MITCHELL | HAMLINE School of Law

William Mitchell Law Review

Volume 40 | Issue 4 Article 3

2014

Letting the Devil Ride: Thirty Years of ANDA Suitability Petitions under the Hatch-Waxman Act

Kurt R. Karst

LETTING THE DEVIL RIDE: THIRTY YEARS OF ANDA SUITABILITY PETITIONS UNDER THE HATCH-WAXMAN ACT

Kurt R. Karst†

Don't let the devil ride
Oh, don't you let the devil ride
If you let the devil ride, he'll wanna drive
Don't let him ride
Don't you let him flag you down
Oh, don't you let him flag you down
If he flags you down, he'll turn your soul around
Don't let him ride
Don't you let him be your boss
Oh, don't you let him be your boss

† Kurt R. Karst is a Director at the Washington, D.C. law firm Hyman, Phelps & McNamara, P.C. The views expressed in this article are the views of the author and do not necessarily represent the views of Hyman, Phelps & McNamara, P.C. or any of its clients.

If you let him be your boss, your soul will be lost
Don't let him ride
Don't let him drive your car
Oh, don't you let him drive your car
If you let him drive your car, he'll surely go too far
Don't let him drive

I. INTRODUCTION

These lyrics from an unknown author of the gospel song *Don't Let the Devil Ride* tell the story of the consequences of allowing the devil to take over one's life by giving into temptation once too often; by crossing the proverbial line in the sand. The lyrics also provide a nice characterization of the Food and Drug Administration's (FDA or "Agency") nearly thirty years of responding to citizen petitions requesting permission to submit an Abbreviated New Drug Application (ANDA) for a proposed drug product that deviates in some respect from the brand-name Reference Listed Drug (RLD) relied on for approval—the so-called "petitioned ANDA."

Submitted pursuant to section 505(j)(2)(C)[1] of the Federal Food, Drug, and Cosmetic Act (FDC Act),[2] as amended by the Drug Price Competition and Patent Term Restoration Act of 1984,[3] which is more commonly known as the Hatch-Waxman Act, the petitioned ANDA was, for several years, a mainstay of the generic drug industry's drug development paradigm.[4] Although the popularity of the petitioned ANDA has waned in recent years, it remains a viable route for many generic drug applicants to obtain approval of a drug product without having to conduct expensive and time-consuming clinical studies. However, the continued success—and reinvigoration—of the petitioned ANDA depends in large part on the FDA's ability to promptly review and act on ANDA suitability petitions within the statutory ninety-day period.

1. Federal Food, Drug, and Cosmetic (FDC) Act § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C) (2012).

2. 21 U.S.C. §§ 301–399f.

3. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.).

4. A similar provision applicable to generic animal drugs was enacted as part of the Generic Animal Drug and Patent Term Restoration Act, Pub. L. No. 100-670, 102 Stat. 3971 (1988). *See also* FDC Act § 512(n)(3), 21 U.S.C. § 360b(n)(3).

This article provides the first ever analysis of the FDA's nearly thirty-year track record of responding to ANDA suitability petitions submitted pursuant to FDC Act section 505(j)(2)(C). Part II traces the history of generic drug development and the petitioned ANDA from a regulation promulgated shortly before the enactment of the Hatch-Waxman Act on September 24, 1984, to the current statute.[5] Part III analyzes almost 1300 suitability petitions submitted to the FDA since September 24, 1984, and provides various data tables on the number of suitability petitions submitted to and acted on by the FDA each year from 1984 to 2013, including the annual average and median timeframes from petition submission to an FDA decision.[6] Part IV suggests some reasons for the decline in the popularity of the petitioned ANDA as a vehicle for obtaining approval of a generic drug.[7] Finally, Part V recommends that the FDA implement procedures to meet the statutory ninety-day deadline for approving or disapproving an ANDA suitability petition, or that Congress amend the FDC Act to provide the FDA with a more practical deadline to rule on a suitability petition.[8]

II. A HISTORICAL ACCOUNT OF THE "PETITIONED ANDA"

The ANDA suitability petition provisions of the FDC Act are short and total slightly more than 150 words:

> If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—
>
> > (i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

5. *See infra* Part II.
6. *See infra* Part III.
7. *See infra* Part IV.
8. *See infra* Part V.

> (ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.[9]

Although the statutory text for the petitioned ANDA is short, the historical context in which the petitioned ANDA was created and developed is not. A broader understanding of the historical milieu leading up to the enactment of the Hatch-Waxman Act, and the provisions of that Act governing generic drug approval, are necessary to understand the development of the petitioned ANDA.

A. The Hatch-Waxman Regulatory Pathway

The first generic drugs[10] were those marketed during the period between the enactment of the FDC Act in 1938[11] and the enactment of the Drug Amendments of 1962[12] without FDA approval, on the theory that the FDA's approval of the brand-name drug (also referred to as a pioneer drug) under a New Drug Application (NDA) based only on safety made the next version an "old" drug.[13] In the period after 1962, the FDA required the

9. FDC Act § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C).

10. The term "generic drug" is not defined in the FDC Act or in the FDA's regulations. It is used, however, generally to refer to a drug product with the same active ingredient as a brand-name drug.

11. FDC Act, ch. 675, 52 Stat. 1040 (1938).

12. Pub. L. No. 87-781, 76 Stat. 780.

13. The 1962 Drug Amendments also required the FDA to evaluate the effectiveness of drug products approved as safe between June 25, 1938, and October 10, 1962. The FDA engaged the National Academy of Science/National Research Council (NAS/NRC) to evaluate the effectiveness of the more than 3400 products approved based upon safety. The NAS/NRC review was broken down into specific drug categories. Review results were submitted to the FDA, which then reviewed and reevaluated the NAS/NRC findings and published its own findings in the *Federal Register*. The FDA's administrative implementation of the NAS/NRC reports is called the Drug Efficacy Study Implementation (DESI) program. DESI covered the products specifically reviewed by the NAS/NRC, as well as the even larger number of Identical, Related, or Similar (IRS) products that had entered the market without FDA approval. *See* 21 C.F.R. § 310.6(b)(1) (2009) (defining "IRS" drugs). If the FDA's final determination classified a drug as effective for its labeled indications, the Agency frequently required sponsors of approved NDAs (referred to as "deemed approved" NDAs) to supplement their applications for continued marketing of the drug, and sponsors of IRS drugs to submit ANDAs seeking approval. If the FDA's final determination classified a drug as ineffective, then, because DESI products were covered by "deemed approved"

submission of an ANDA for each generic drug, but did not permit ANDAs to be submitted for brand-name drugs approved after 1962.[14] This meant that a second version of a post-1962 brand-name drug had to obtain full NDA approval. A full NDA was economically prohibitive.

