfizer's January 16, 2003 press release, released the same day as the Federal Circuit's opinion, stated that:

> Today's Appellate Court decision concerning the Neurontin '479 neurodegenerative disease patent has no bearing on the likelihood or timing for the entry of generic gabapentin. Pfizer continues to believe that the likelihood and timing of generic entry will depend on FDA decisions regarding approval of generic applications and ultimately on the outcome of the litigation relating to its '482 patent. Today's court decision does not affect the status of the litigation on the '482 patent.

Press Release Pfizer (Jan. 16, 2003), *available at* http://www.pfizer.com/are/news_releases/mn_2003_0116.html. Warner-Lambert is currently defending an infringement action related to the claims of the '482 patent. *See supra* note 136, at § 355(d).

185. Purepac Pharm., Co. v. Thompson, 238 F. Supp. 2d 191 (D.D.C. 2002).

186. *Id.* at 195.

sought, unsuccessfully, to prevent the ANDA's of its competitors, including Apotex, from being approved by the FDA.[187]

In *Purepac Pharmaceutical Co. v. Thompson*, Purepac, a generic drug manufacturer, sought FDA approval to sell gabapentin only for the treatment of epilepsy, *and no other use*.[188] This is consistent with the regulations and statutes because, as discussed above, an ANDA can only seek approval for a use already approved under a NDA.

Purepac, in preparing its ANDA, reviewed the same Orange Book-listed patents as those Apotex reviewed. Purepac, however, decided to submit *only a section (viii) statement* with respect to the '479 patent, as opposed to the strategy adopted by Apotex, which submitted *both a section (viii) statement and a paragraph (IV) certification*.[189] The paragraph (IV) statement submitted by Apotex, according to the Federal Circuit, "although formally labeled as a 'paragraph IV certification,' . . . with respect to the neurodegenerative method patent [it] was effectively a statement of non-applicable use pursuant to 21 U.S.C. § 355(j)(2)(A)(viii)."[190] Thus, faced with a use patent that claims a non-approved use, one generic filed a paragraph (IV) statement (which the Federal Court said was technically a section (viii) statement) while another filed a section (viii) statement. The District Court for the District of Columbia, of course not having the Federal Circuit's opinion before it, was asked to enjoin the FDA from approving Apotex's ANDA and to determine whether the FDA's denial of Purepac's ANDA, containing only a section (viii) statement, violated the Administrative Procedure Act.[191] Purepac was ultimately denied relief by the court.

This all began in March 1998 when Purepac filed an ANDA with the FDA seeking approval to market generic versions of gabapentin tablets and capsules for the treatment of epilepsy.[192] With its ANDA, Purepac submitted patent declarations with respect to the patents listed by Warner-Lambert.[193] Purepac submitted a paragraph (III) certification with respect to the '544 epilepsy method patent as it was set to expire on July 16, 2000.[194] Purepac submitted paragraph (IV) certifications for the '476 monohydrate and the '482 patents.[195] In contrast to these statements, and pertinent to this review, Purepac submitted a section (viii) statement with respect to the '479 neurodegenerative disease

187. *Id.*

188. *Id.*

189. *See Warner-Lambert*, 316 F.3d at 1360; *Purepac*, 238 F. Supp. 2d at 200 n.13.

190. *Warner-Lambert*, 316 F.3d at 1360.

191. *See* 5 U.S.C. § 706 (2000).

192. *Purepac*, 238 F. Supp. 2d at 198.

193. *Id.* at 199.

194. When the '544 patent expired, it was removed from the Orange Book. *See id.* at 198 n.9.

195. U.S. Pat. No. 6,054,482 (issued Apr. 25, 2000). The claims are not relevant to Purepac's ANDA. *Purepac*, 238 F. Supp. 2d at 197 n.7.

patent. Purepac defended its submission of a section (viii) statement with respect to the '479 by asserting that, based on Warner-Lambert's submissions to the FDA[196] and the FDA's use code assigned to the '479 patent,[197] the '479 patent claimed the use of gabapentin to treat neurodegenerative diseases. Because its ANDA was seeking approval to market gabapentin to treat epilepsy, Purepac "concluded that a section (viii) statement was appropriate."[198]