Competitive pressure drove some generic drug companies to market both pre- and post-1962 drugs without FDA approval, arguing that an active ingredient became available as an "old" drug after initial FDA approval. The FDA's attempts to suppress this practice culminated in the 1983 Supreme Court decision *United States v. Generix Drug Corp.*[15] The Court accepted the FDA's position that "old drug" status applied not to the active ingredient, but to the individual finished product. Hence, each new version of a drug was a "new drug"[16] requiring FDA approval no matter how many times the FDA had approved its active ingredient.[17]

Aware that the Agency's own policies and interpretations were preventing generic competition for post-1962 drugs, the FDA took two steps: (1) the development of the so-called "paper NDA" policy and (2) the development of ANDA regulations for post-1962 drug products. In 1978, the FDA adopted the "paper NDA" policy, under which the Agency accepted a combination of product-specific data and published literature about an active ingredient in satisfaction of the approval requirements for a full NDA.[18] The FDA's "paper

NDAs, the Agency was required to follow administrative hearing procedures to withdraw the NDA.

14. *See* 35 Fed. Reg. 6574 (Apr. 24, 1970).

15. 460 U.S. 453 (1983).

16. A product that is a "new drug" within the meaning of FDC Act section 201(p) may not be introduced into interstate commerce unless there is an approved marketing application (e.g., an NDA), or unless an exemption has been granted permitting the introduction of the drug into interstate commerce (e.g., an effective Investigational NDA).

17. Over-the-counter drug products marketed pursuant to a monograph are an exception to this rule. *See* 21 C.F.R. pt. 330 (2013).

18. *See* NDAs for Duplicate Drug Products of Post-1962 Drugs, 46 Fed. Reg. 27,396 (May 19, 1981). The "paper NDA" policy is described in a July 31, 1978 FDA staff memorandum. The policy was not originally published in the *Federal Register* because the FDA determined that rulemaking procedures were not required because "the policy is a lawful exercise of [the] FDA's statutory authority" 45 Fed. Reg. 82,052 (Dec. 12, 1980). The FDA was challenged on this issue in court and won. *See* Burroughs Wellcome Co. v. Schweiker, 649 F.2d 221, 225 (4th Cir. 1981). Subsequently, in separate litigation, the United States District Court for the Northern District of Illinois ruled that upon publication of the FDA's policy in

NDA" policy essentially permitted the sponsor of an application for a "duplicate" of a post-1962 drug product (i.e., a drug product that contained the same active ingredients as an already marketed product, in a similar or identical dosage form, and for the same indications) to submit published studies and "bridging" data in support of its application.[19] However, because the "paper NDA" approach required published literature rather than information not publicly available, it had limited utility for most drugs.[20]

In 1978, the FDA also issued proposed regulations in which the Agency expressed its intent to extend its pre-1962 ANDA regulations to post-1962 drugs.[21] The FDA began to develop these regulations in the early 1980s, but never published them. The FDA's initiative was controversial because it reportedly would have required a substantial waiting period after initial approval of the brand-name drug before any ANDA could be approved for a generic version. Congressional interest in the FDA's initiative, however, coincided with a broader effort to develop legislation that would promote both competition and innovation in the pharmaceutical industry.[22]

the *Federal Register*, the Agency could implement it without rulemaking procedures. *See* Am. Critical Care v. Schweiker, No. 81-C-252, 1981 Dist. Lexis 12363 (N.D. Ill. May 13, 1981).

19. The published studies requirement could be met by referencing data available in published literature, laboratory reports, physician evaluation forms, and even unpublished reports when available and necessary. However, the underlying data did not have to be included or referenced, as was required under the FDA's old interpretation of "full reports" in FDC Act section 505(b)(1). Reference to information not publicly available was not permitted, including information in the innovator product's NDA. The "bridging" data requirement could be met by submitting data from a bioavailability/bioequivalence study comparing the drug that was the subject of the "paper NDA" to the approved drug "to show that the drug is comparable in blood levels (or dissolution rate, as required) to the innovator's product." NDAs for Duplicate Drug Products of Post-1962 Drugs, 46 Fed. Reg. at 27,397.

20. The FDA revoked the "paper NDA" policy in 1989 when the Agency proposed regulations implementing the Hatch-Waxman Act. *See* Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,890 (proposed July 10, 1989).

21. *See* Abbreviated New Drug Applications, 43 Fed. Reg. 39,126, 39,128 (proposed Sept. 1, 1978).

22. *See, e.g.*, Drug Regulation Reform Act, H.R. 2217, 96th Cong. (1979); Drug Regulation Reform Act, H.R. 12980, 95th Cong. (1978).

The FDA's extended approval process after 1962 undercut the value of drug patents, which are granted early in the development process, and much of their then-seventeen-year term from issuance (now twenty-year term from filing) was eaten up before the FDA granted marketing approval. Congress engineered a compromise in which brand-name drug companies could obtain a patent term extension and generic drug companies could obtain ANDA approval for pre- and post-1962 drugs. The compromise was enacted on September 24, 1984, as the Hatch-Waxman Act.[23]

The Hatch-Waxman Act resulted from years of legislative effort and pharmaceutical industry engagement. The goals of this legislation were: (1) to provide a shortened, predicable pathway for manufacturers to more quickly market generic versions of brand-name drugs; (2) to restore some of the patent protection that innovator drug developers often lost while their products were under FDA review; and (3) to substantially lower the cost to consumers of drugs the FDA has determined do not require additional safety and effectiveness testing.[24]

The Hatch-Waxman Act amended, among other things, the new drug approval provisions of the FDC Act to add section 505(j).[25] Section 505(j) formalized the legal structure for generic drugs, under which an ANDA containing bioequivalence data to a brand-name drug—i.e., the RLD, which is defined as "the listed drug identified by [the] FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application"[26]—among other data and information, was sufficient for the FDA to consider approval. The Hatch-Waxman Act also amended the new drug approval provisions of the FDC Act to add section 505(b)(2) in an attempt to codify the FDA's "paper NDA" policy[27] and the patent laws to authorize a patent term extension

23. Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 and 35 U.S.C.).

24. *See* H.R. REP. NO. 98-857, pt. 2, at 14 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2698.

25. 21 U.S.C. § 355(j) (2012).

26. 21 C.F.R. § 314.3(b) (2013).