Purepac defended its use of a section (viii) statement in a March 5, 1999 letter to the FDA.[199] In this letter, Purepac argues that a section (viii) statement is proper, and that a paragraph (IV) certification is improper, because "the '479 patent is a method of use patent covering an indication which is not present in the innovator's [Warner-Lambert's] approved labeling."[200] The FDA responded by stating that it was not the agency's duty to correct information in Orange Book listings and informed Purepac of its right to use 21 C.F.R. § 314.53(f) to challenge Warner-Lambert's submission of the '479 patent for inclusion in the Orange Book.[201] Interestingly, the FDA's letter indicated that it had contacted Warner-Lambert's patent attorney, who, incidentally, verified the propriety of the '479 patent's listing in the Orange Book. Based on this, the FDA concluded that it could not confirm that the use of a section (viii) statement was proper. To recapitulate, although Warner-Lambert had affirmatively stated that the '479 patent only claims the use of Neurontin® to treat neurodegenerative disease, coupled with the fact that the FDA gave the '479 patent a use code different from the approved use, the FDA still would accept Purepac's section (viii) statement simply because Warner-

196. During the NDA process, Warner-Lambert declared at least twice that the '479 patent claims a method for treating neurodegenerative diseases. *Warner-Lambert*, 316 F.3d at 1352. In other statements, Warner-Lambert declared that "the '479 patent, the '544 patent, and the '476 patent together 'cover the composition, formulation and/or method use of Neurontin®.'" *Purepac*, 238 F. Supp. 2d at 198. Warner-Lambert did not, however, specify if they were asserting any particular use. *Id.* at 198 n.10.

197. When patents are submitted to the FDA for Orange Book listing the FDA assigns "use codes" to the patents. *Id.* at 198. The codes "allow interested parties, including ANDA applicants, to determine the particular medical uses of brand-name drugs asserted by the various use patents listed in the Orange Book." *Id.* *See also* Abbreviated New Drug Application Regulations; Patent & Exclusivity Provisions, 59 Fed. Reg., *supra* note 33, at 50,346 ("In addition for a use patent, FDA includes in the Orange Book a code identifying the indication covered by the patent.").

198. *Purepac*, 238 F. Supp. 2d at 199.

199. *Id.*

200. *Id*.

201. *Id.* 21 C.F.R. § 314.53(f) is discussed in Section IV, infra. Purepac, at oral argument, stated that it chose not to invoke 21 C.F.R. § 314.53(f) because it had no dispute over Warner-Lambert's listing of the patent since neither company treated the '470 patent as claming the use of treating epilepsy. *Id.* In hindsight, it is apparent that Purepac should have attempted to invoke this regulatory measure. *Purepac*, 238 F. Supp. 2d at 199.

Lambert maintained its listing in the Orange Book. Essentially, through additional letters to Purepac, the FDA took the position that if a party lists a patent in the Orange Book and there is only one approved use, any use patents listed must somehow claim that use (otherwise that party would be improperly listing a patent).

Ultimately, the FDA resolved that if Purepac wanted its ANDA approved, it had to submit a paragraph (IV) certification, and thus, expose itself to infringement liability and suffer the consequences of a 30-month stay.[202] Purepac knew that Warner-Lambert would not hesitate to bring suit under 35 U.S.C. § 271(e) as Warner-Lambert had already brought suit against Purepac and Apotex for paragraph (IV) statements regarding patents other than the '479 patent, the Orange Book listing of which is not questioned. Thus, the FDA refused to approve Purepac's ANDA without a paragraph (IV) statement regarding the '479 patent.[203]

Meanwhile, Purepac's competitor, Apotex, had submitted an ANDA containing both a paragraph (IV) and a section (viii) statement with respect to the '479 patent. Although Apotex was the second company to file an ANDA seeking to market gabapentin,[204] it was the first to file an ANDA containing a paragraph (IV) certification with respect to the '479 patent (making it eligible for the 180-day market exclusivity period and making it liable for an infringement action). As discussed above, Warner-Lambert did bring suit against Apotex. The Federal Circuit ultimately held that Apotex's paragraph (IV) certification was, in essence, the same as a section (viii) statement, and that Warner-Lambert did not have a cause of action against Apotex under 35 U.S.C. 271(e)(2).[205]

In related litigation, Warner-Lambert had already brought suit against Purepac in two separate actions in New Jersey. Inexplicably, one action was based on Purepac's section (viii) statement with respect to the '479 patent (recall, a section (viii) statement does not give rise to a cause of action, a paragraph (IV) certification is a condition precedent to any such suit). The other action was based on the '476 patent, for which Purepac had filed a paragraph (IV) certification. In addition, Warner-Lambert brought an infringement action against Purepac for its paragraph (IV) certification with respect to the '482 patent as well. In light of this litigation, it is reasonable for Purepac to want to avoid additional litigation by simply supplying a section (viii) statement with its ANDA with respect to the '479 patent.

202. *Id.*

203. *Id.*

204. Apotex's application was filed April 17, 1998. *Id.* at 200. Purepac's application, containing the section (viii) statement was filed March 1998. *Id.* at 198.

205. Warner-Lambert also brought a Section 271(e)(2) infringement action against Apotex for its filing of an ANDA containing a paragraph (IV) certification with respect to the '482 patent. Warner-Lambert Co. v. Apotex Corp., 316 F.3d 1348, 1354 (Fed. Cir. 2003).

Purepac, faced with the FDA approving Apotex's ANDA after the stay was lifted in that action, brought suit against the FDA seeking to enjoin it from acting on Apotex's application and seeking an order directing the FDA to approve its application.[206] The court ultimately refused to enjoin the FDA from acting on Apotex's application.[207] With the resolution of Warner-Lambert's suit against Apotex, as resolved by the Federal Circuit, the FDA will likely approve Apotex's ANDA for gabapentin unless Warner-Lambert successfully appeals to the United States Supreme Court. Thus, Purepac's decision to submit a section (viii) statement, *instead of a paragraph (IV) certification*, will likely result in the approval of its competitor's ANDA before its own, resulting in loss of the 180-day market exclusivity period. This is Purepac's lot, despite the Federal Circuit, one month later, holding that the Apotex's paragraph (IV) certification was essentially a section (viii) statement and that Warner-Lambert did not have a cause of action against an ANDA submitting a section (viii) statement with respect to the '479 patent.

For the sake of resolution, it should be noted that the district court deciding Purepac's fate held that the FDA had no rational basis for denying Purepac's ANDA for gabapentin because of their inclusion of the section (viii) statement.[208] The court stated that the FDA's position that the '479 patent claims the use of treating epilepsy, simply because it is listed in the Orange Book for a drug that had only one approved use (treating epilepsy) could not stand.[209] The FDA, throughout the controversy, insisted that the issue concerned the '479 patent claims, and that it was not equipped to make such determinations.[210] The FDA, in fact, has specifically disclaimed any role in determining what uses a particular patent claims.[211]

The agency's "self-abnegation" creates a possible conflict between NDA holders and ANDA applicants over the proper scope of a use patent. Essentially the facts would be similar to that surrounding Purepac's ANDA for gabapentin. The NDA would list various patents in the Orange Book, including composition, formulation, and use patents. The use patents listed would include both approved and non-approved uses. If there was only one approved use, the FDA (or some other arbitrator, e.g., the courts) would then

206. *Purepac*, 238 F. Supp. 2d at 201.

207. *Id.* at 211.

208. *Id.* at 204.

209. *Id.* at 205.

210. *Id.*

211. *Purepac*, 238 F. Supp. 2d at 204. *See also* Abbreviated New Drug Application Regulations; Patent & Exclusivity Provisions, 59 Fed. Reg., *supra* note 33, at 50,345 (the "FDA does not have the resources to review patent information for its accuracy and relevance to an NDA."); Abbreviated New Drug Application Regulations, 54 Fed. Reg. *supra* note 33, at 28,909 ("Because the FDA has no experience in the field of patents, the agency has no basis for determining whether a use patent covers the use sought by the generic applicant.").

have to determine whether the listed use patents claimed the approved use. The FDA has long taken the position that it does not want this job.[212] The courts have upheld the FDA as taking a "purely ministerial" role.[213] The resulting situation, however, is that a generic manufacturer, making an absolutely proper section (viii) statement, can lose its priority to a subsequent ANDA by the competitor taking the risk to file the first paragraph (IV) certification.