27. A section 505(b)(2) application differs from a "paper NDA" in that it permits the sponsor of a drug that may differ substantially from a drug listed in the FDA's Orange Book to rely on the FDA's determination of the safety and effectiveness of a listed drug and/or on published studies or studies in an NDA (or NDAs) sponsored by another person, together with studies generated on its own drug product, as a way to satisfy the requirement of "full reports" of safety and

for time lost during the regulatory review period[28] and to permit a safe harbor for generic drug companies to perform research and tests in preparation of regulatory approval.[29]

The premise of FDC Act section 505(j) is that an ANDA drug is the "same as" the brand-name RLD. However, differences are allowed in route of administration, dosage form, and strength, as well as in an active ingredient in a combination drug product. Those differences must first be approved by the FDA under a suitability petition as not requiring clinical investigations.[30] Section 505(j)(2)(A)[31] states that an ANDA that is not the subject of an approved suitability petition must contain information to show, among other things, that the active ingredient, "the route of administration, the dosage form, and the strength of the new drug are the same as those of the [RLD]."[32]

An ANDA must contain, among other things identified in the FDC Act and in the FDA's ANDA format and content regulations,[33] information demonstrating that the generic version is bioequivalent to the RLD.[34] This information may come from *in vivo* (human) and/or *in vitro* (test tube) studies.[35] The purpose of demonstrating bioequivalence is to determine whether a proposed drug product's formulation or manufacturing affect the rate or extent to which the active ingredient reaches the primary site of action. Although data and information demonstrating *in vivo* bioequivalence is often required, the FDA may waive this requirement if *in vivo* bioequivalence is considered self-evident, or for other reasons.[36]

effectiveness. As with the old "paper NDA" policy, "bridging" studies to the listed drug are necessary. An application that is for a duplicate of a drug listed in the Orange Book and eligible for approval under FDC Act section 505(j) may not be submitted as a section 505(b)(2) application.

28. *See* 35 U.S.C. § 156 (2006).

29. *See id.* § 271(e)(1).

30. *See* FDC Act § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93.

31. 21 U.S.C. § 355(j)(2)(A) (2012).

32. FDC Act § 505(j)(2)(A)(iii), 21 U.S.C. § 355(j)(2)(A)(iii).

33. *See generally* 21 C.F.R. § 314.94.

34. *See* FDC Act § 505(j)(2)(A)(iv), 21 U.S.C. § 355(j)(2)(A)(iv). The term "bioequivalence" is defined in the FDC Act and the FDA's regulations. *See* FDC Act § 505(j)(8)(B), 21 U.S.C. § 355(j)(8)(B); 21 C.F.R. § 320.1(e).

35. *See generally* 21 C.F.R. § 320.

36. *See id.* § 320.22.

Under the FDC Act, ANDA approval is subject to several restrictions. First, the Hatch-Waxman Act included nonpatent marketing exclusivity provisions of three or five years to compensate brand-name drug companies for allowing reliance on their proprietary research.[37] Second, as explained below, an ANDA applicant must notify an NDA holder and patent owner if a patent listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the "Orange Book" because of its orange cover) claims the RLD; if the NDA owner timely files a patent infringement suit, approval of the ANDA could be delayed. Third, an ANDA drug product must contain the "same" active ingredient as the brand-name drug and have essentially the same labeling, including indications, warnings, contraindications, etc.

The FDC Act and FDA regulations require each NDA sponsor to submit with its application

> the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the [NDA] 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.[38]

FDA regulations clarify that "such patents consist of drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents."[39] Thus, in order to list a patent in the Orange Book: (1) the patent must claim the drug or a method of using the drug that is the subject of the NDA; and (2) a claim of patent infringement could reasonably be asserted by the NDA holder or patent owner for the unauthorized manufacture, use, or sale of the drug that is the subject of the NDA.[40]

37. *See* FDC Act § 505(c)(3)(E)(j)(5)(F), 21 U.S.C. § 355(c)(3)(E)(j)(5)(F).

38. FDC Act § 505(b)(1), 21 U.S.C. § 355(b)(1).

39. 21 C.F.R. § 314.53(b)(1).

40. *See* Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not Be Infringed, 68 Fed. Reg. 36,676 (June 18, 2003) (codified at 21 C.F.R. pt. 314).

Once an NDA is approved, the FDA is required to publish information in the Orange Book on the patents claiming the drug or a method of using it.[41] If a new patent meeting the requirements of FDC Act § 505(b)(1) and the FDA's patent listing regulations is issued while an NDA is pending FDA review or after NDA approval, the NDA sponsor is required to submit information on the patent to the FDA within thirty days of issuance.[42]

An ANDA for a generic version of an innovator drug must contain one of four possible certifications "with respect to each patent which claims the [innovator] drug . . . or which claims a use for such listed drug . . . and for which information is required to be filed" by the NDA holder which is listed in the Orange Book.[43] If there are patents on the drug, and the ANDA applicant does not want to challenge one or more of them, then the applicant submits a "Paragraph III" certification to each patent it does not want to challenge, and the FDA cannot approve the application until the patents have expired.[44] If a patent has already expired, or if the required patent information has not been filed, then the ANDA applicant submits a "Paragraph II" or "Paragraph I" certification, respectively.[45] If the ANDA applicant wants to challenge a patent listed in the Orange Book, then the applicant submits a "Paragraph IV" certification, claiming that the "patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the [ANDA] is submitted."[46]

As an alternative to these four certifications, if the listed drug is covered by an Orange Book–listed "method of use patent which does not claim a use for which the [ANDA] applicant is seeking approval," then the application must contain "a statement that the method of use patent does not claim such a use."[47] This is often referred to as a "section viii statement" and it permits a generic applicant to "carve out" of its proposed labeling a patent-protected

41. *See* FDC Act § 505(b)(1), (c)(2), 21 U.S.C. § 355(b)(1), (c)(2).

42. *See* FDC Act § 505(c)(2), 21 U.S.C. § 355(c)(2); *see also* 21 C.F.R. § 314.53(c)(2)(ii), (d)(1) and (d)(3).

43. FDC Act § 505(j)(2)(A)(vii), 21 U.S.C. § 355(j)(2)(A)(vii).

44. *See* FDC Act § 505(j)(2)(A)(vii)(III), (j)(5)(B)(ii), 21 U.S.C. § 355(j)(2)(A)(vii)(III), (j)(5)(B)(ii).

45. *See* FDC Act § 505(j)(2)(A)(vii)(I)–(II), (j)(5)(B)(i), 21 U.S.C. § 355(j)(2)(A)(vii)(I)–(II), (j)(5)(B)(i).

46. FDC Act § 505(j)(2)(A)(vii)(IV), (j)(5)(B)(iii), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), (j)(5)(B)(iii).