2. Neurontin® in Other Cases

There are a total of twenty-five published cases mentioning Neurontin®. Six of these involve Warner-Lambert's Orange Book listings. There are the suits brought against Apotex and Purepac, the district court decisions and the Federal Circuit decision. The majority of these cases, sixteen, are cases involving individuals bringing suit for various causes of action against the Commissioner of Social Security and other government agency heads in order to receive Neurontin® as a prescription drug. These cases do not involve the Orange Book listings. Two other cases are worth mentioning, as is a recently coordinated multidistrict litigation antitrust action.

In the antitrust litigation,[214] seventeen antitrust actions pending in six districts were transferred to a single district in the District of New Jersey.[215] All of the actions are purported class actions alleging that Warner-Lambert Co., and its parent, Pfizer, Inc., violated antitrust laws and excluded generic competition for gabapentin by "bringing sham patent infringement actions against a number of generic drug manufacturers."[216] A number of the underlying plaintiffs are organizations that pay for prescription drugs.[217] As the antitrust suit continues to play out, it will, undoubtedly, look to the various decisions involving Orange Book listings by Warner-Lambert. The use of antitrust law is certainly one way that potential inequitable results brought about by improper Orange Book listings could be remedied. It is, however,

212. Abbreviated New Drug Application Regulations; Patent & Exclusivity Provisions, 59 Fed. Reg., *supra* note 33, at 50,348 (October 3, 1994).

213. *See* aaiPharma Inc. v. Thompson, 296 F.3d 227, 243 (4th Cir. 2002) (upholding the FDA's "purely ministerial approach to the Orange Book listing process.").

214. *See In re* Neurontin Antitrust Litig., 217 F. Supp. 2d 1380 (Judicial Panel on Multidistrict Litigation) for the latest order consolidating seventeen antitrust actions pending in six districts.

215. The case consolidated seven actions in the Southern District of New York, five actions in the District of New Jersey, two actions in the Eastern District of Pennsylvania, and one each in the Northern District of California, the Eastern District of Michigan, and the Eastern District of New York. *Id.*

216. *Id.*

217. Some of the plaintiffs include: Louisiana Wholesale Drug Company, Inc., Health & Benefit Trust Fund of the International Union of Operating Engineers Local Union 94, and Action Alliance of Senior Citizens of Greater Philadelphia. *Id.* at 1381-82.

only partially satisfactory because it would still allow a company to list the patents in the first place, thus causing unneeded patent litigation.

The remaining two cases involve a former Parke-Davis employee who brought a qui tam action against his former employer. In *United States ex rel. Franklin v. Parke-Davis*[218] the qui tam relator brought an action under the False Claims Act ("FCA")[219] against Parke-Davis alleging, inter alia, that Parke-Davis engaged in a fraudulent scheme to promote sale of drugs for "off-label" uses and that the illegal marketing campaign caused the submission of false claims to the Veteran's Administration and to the federal government for Medicaid reimbursement.[220] This case is still pending, but from it, two published opinions have issued.[221]

In these two opinions, the relator, Dr. David Franklin, alleges that Parke-Davis engaged in a fraudulent scheme to promote the sale of Neurontin® for "off-label" uses. Dr. Franklin[222] conveys the tale as a Parke-Davis employee over the entire five months he worked as a "medical liaison" in 1996.[223] Dr. Franklin alleges that despite Neurontin® being solely approved for the treatment of epilepsy in doses from 900 to 1,800 mg per day, Parke-Davis instructed its medical liaisons to make exaggerated or false-claims concerning the safety and efficacy of Neurontin® for "off-label" uses.[224] The liaisons, allegedly, were instructed to convey that Neurontin® could be prescribed for various off-label uses in amounts up to 4,800 mg per day.[225] Parke-Davis also allegedly instructed doctors on how to receive government reimbursement for prescriptions written for off-label uses and gave illegal "kickbacks" to doctors in forms varying from sums of money for "drug studies" and for their services as "consultants" or "preceptors."[226] Dr. Franklin's nine-count *qui tam* action remained filed under seal for almost five years before the United States finally decided to participate, but only in the capacity of *amicus curiae*.[227] At this point in the litigation, the claims regarding Neurontin® survived motions to dismiss for failure to plead the fraud aspects with the requisite particularity.[228]