47. FDC Act § 505(j)(2)(A)(viii), 21 U.S.C. § 355(j)(2)(A)(viii).

use, provided that the omission of such protected information does not "render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use."[48]

A generic applicant making a Paragraph IV certification must notify the NDA holder and patent owner that an application has been submitted to the FDA, once the Agency determines that the ANDA is substantially complete. The notice must include a "detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed," and must "state that an application . . . has been submitted . . . for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification."[49]

The NDA holder or patent owner has forty-five days from the date of receipt of such notice to file a suit for patent infringement.[50] If a patent infringement suit is brought by the NDA holder or the patent owner within the forty-five day period, then the FDA cannot approve the ANDA until the earlier of: (1) the expiration of a single thirty-month stay of approval, which may be shortened or lengthened by the court if "either party to the action fail[s] to reasonably cooperate in expediting the action";[51] (2) the date on which a district court enters judgment in favor of the defendant (i.e., the ANDA applicant) that the patent is invalid or not infringed (or on the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed);[52]

48. 21 C.F.R. § 314.127(a)(7) (2013). An ANDA applicant must make an additional certification (or submit an additional "section viii statement") as to any new patent listed in the Orange Book while its application is pending if the NDA holder submits the new patent to the FDA for Orange Book listing within thirty days of patent issuance. *See id.* § 314.94(a)(12)(vi). Post-MMA, a Paragraph IV certification to a later-listed patent will not result in an additional thirty-month stay of ANDA approval. *See* FDC Act § 505(c)(2), 21 U.S.C. § 355(c)(2); *see also* 21 C.F.R. § 314.53(c)(2)(ii).

49. FDC Act § 505(j)(2)(B)(ii), 21 U.S.C. § 355(j)(2)(B)(ii).

50. *See* FDC Act § 505(j)(5)(B)(iii), 21 U.S.C. § 355(j)(5)(B)(iii).

51. *Id.*

52. The statutory language regarding settlement orders and consent decrees was added post-MMA. *Compare* FDC Act § 505(j)(5)(B)(iii), 21 U.S.C. § 355(j)(5)(B)(iii) (2002), *with* FDC Act § 505(j)(5)(B)(iii), 21 U.S.C. § 355(j)(5)(B)(iii) (2012).

or (3) if the district court enters judgment in favor of the plaintiff (i.e., the NDA holder or patent owner) and that decision is appealed by the ANDA applicant, the date on which the court of appeals enters judgment in favor of the ANDA applicant that the patent is invalid or not infringed (or on the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed).[53]

If the judgment of the district court is not appealed or is affirmed by the court of appeals, then the approval will be made effective on the date specified by the district court in a court order.[54] If a patent infringement suit is not brought by the NDA holder or the patent owner within the forty-five-day period, then the FDA can approve the ANDA at any time.[55]

The Hatch-Waxman Act established an incentive for generic manufacturers to submit Paragraph IV certifications and to challenge Orange Book–listed patents as invalid or not infringed, by providing for a 180-day period of marketing exclusivity.[56] This means, in certain circumstances, an applicant who submits the first ANDA containing a Paragraph IV certification to an Orange Book–listed patent is protected from competition from other generic versions of the same drug product for 180 days. Prior to the December 2003 enactment of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA),[57] 180-day exclusivity was patent-based, such that a period of 180-day exclusivity could arise from each Orange Book–listed patent. Pre-MMA, 180-day exclusivity began on (i.e., was triggered by) the earlier of the date the FDA "receive[d] notice from the applicant . . . of the first commercial marketing of the drug" under the first ANDA or "the date of a decision of a court in [a patent infringement action] holding the patent which is the subject of the certification to be invalid or not infringed."[58]

53. FDC Act § 505(j)(5)(B)(iii)(II)(aa), 21 U.S.C. § 355(j)(5)(B)(iii)(II)(aa) (2012).

54. FDC Act § 505(j)(5)(B)(iii)(II)(bb), 21 U.S.C. § 355(j)(5)(B)(iii)(II)(bb).

55. FDC Act § 505(j)(5)(B)(iii), 21 U.S.C. § 355(j)(5)(B)(iii).

56. *See* Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,894 (proposed July 10, 1989).

57. Pub. L. No. 108-173, 117 Stat. 2066 (2003).

58. FDC Act § 505(j)(5)(B)(iv), 21 U.S.C. § 355(j)(5)(B)(iv)(I) (2000).

Post-MMA, 180-day exclusivity is generally product-based, such that there is a single 180-day exclusivity period with respect to each listed drug. Only a "first applicant"—"an applicant that, on the first day on which a substantially complete application containing a [Paragraph IV Certification] is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a [Paragraph IV Certification] for the drug"—can qualify for 180-day exclusivity.[59] Post-MMA, there is only a single trigger to 180-day exclusivity: first commercial marketing. A first applicant that qualifies for 180-day exclusivity can forfeit eligibility for such exclusivity under various circumstances.[60]

An ANDA subject to an approved suitability petition is treated like any conventional ANDA not requiring the approval of a suitability petition submitted pursuant to section 505(j) of the FDC Act. That is, an ANDA subject to an approved suitability petition must contain a certification to each Orange Book–listed patent covering the RLD, is subject to a thirty-month stay of approval, and is eligible for a period of 180-day exclusivity vis-à-vis subsequent Paragraph IV ANDA filers for the same drug product approved under the applicable suitability petition.[61]

Once the FDA approves an ANDA, information about the drug product is added to the FDA's Orange Book, including whether or not the approved generic drug is considered a "therapeutic equivalent" to, and thus substitutable for, the brand-name RLD relied on for approval. The term "therapeutic equivalence" is not defined in the FDC Act or in FDA ANDA regulations; however, "[d]rug products are considered to be therapeutic equivalents only if they are *pharmaceutical equivalents* and if they can be expected to have the same clinical effect and safety profile when administered

59. FDC Act § 505(j)(5)(B)(iv)(II)(bb), 21 U.S.C. § 355(j)(5)(B)(iv)(II)(bb) (2012).

60. *See generally* FDC Act § 505(j)(5)(D)(i)(I)–(VI), 21 U.S.C. § 355(j)(5)(D)(i)(I)–(VI) (2012) (listing failure to market the drug within a specified timeframe, withdrawing the application, amending or withdrawing patent certification, failing to obtain tentative approval, entering an agreement with another applicant, and expiration of patent).

61. *See, e.g.*, FOOD & DRUG ADMIN., ANDA 76-642/S-005, S-006, S-007 and S-008, LETTER (Oct. 19, 2007) (Hydrocodone Bitartrate and Ibuprofen Tablets, 2.5 mg/200 mg (new strength)); FOOD & DRUG ADMIN., ANDA 77-660, LETTER (July 31, 2007) (Escitalopram Oxalate Capsules, 5 mg (base), 10 mg (base) and 20 mg (base) (new dosage form)).

to patients under the conditions specified in the labeling" (i.e., bioequivalent).[62]

FDA regulations define the term "pharmaceutical equivalents" to mean "drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient . . . that deliver identical amounts of the active drug ingredient over the identical dosing period."[63] Because therapeutic equivalence requires that two drug products be pharmaceutically equivalent in order to be substitutable, "pharmaceutical alternatives" are not therapeutic equivalents and are not substitutable for the RLD relied on for approval. Pharmaceutical alternatives are "drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester."[64] Thus, products approved pursuant to an approved suitability petition are pharmaceutical alternatives and are not listed in the Orange Book as therapeutically equivalent to, and substitutable for, the RLD.

B. The Development of the Petitioned ANDA

As discussed above, even before the enactment of the Hatch-Waxman Act in 1984, the FDA had already created by regulation and under Agency policy approval processes for generic drugs: ANDAs for generic version of drug products approved under NDAs prior to 1962, and "paper NDAs" for versions of drug products approved post-1962 under an NDA. It was in this milieu that the petitioned ANDA was also created.

In 1978, the FDA proposed regulations to limit the availability of the then-existing ANDA procedures, generally, to drug products approved under an NDA between 1938 and 1962 subject to a Drug Efficacy Study Implementation (DESI) program finding if the proposed generic version was the same as (i.e., identical to) the NDA-approved drug product in terms of dosage form, strength,

62. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENTS, at vii (34th ed. 2014) (emphasis added) (commonly known as "The Orange Book"). "[The] FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product." *Id.*

63. 21 C.F.R. § 320.1(c) (2013).

64. *Id.* § 320.1(d).

route of administration, active ingredient, and conditions of use.[65] Specifically, the FDA proposed to amend the Agency's new drug regulations to provide:

> A finding by the Commissioner of Food and Drugs that an [ANDA] is appropriate for a drug product is limited to products that are the same in dosage form, route of administration, kind and amount of active ingredient, indication(s), and any other conditions of use as the drug product that was the subject of the finding. A determination that an [ANDA] is the appropriate form of application for a drug product does not apply to a similar or related drug product unless the notice of that finding specifies that it applies to a particular similar or related product and that product is described.[66]

This limitation on the availability of the ANDA procedures was necessary because, according to the FDA, "applicants continue to submit ANDA's [sic] for products clearly not subject to the finding in a DESI notice that an ANDA is appropriate."[67] As the FDA further explained, the Agency's findings of safety and effectiveness for an NDA-approved drug are generally drug-product specific. A change, such as a different strength or route of administration, "may affect the safety or the effectiveness of the related product or at least raise a question about safety or effectiveness that cannot be answered without additional data."[68]

To reach a conclusion on whether the FDA's previous finding of safety and effectiveness could extend to a nonidentical version of the NDA-approved drug, the FDA proposed the creation of an administrative procedure, allowing prospective ANDA applicants to petition the FDA pursuant to the Agency's citizen petition procedures at 21 C.F.R. § 10.30 to submit an ANDA for a drug product similar or related to an NDA-approved drug product.[69] The FDA's proposal was finalized in January 1983[70] and heralded in the era of the ANDA suitability petition. Under the FDA's final rule, the Agency would accept an ANDA "only if it has made a finding that an abbreviated application is suitable for the drug product."[71]

65. *See* 43 Fed. Reg. 39,126 (proposed Sept. 1, 1978).
66. *Id.* at 39,129.
67. *Id.* at 39,128.
68. *Id.* at 39,127.
69. *See id.*
70. *See* 48 Fed. Reg. 2751 (Jan. 21, 1983).
71. 21 C.F.R. § 314.2(b)(1) (1984).

An FDA finding that an ANDA "is suitable for a drug product . . . that is the same in active ingredient, dosage form and strength, route of administration, and conditions of use as the drug product that was the subject of the finding."[72] "For a drug product that was similar but different in one or more of these characteristics," however, the FDA regulation provided that "an [ANDA] will be accepted [for review] only if [FDA] has made a separate finding of suitability."[73] As the regulation further explained:

> A prospective applicant may seek a determination of the suitability of an [ANDA] for a product that the applicant believes similar or related to a drug product that has been declared to be suitable for an [ANDA]. Extension of the finding that a drug product is safe and effective to another product will ordinarily be limited to other dosage forms for the same route of administration or to closely related ingredients. If preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an [ANDA] is not suitable for the similar or related drug product.[74]

To obtain an FDA finding of ANDA suitability, the Agency instructed prospective applicants to submit a citizen petition in which "[t]he petitioner shall set forth the reasons that justify extending the finding that an [ANDA] is suitable for one product to the similar or related product proposed to be marketed."[75] The FDA also required each ANDA submitted to the Agency "to contain a reference to the finding of the [FDA] that an abbreviated application is suitable for the specific product that is the subject of the application."[76] Notwithstanding the detailed nature of the

72. *Id.* § 314.2(b)(2).

73. *Id.*

74. *Id.* § 314.2(c).

75. *Id.* § 314.2(d). The regulation further provides that "[a] new drug application submitted in the form of an [ANDA] for a drug product that has not been the subject of a finding that allows an abbreviated application for the product will be considered to be a petition under § 10.30 of this chapter and will be processed as such." *Id.* § 314.2(e).

76. *Id.* § 314.2(f). In 1985, the FDA completed a revision and reorganized certain of the Agency's regulations and moved § 314.2 to 21 C.F.R. § 314.55. *See* New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7466 (Feb. 22, 1985). Section 314.55 was removed in 1992 with the promulgation of final regulations implementing the ANDA provisions of the Hatch-Waxman Amendments.

FDA's final rule, it did not specify any timeframe or deadline for the FDA to approve or disapprove a suitability petition.

Slightly more than a year and nine months after the FDA promulgated its ANDA suitability petition regulations, the Hatch-Waxman Act was enacted and created the contemporary ANDA procedures applicable to generic versions of all FDA-approved drugs. Among other things, the Hatch-Waxman Act effectively codified the suitability petition procedures that the FDA had promulgated.[77]

In creating the ANDA suitability petition process, Congress noted that four types of changes are permitted to be made by a suitability petition—a change in dosage form, strength, route of administration, or, in the case of a combination drug product, a change in one active ingredient—and that these are "the only changes from the listed drug for which an applicant may petition [the FDA]."[78] Congress also, however, wisely added a requirement that the FDA timely rule on ANDA suitability petitions. Under the statute, the FDA "shall approve or disapprove a petition . . . within ninety days of the date the petition is submitted" to the Agency.[79]

The FDA issued proposed regulations in 1989 to implement the Hatch-Waxman Act,[80] and finalized those regulations regarding ANDA submission and approval in 1992.[81] The regulations concerning ANDA suitability petitions, which are located at 21 C.F.R. § 314.93, were finalized with relatively little opposition.[82] The regulations detail the content and format of a suitability petition,[83] the conditions under which the FDA will approve or

See Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950, 17,983 (Apr. 28, 1992).

77. Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585, 1587 (1984) (codified as amended at 21 U.S.C. § 355(j)(2)(C) (2012)).

78. H.R. REP. NO. 98-857, pt. 1, at 23 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2656. As an alternative to submitting an ANDA subject to an approved suitability petition for these types of changes, a company may instead submit a section 505(b)(2) application. *See* FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY, APPLICATIONS COVERED BY SECTION 505(B)(2), at 4 (1999).