218. There are two reported decisions in this case, 147 F. Supp. 2d 39 (D. Mass. 2001); and 210 F.R.D. 257 (D. Mass. 2002).

219. 31 U.S.C. § 3729-33 (2000).

220. United States *ex rel* Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 43 (D. Mass. 2001).

221. *See id.*

222. Dr. Franklin holds a doctorate degree in biology, has co-authored five scientific publications, is listed as the inventor on a patent application (pending as of 2001), and received a two-year research fellowship with Harvard Medical School and the Dana Farber Cancer Institute in Boston in 1992. *Id*. at 44.

223. *Id*.

224. *Id.* at 45.

225. *Franklin*, 147 F. Supp. 2d at 45.

226. *Id.* at 46.

227. *Id.*

228. *Id.* at 49.

The other reported decision involves the New York Times Company, publisher of the *New York Times* and the *Boston Globe*, and the National Broadcasting Company, Inc.'s successful bid to intervene in order to modify a protective order.[229] These media entities were successful in altering a protective order as overbroad and in violation of the First Amendment.[230] The cases make for good reading but stray from the topic of the listing of patents in the Orange Book. It is worth noting, however, that the off-label use of Neurontin® has, unfortunately, been implicated with at least one death, a suicide, when the drug was prescribed for the treatment of bipolar disorder.[231] When rethinking the law, Congress may want to provide further guidance for the FDA's policy of allowing seemingly unlimited off-label uses for drugs. Turning from this digression back to Orange Book cases, it is worth reviewing how other Orange Book listing cases have been handled by the courts.

IV. RELIEF FOR AGGRIEVED PARTIES

The above review of recent cases might lead one to believe that there are no remedies available to a party who believes that a patent is improperly listed in the Orange Book. It is almost that bad. One court has recognized that "[i]n short, [the] FDA's position is that if the NDA holder stands on its Orange Book listing, aggrieved parties are out of luck."[232] Essentially, the FDA has concluded that disputes about the propriety of Orange Book listings and the scope of listed patents are best resolved in private litigation, not by or through the agency.[233] There is, however, one regulatory tool at the aggrieved parties disposal, that being 21 C.F.R. 314.53(f).

Food and Drug Administration regulations do provide for correction of "patent errors."[234] This mechanism, however, is of little use. Under the regulation, "any person" that disputes the accuracy of an Orange Book listing, or if the failure to list a patent is questioned, that party may notify the FDA of such disputed listing in writing.[235] The FDA, in turn:

> [W]ill then request of the applicable new drug application holder that the correctness of the patent information or omission of patent information be

229. 210 F.R.D. at 257.

230. The government opposed modifying the protective order, arguing that modification that would allow media access "would interfere with ongoing investigations." *Id.* at 258 n.3. The court, however, noted that the "action was filed in 1996 and the government [still has] not decided whether to intervene. Molasses moves more quickly." *Id.*

231. As reported by National Public Radio's Snigdha Prakash, *All Things Considered*, January 16, 2003, *available at* http://www.npr.org.

232. aaiPharma Inc. v. Thompson, 296 F.3d 227, 237 (4th Cir. 2002).

233. *See* Abbreviated New Drug Application Regulations; Patent Exclusivity Provisions, *supra* note 33, at 50, 348.

234. 21 C.F.R. § 314.53(f) (1998).

235. *Id.*

> confirmed. Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list. If the new drug application holder does not change the patent information submitted to FDA, . . . despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.[236]

This provision has no teeth in it whatsoever. Basically, the NDA simply has to verify its listings, an entirely self-serving opportunity with no agency interaction. An ANDA is better off not even asking for the FDA to seek confirmation from the NDA. The ANDA would simply give the NDA more advance notice than in its paragraph (IV) certification. This area is ripe for the FDA to promulgate new regulations. This lack of regulation is, however, consistent with the FDA's position that it will maintain a purely ministerial role in the Orange Book listings.