79. 21 U.S.C. § 355(j)(2)(C) (2012).

80. *See* Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872 (proposed July 10, 1989).

81. *See* Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17,950 (April 28, 1992).

82. *See id.* at 17,951–52 (discussing the FDA's decision to make suitability petitions publicly available).

83. *See* 21 C.F.R. § 314.93(a)–(d) (2013).

disapprove a suitability petition within ninety days after submission,[84] and when the FDA may withdraw approval of a suitability petition.[85]

There are no binding rules governing the FDA's procedures in processing ANDA suitability petitions. The FDA's normal procedure has been to have a petition first go to the Office of Generic Drugs (OGD), which is responsible for preparing a synopsis of the petition and providing its views on appropriate resolution to the FDA's Suitability Petition Committee. The committee either approves the action on the petition recommended by the OGD or refers the matter to other FDA components for further review. Once a decision is prepared and, if necessary, reviewed by the FDA's office of chief counsel, the approval or denial is sent to the petitioner by the OGD.[86]

From the enactment of the Hatch-Waxman Act until 2003, the FDA's consideration of and action on ANDA suitability petitions, although slow, was not generally affected by other changes in the law. That changed with the December 3, 2003 enactment of the Pediatric Research Equity Act of 2003 (PREA).[87] PREA amended the FDC Act to add new section 505B.[88] It significantly affected the FDA's previous ANDA suitability petition decisions and the Agency's ability to approve future suitability petitions for certain proposed changes.

PREA essentially codified the FDA's 1998 "Pediatric Rule."[89] Under the Pediatric Rule, in order to promote more comprehensive pediatric testing and labeling, the FDA required

84. *See id.* § 314.93(e).

85. *See id.* § 314.93(f) ("[The] FDA may withdraw approval of a petition if the [A]gency receives any information demonstrating that the petition no longer satisfies the conditions under paragraph (e) of this section.").

86. *See generally* CTR. FOR DRUG EVALUATION & RESEARCH, FOOD DRUG ADMIN., MAPP 5240.5 MANUAL OF POLICIES AND PROCEDURES: OFFICE OF GENERIC DRUGS ANDA SUITABILITY PETITIONS (2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM365676.pdf.

87. Pub. L. No. 108-155, 117 Stat. 1936 (codified as amended at 21 U.S.C. §§ 284m, 355–355c (2012)).

88. *Id.* § 2, 117 Stat. at 1936 (codified as amended at 21 U.S.C. § 355c).

89. *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998) (codified at 21 C.F.R. §§ 201, 312, 314, 601); *see also* 21 C.F.R. §§ 201.23, 314.55, 601.27 (1999).

manufacturers submitting certain applications to evaluate the safety and effectiveness of their products in pediatric populations, unless the requirement was waived or deferred by the FDA.[90] The Pediatric Rule became effective on April 1, 1999, but was invalidated in October 2002 by the United States District Court for the District of Columbia as exceeding the FDA's statutory authority under the FDC Act.[91] Legislation was pursued that would enable the FDA to require pediatric studies for certain applicants, culminating in the enactment of PREA.

Under PREA as initially enacted, Congress granted the FDA with the statutory authority to require pediatric studies in certain defined circumstances retroactive to April 1, 1999.[92] Specifically, the statute states that an applicant "that submits . . . an application (or supplement to an application) . . . under section [505 of the FDC Act] for a *new active ingredient*, new indication, *new dosage form*, new dosing regimen, or *new route of administration* . . . shall submit with the application" the results of pediatric studies assessing "the safety and effectiveness of the drug . . . for the claimed indications in all relevant pediatric subpopulations; and . . . to support dosing and administration for each pediatric subpopulation for which the drug . . . is safe and effective," unless the FDA defers or partially or fully waives this requirement.[93]

An ANDA requiring an approved suitability petition for a change in the RLD in an active ingredient, route of administration, or dosage form triggers PREA because it is a type of application submitted under FDC Act section 505. The only change permitted

90. *See* Kurt R. Karst, Comment, *Pediatric Testing of Prescription Drugs: The Food and Drug Administration's Carrot and Stick for the Pharmaceutical Industry*, 49 AM. U. L. REV. 739, 754 (2000).

91. Ass'n of Am. Physicians & Surgeons v. FDA, 226 F. Supp. 2d 204, 222 (D.D.C. 2002).

92. *See* Pediatric Research Equity Act, §§ 2, 4, 117 Stat. at 1936, 1942; *see also* Letter from Gary Buehler, Dir., Office of Generics, FDA Ctr. for Drug Evaluation & Research, to Richard S. Morey, Att'y, Kleinfeld, Kaplan & Becker (Feb. 11, 2004), *available at* http://www.fda.gov/ohrms/dockets/dailys/04/June04/061004/04p-0262-cp00001-Tab-3-vol1.pdf ("PREA applies retroactively to all suitability petitions submitted on or after April 1, 1999, and affects suitability petitions already approved as well as those currently pending or not yet submitted.").

93. FDC Act § 505B(a)(1)–(4), 21 U.S.C. § 355c(a)(1)–(4) (2012) (emphasis added).

by a suitability petition that does not trigger PREA is a change in strength from the RLD.[94]

FDC Act section 505(j)(2)(C)(i) requires that the FDA deny a suitability petition if "investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug." The requirement to conduct (or even a deferral from conducting) pediatric studies triggers the statutory requirement to deny a suitability petition. Thus, unless the FDA fully waives the PREA pediatric studies requirement, the Agency must deny a suitability petition that requests permission to submit an ANDA for a change in route of administration, dosage form, or active ingredient vis-à-vis the RLD. The FDA stated this interpretation as early as 2004,[95] and later withdrew approval of 128 suitability petitions in accordance with PREA.[96]

III. SLOTH: THE FDA'S ANDA SUITABILITY PETITION DECISION TRACK RECORD

Over the thirty years that the FDA has reviewed and acted on ANDA suitability petitions, the Agency has fallen victim to one of the seven deadly sins: sloth. A review of nearly 1300 ANDA suitability petitions submitted to the FDA since the enactment of the Hatch-Waxman statutory provision creating them shows that the FDA has been largely unable to meet the mandatory statutory ninety-day deadline of approving or disapproving a petition, particularly in recent years, despite a decline in the number of petitions submitted to the FDA.

The tables included in the appendix to this article are the culmination of this author's review of myriad sources of

94. *See* FDC Act § 505B(a)(1)(A), 21 U.S.C. § 355c(a)(1)(A) (listing as affected by PREA, a marketing application for approval of a "new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration")

95. *See* Letter from Gary Buehler, *supra* note 92 ("If the change proposed in an ANDA suitability petition does not qualify for a full waiver of the pediatric studies, the approval of that petition will be revoked because, under PREA, clinical studies are required to demonstrate the safety and or effectiveness of the change.").