To further frustrate the plight of the ANDA, it has been held that a generic drug manufacturer has no cause of action under either the Hatch-Waxman Act or the patent laws to obtain declaratory or injunctive relief requiring an NDA holder to "delist" a patent improperly listed in the Orange Book.[237] The Federal Circuit, however, has suggested that a cause of action lies under the Administrative Procedures Act ("APA").[238] In *Andrx Pharmaceuticals, Inc. v. Biovail Corporation* the Federal Circuit suggests that a generic manufacturer could bring an APA challenge against the FDA based on the agency's failure to inquire into the correctness of an Orange Book listing. [239] The Fourth Circuit decision in *aaiPharma*, however, seems to wholly oppose this possible cause of action. In *aaiPharma*, the Fourth Circuit endorsed the FDA's position that its role in Orange Book listings is purely ministerial.[240] The *aaiPharma* decision essentially insulates and shields the FDA from an APA lawsuit based on improper Orange Book listings.

The *Purepac* case, however, apparently recognizes one cause of action that still might exist under the APA. Namely, that an ANDA could argue that a section (viii) statement is proper and the FDA's rejection of such statement is arbitrary and capricious. Recall, however, that in *Purepac*, the ANDA holder was not successful in preventing the FDA from allowing its competitor's

236. *Id.*

237. *See* Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323, 1332 (Fed. Cir. 2002); *cf.* Andrx Pharm., Inc. v. Biovail Corp., 276 F.3d 1368, 1378-79 (Fed. Cir. 2002) (affirming *Mylan*, but suggesting that a generic manufacturer could bring an APA challenge against the FDA based on the agency's failure to inquire into the correctness of an Orange Book listing). The Federal Circuit's suggestion, however, has apparently been quashed by the Fourth Circuit's decision in *aaiPharma*. *See supra* note 108, effectively closing the door on an APA challenge.

238. *Andrx*, 276 F.3d at 1374.

239. *Id.*

240. aaiPharma v. Thompson, 296 F.3d 227, 230 (4th Cir. 2002).

ANDA for the same generic drug. Thus, there clearly is tension between the Fourth Circuit decision and the Federal Circuit's interpretation of how the APA can be used by aggrieved ANDA applicants.

V. STATUTORY IMPROVEMENTS

Even when laws have been written down, they ought not always remain unaltered.

-Aristotle[241]

With the bench unequivocally holding that there is not a clearly recognizable cause of action against an NDA who improperly lists a patent or patents in the Orange Book, there appears to be little relief for those unjustly stifled in their efforts to bring a generic to market. There are, however, legislative changes in the works.

As of this writing, a bill has been introduced in Congress that would amend the Federal Food, Drug, and Cosmetic Act with the stated intent of providing greater access to affordable pharmaceuticals. The bill, entitled the "Greater Access to Affordable Pharmaceuticals Act of 2003," was introduced January 7, 2003 by Senator Susan Collins.[242] In introducing the bill, Senator Collins remarked that the bipartisan bill will make prescription drugs more affordable and promote competition in the pharmaceutical industry. Senator Collins noted that "[p]rescription drug spending in the United States has increased by 92 percent over the past 5 years to almost $120 million."[243] The Congressional Budget Office estimates that, if enacted, the amendments would cut our Nation's drug costs by $60 billion over the next 10 years.[244] Senator Collins noted that the bill is supported by coalitions representing the governors, insurers, businesses, organized labor, senior groups, and individual consumers who foot the bill for expensive drugs.[245]

Senator Collins again, in her introductory remarks, recognized that the Hatch-Waxman Act now allows generics to enter the market immediately upon expiration of "the patent" as compared to the three to five years before the enactment of the Act. She notes, however, that "[i]f Hatch-Waxman were to work as it was intended, consumers could expect to save between fifty and

241. BARNES & NOBLE BOOKS , THE LAWYER'S QUOTATION BOOK: A LEGAL COMPANION (John Reay-Smith ed., 1992).

242. New Bill (S. 54) to Improve Access to Generic Drugs, Cong. Rec., S54, S54-59 (January 7, 2003), *reprinted in* 65 Pat. Trademark & Copyright J. (BNA) 260 (January 17, 2003) (hereinafter "Senator Collins"). Senator Collins (R) is senator for the state of Maine.