96. *See* Withdrawal of Approval of 128 Suitability Petitions, 72 Fed. Reg. 8184 (Feb. 23, 2007).

information showing citizen petitions submitted to the FDA between September 24, 1984, and December 31, 2013, and identified in such records as ANDA suitability petitions. Although the FDA posts a list of ANDA suitability petitions on the Agency's website,[97] that list is incomplete. The FDA's list omits, for example, approved suitability petitions withdrawn as result of the enactment of PREA and any suitability petitions submitted before March 31, 1999. In order to form a more complete account of the FDA's record of acting on suitability petitions, the author's analysis includes such petitions without regard to their ultimate withdrawal of approval as a result of PREA.[98]

For each year from 1984 to 2013, the author tabulated the number of ANDA suitability petitions submitted to the FDA. Those results are shown in Table 1 in the appendix to this article. After tabulating the number of suitability petitions submitted to the FDA annually, the author examined for each year the number of petitions the FDA approved and denied, the number of petitions withdrawn by the petitioner before receiving a substantive response from the FDA, and the number of petitions that remain pending as of December 31, 2013. Those results are shown separately in Tables 2–5, with Table 6 showing, in line graph format, the combined data in Tables 2–5.

Next, the author calculated for each year cohort the average and median times for the FDA to respond to a petition by either approving or disapproving the petition, based on the date of petition submission to the FDA and the date of the Agency's response. For this analysis, petitions withdrawn by the petitioner before an FDA approval or disapproval decision were excluded from the calculation. In addition, separate calculations were performed for each year cohort that both exclude and include

97. *See Suitability Petitions*, FOOD & DRUG ADMIN., http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm120944.htm (last updated Feb. 5, 2014).

98. Omitted from this analysis are sixteen ANDA suitability petitions submitted to the FDA prior to the September 24, 1984, enactment of the Hatch-Waxman Act, when the FDA's suitability petition regulations were in force, regardless of whether or not the FDA approved or disapproved such petitions after September 24, 1984. Because the FDA's suitability petition regulations did not require the FDA to decide on such petitions within a defined period, there was no specific expectation at the time of submission that the FDA would approve or disapprove these petitions within ninety days.

suitability petitions pending an FDA approval or disapproval decision as of December 31, 2013.

When including pending petitions, the number of days pending was calculated based on the day of petition submission to the FDA and as of December 31, 2013. Those results are shown in Tables 7–12, with Tables 9 and 12 comparing the average and median numbers of days to an FDA decision both where pending petitions are excluded and included, respectively. Because there are ANDA suitability petitions pending, an FDA decision as far back as 2001 (Table 6), excluding pending petitions yields *actual* annual average and median FDA decision timeframes, and that are significantly less than the *possible* annual average and median FDA decision timeframes calculated when such pending petitions are included. Ultimately, if such petitions are not withdrawn and are ruled on by the FDA, then their potentiality will be actualized.

Each table appears, at first blush, to reflect a significant downward trend in recent years in the average and median times for the FDA to rule on a suitability petition, regardless of whether or not pending petitions are included or excluded from the analysis. The "trend" is somewhat illusory, however, for two related reasons. First, there are a large number of pending suitability petitions submitted to the FDA in recent years that the Agency has not yet approved or disapproved. Second, for purposes of our analysis, the author needed to institute a cutoff date of December 31, 2013 that is artificial. As such, petitions submitted to the FDA in recent years but not yet ruled on have not "aged" to the extent that older petitions—whether or not yet ruled on by the FDA—have "aged." If the FDA were to promptly approve or disapprove pending petitions submitted to the Agency in recent years, then there would, in fact, be a downward trend in average and median times. If, however, the FDA allows pending petitions submitted to the Agency in recent years to languish without a ruling, then the Agency's actual decision timeframe will remain high.

One trend that is not illusory is an upward trend in decision timeframes beginning around 2002 or 2003 and peaking around 2007. The start of this trend generally coincides with the enactment of PREA, and may reflect additional time taken by the FDA's OGD to rule on suitability petitions because of the need to consult other

FDA components on pediatric testing issues, such as the FDA's Pediatric Review Committee (PeRC).[99]

Finally, the author consolidates several of the tables above to show, in Tables 13 and 14, an overview of the numbers of petitions submitted, withdrawn, and acted on by the FDA vis-à-vis the average and median figures shown above (in line graph format), both including and excluding pending petitions. In order to show all of these data on a single table, the numbers showing average and median FDA response timeframes (both including and excluding pending suitability petitions) have been reduced by a factor of ten (i.e., 100 = 10).

IV. LOSS OF FAITH: POSSIBLE REASONS FOR THE DECLINE IN THE POPULARITY OF THE PETITIONED ANDA

Two trends in particular stand out when examining the tabular results presented in Part III of this article: (1) despite initial excitement, the generic drug industry's interest in ANDA suitability petitions has waned, particularly in the past four years; and (2) despite some early success, the FDA has been unable to meet, on an annual basis for petitions submitted in each cohort year, the statutory ninety-day deadline for approving or disapproving ANDA suitability petitions. Indeed, as shown in Tables 15 and 16, adding linear trend lines to two of the tables from Part III above clearly shows the number of ANDA suitability petitions on the downswing and the FDA's average and median response times (even excluding pending petitions) on the upswing.

It is logical to conclude that the two trends are related. The longer it takes for the FDA to approve or disapprove an ANDA suitability petition, the less incentive there is for the generic drug industry to submit such petitions, because it is unknown if the FDA will rule on the petition in a reasonable timeframe so that a generic drug company can plan its development of a drug accordingly.[100]

99. *See generally* 21 U.S.C. § 355d (2012) (establishing the PeRC).

100. Curiously, no generic drug company has yet, to this author's knowledge, challenged the FDA in court over the Agency's unreasonable delay in ruling on an ANDA suitability petition. Nevertheless, there appears to be a basis for such a challenge under the Administrative Procedures Act (APA), 5 U.S.C. §§ 501–596 (2012), alleging that the FDA failed to perform a nondiscretionary statutory duty to timely act upon an ANDA suitability petition within ninety days. Indeed, there is precedent for courts compelling the FDA to act on a mandatory obligation when plaintiffs have alleged unreasonable delay. In *Sandoz, Inc. v. Leavitt*, 427 F. Supp.

In other words, the generic drug industry has lost faith in the ANDA suitability petition process.[101] Part V of this article proposes how the FDA (or Congress) can redeem the faith of the generic drug industry in the suitability petition process; however, before moving on to that final topic, it bears noting that the glacial pace at which the FDA rules on suitability petitions is not the sole factor for the generic drug industry's waning interest in submitting suitability petitions to the FDA. A couple of other factors are relevant.