243. *Id.*

244. *Id.*

245. Not to make light of the situation, but the Patent Bar is conspicuously absent from her list. To date and to the author's knowledge, the American Bar Association's Section of Intellectual Property has not taken a position on the proposed legislation.

sixty percent on . . . drugs as lower cost generic alternatives become available as . . . patents expire."[246]

Senator Collins further recognized that "[d]espite its past success, however, it is becoming increasingly apparent that the Hatch-Waxman Act has been subject to abuse.[247] While many pharmaceutical companies have acted in good faith, there is mounting evidence that some brand name generic drug manufacturers have attempted to 'game' the system by exploiting legal loopholes in the current law.[248] Senator Collins alleges that brand-name companies can delay a generic drug from going to market for years.[249] A 'new' patent for an existing drug can be awarded for merely changing the color of a pill or its packaging.[250] For example, BMS delayed generic competition on Platinol, a cancer treatment, by filing a patent on the brown bottle it came in.[251] Obviously these remarks were made on the floor of the Senate and not by the Commissioner of Patents. Senator Collins' remarks were, admittedly, based on the testimony of the Chairman of the Federal Trade Commission, Timothy Muris, made before the Senate Commerce Commission.[252] Drug companies cannot get a continuation patent by simply "changing the color of a pill" or claiming a "brown bottle." This simply is not the patent law. Senator Collins' remarks, however, do appear targeted at certain formulation and packaging patents that can, because of the specific scope of their claims, potentially exclude generic drug manufacturers from entering the market. The patents, however, may also spur innovation. Additionally, Senator Collins references the antitrust violations associated with drugs such as Cardizem CD®. The producer of Cardizem CD® brought patent and trademark infringement actions against a generic manufacturer. The manufacturer offered a settlement to pay the generic company more than $80 million in return for keeping the generic drug off the market. Such actions, according to Senator Collins, caused users of Cardizem CD® , which treats high blood pressure, chest pains and heart disease, to pay $73 a month when the generic would have cost about $32 a month. The remarks rely heavily on the FTC's report on the loopholes of the Hatch-Waxman Act. The proposed amendments are fashioned to close these loopholes.

The proposed amendments appear to make major changes to the Orange Book listing practice.[253] For one, an NDA holder would be required to list,

246. *See* Senator Collins, *supra* note 242, at S58.

247. *Id.* at S54-9.

248. *Id.*

249. *Id.*

250. *Id.*

251. *See* Senator Collins, *supra* note 242, at S54-9.

252. *Id.*

253. The major amendments occur in 21 U.S.C. § 355(c)(2), (c)(3), and (j)(5). The amendments to subsection (j)(5) exclude patents that claim a process for manufacturing listed

inter alia, the patent number, the expiration date of the patent, with respect to each claim, if the patent claims a method use, the approved use covered by the claim, and a declaration that the applicant, as of the date of the filing, has provided complete and accurate patent information for all patents listed. The introduction of these provisions forces the NDA holder to make clear how a listed patent relates to the drug at issue *and its approved uses*. Conversely, an ANDA applicant would have to file either a section (vii) paragraph (IV) statement or a section (viii) statement with respect to each claim of a listed patent. This would appear to close the loophole that created the *Apotex* and *Purepac* dilemmas. In addition, it would appear to create criminal liability under 18 U.S.C. § 1001 for making false declarations as well.

In addition, and most importantly, the proposed legislation creates a private right of action to challenge Orange Book patent listings. The provision allows an ANDA applicant to file a civil action that corrects the patent information submitted by an NDA holder by way of deleting certain patents or seeking a declaration that the patent does not claim the approved drug or that the patent does claim an approved use of the drug. The section does, however, specifically preclude an award of damages.[254]

Other remarkable amendments include: (1) a provision that apparently bars a patent holder from ever bringing suit against an ANDA holder if suit is not brought within 45 days of the NDA receiving notice of the ANDA's paragraph (IV) certification, (2) a provision that limits the 180-day exclusivity period awarded to first-filed ANDAs to those situations where the applicant has not committed a "forfeiture event,"[255] (3) the 180-day exclusivity period will not be awarded if the ANDA holder is implicated in a civil suit brought against the ANDA for patent infringement, and (4) the NDA holders are entitled to more detailed notices from ANDAs, such as "a description of the [ANDA's] proposed drug substance, drug formulation, drug composition, or method of use."[256] The bill also allocates five million dollars for implementing them and carrying out the amendments.[257]

drug and patents that issue after the NDA is approved from the 30-month stay. 21 U.S.C. § 355(j)(5). In addition, it is the author's interpretation that an NDA holder listing a patent issued after the NDA is approved would be required to bring a suit, accompanied by a motion for preliminary injunction, in order to invoke the 30-month stay.

254. *See* Senator Collins, *supra* note 242, at S55.

255. The forfeiture events include: (a) failure to market the generic drug, (b) withdrawal of an application, (c) the applicant amends their certification made with respect to the Orange Book patents, (d) failure of obtain approval of the application, (e) failure to challenge new patent information submitted by the NDA holder, and (f) engaging in unlawful conduct. *See* Senator Collins, *supra* note 242, at S57. This last provision, regarding unlawful conduct, is most likely directed to settlement agreements between ANDA's and NDA's wherein the ANDA agrees to refrain from entering a market to which they have a right to enter in exchange for a payment. *Id.*

256. *See* Senator Collins, *supra* note 242, at S57.

257. *Id.* at S57.

Interestingly, the proposed legislation does not include two of the recommendations proposed in the FTC Study from 2002. In particular, any limitation on the number of 30-month stays is conspicuously absent. This absence is likely because the NDA should be entitled to an additional 30-month stay if a *later-issued* patent becomes a *later-listed* patent. If only one 30-month stay were allowed, an ANDA could receive FDA approval before the conclusion of an infringement suit and the ANDA could, to the degree it felt comfortable, begin marketing the generic drug while risking defeat in the infringement action. Any limitations on the type of patents, i.e., metabolite, product by process patents, that can be listed in the Orange Book are not incorporated into the proposed bill as well.

The proposed legislation appears to fill many of the "loopholes" found in the current law. The impact such legislation may have on the pharmaceutical industry and the intellectual property law community in general is yet to be seen. It is likely that Congress will pass some bill that addresses prescription drug costs in light of budget constraints in government support of healthcare. Such legislation, when ultimately enacted, will certainly spawn additional litigation. The issues, however, should be much narrower than found in the cases discussed herein.

So is the Hatch-Waxman Act, as it stands today, a good law? It has definitely done much to protect the rights of innovators and to move generic prescription drugs to market. Before its enactment, patentees were able to extend their monopolies past the legal expiration dates of their patents. The Act balanced the playing field between the generic drug manufacturers and the branded manufacturers. In the future, hopefully a new balance will be struck; a balance that clearly defines the rights of both the patentees and the generic drug manufacturers. Only at that point will the original intention of the Hatch-Waxman Act be realized.

VI. CONCLUSIONS

The Hatch-Waxman Act was passed to strike a balance between competing interests, the rights of pioneer drug manufacturers and the consuming public. The provisions therein have done much to meet these difficult-to-reach goals. There are, however, two major hurdles to fully reaching the Act's goals: (1) improper Orange Book listings, and (2) the unrestricted practice of allowing prescription drugs to be prescribed for "off-label" uses. The practice that has developed with respect to Orange Book listings has created opportunities for NDA holders, be they generic or branded drug manufacturers, to potentially improperly expand the scope of their patents. The courts have now ruled on the relevant statutory language, holding that there is not a cause of action for a party aggrieved by an Orange Book listing. In order to fully realize the intent of the Hatch-Waxman Act, Congress must amend the laws as they exist today to provide, *inter alia*, a private right of action for aggrieved parties.