As discussed in Part II of this article,[102] PREA significantly affected the FDA's ability to approve suitability petitions seeking permission to submit an ANDA for a drug product that deviates from the RLD in dosage form, route of administration, and active ingredient in a combination drug product. As a result, fewer suitability petitions have been submitted to the FDA requesting permission for such changes. For example, of the twenty-three suitability petitions submitted to the FDA in 2011, eighteen of them requested permission to submit an ANDA for a new strength, while four requested permission for a new dosage form, and one for both a new strength and new dosage form.

2d 29, 41 (D.D.C. 2006), the plaintiff successfully sued the FDA for not approving or disapproving its NDA in over 1000 days (over five times the statutory deadline of 180 days). In *In re Barr Laboratories, Inc.*, 930 F.2d 72, 73 (D.C. Cir. 1991), the plaintiff sought a writ of mandamus compelling the FDA to either approve or disapprove twenty-three of Barr's ANDAs, claiming that the FDA had repeatedly missed the statutory 180-day deadline. The court did not grant relief to the plaintiff, finding that granting the writ would only put Barr at the head of the queue and simply move all others back one space. *See id.* at 75. The court did, however, hold that the FDA's compliance with the 180-day deadline was mandatory and not merely a policy recommendation. *See id.* at 76.

101. Whether the FDA has also lost faith in the ANDA suitability petition process, because of a low "rate of return" on the investment needed to review and act on suitability petitions, is another factor that may affect the lengthy FDA decision process. That is, if the FDA is of the mindset that the Agency's approval of suitability petitions is not resulting in the submission and approval of ANDAs based on those decisions, then there is a disincentive for the FDA to promptly review and rule on suitability petitions. Unfortunately, because specific information about ANDA submissions is maintained by the FDA as confidential information, it is impossible to gauge the success of the suitability petition process by virtue of the number of ANDA submissions made based on an approved suitability petition, as not all applications submitted to the FDA are approved. Although it might be possible to tabulate the number of petitioned ANDAs the FDA has ever approved, this author has not yet attempted to undertake that monumental task.

102. *See supra* notes 89–96 and accompanying text.

Another factor that may affect the number of ANDA suitability petitions submitted to the FDA annually is the growing popularity of the section 505(b)(2) NDA as a route to obtain approval of a drug product that deviates in some respect from a brand-name drug approved under an NDA. A generic drug manufacturer may use the section 505(b)(2) NDA route as an alternative to submitting an ANDA subject to an approved suitability petition for each of the types of changes permitted via a suitability petition, as well as myriad other changes not permitted under the ANDA approval route.[103] Indeed, when faced with the decision of either petitioning the FDA for *permission* to submit an ANDA, the submission of which may not occur for several years, or immediately submitting a section 505(b)(2) NDA to the FDA without having to first request, and then await, the Agency's permission, companies may well choose the latter option. Although the submission of a section 505(b)(2) application is more costly than an ANDA submission,[104] the FDA is almost certain to take an approval action on a section 505(b)(2) NDA before an ANDA,[105]

103. *See* FOOD & DRUG ADMIN., *supra* note 78, at 4.

104. Under the Prescription Drug User Fee Amendments of 2012 (PDUFA) of the Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, tit. I, 126 Stat. 993, 996 (2012), the FDA is authorized to collect user fees for certain applications for approval of drug and biological products, on establishments where the products are manufactured, and on such products. The fee to submit a section 505(b)(2) application to the FDA in fiscal year 2014 that does not contain clinical data is $1,084,550. *See* Notice, Prescription Drug User Fee Rates for Fiscal Year 2014, 78 Fed. Reg. 46,980 (Aug. 2, 2013). Similarly, under the Generic Drug User Fee Amendments of 2012 (GDUFA), tit. III, 126 Stat. at 1008, the FDA is authorized to collect user fees for certain applications for approval of a generic drug, among other types of fees. The fiscal year 2014 ANDA fee is $63,860. *See* Notice, Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014, 78 Fed. Reg. 46,977 (Aug. 2, 2013).

105. Under the latest iteration of PDUFA, the FDA agreed to act on ninety percent of the NDAs typically submitted to the Agency within either ten months of the receipt date (standard applications) or within six months of the receipt date (priority applications). *See* Food & Drug Admin., *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017*, http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf (last visited Apr. 28, 2014). Under GDUFA, the FDA has agreed to certain performance goals concerning ANDA approval actions; however, those goals do not go into effect until fiscal year 2015. *See* Food & Drug Admin., *GDUFA Program Performance Goals*

thereby allowing a company to earn a return on its investment quicker than if it had chosen the ANDA suitability petition route.

A corollary to a company choosing to submit a section 505(b)(2) NDA to the FDA instead of availing itself of the suitability petition route to ANDA submission and approval is that approval of a section 505(b)(2) NDA may be used to "short circuit" a generic drug sponsor's plans to obtain approval of a petitioned ANDA for the same change covered by an approved section 505(b)(2) NDA. First, the FDA will not approve a pending suitability petition for a change that describes an approved pharmaceutically equivalent drug product, because the suitability petition process is intended for a proposed "drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug."[106] Second, the FDA has historically required a generic drug applicant with a pending ANDA subject to an approved suitability petition to change RLD and provide appropriate bioequivalence information once the Agency has approved an application for the drug product covered by the suitability petition.[107] A change made to the statute by the 2003 MMA, however, precludes the sponsor of a pending ANDA from amending its application to change RLD.[108] Instead, the FDA requires the submission of a new ANDA citing the appropriate RLD, containing sufficient information to demonstrate bioequivalence to that RLD, and certifications to any patents listed in the Orange Book for that RLD.[109]

Finally, it should be noted that the FDA has limited resources, but an increasing amount of responsibility. This likely requires the FDA to choose which tasks and obligations should take precedence over others. With respect to ANDAs, the FDA has seen a near-

and Procedures, http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf (last visited Apr. 28, 2014).

106. 21 C.F.R. § 314.93(b) (2013).

107. *See* Letter from Janet Woodcock, Dir., Ctr. for Drug Evaluation Research, to Mark S. Aikman, Vice President, Regulatory Affairs and Quality Assurance, Osmotica Pharm. Corp. (Nov. 25, 2008) (quoting Letter from G. Buehler, Dir., Office of Generic Drugs, Food & Drug Admin., to Undisclosed Applicants Regarding ANDAs for Carboplatin Injection, 10 mg/mL (Aug. 12, 2004)), *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2008-P-0329-0016.

108. *See* FDC Act § 505(j)(2)(D)(i), 21 U.S.C. § 355(j)(2)(D)(i) (2012).

109. *See* Letter from Janet Woodcock, *supra note* 107.

tripling of applications submitted to the Agency over the past decade, resulting in a significant backlog of applications. The "slippage" in reviewing and acting on suitability petitions and the increase in ANDA submissions and the backlog of pending applications are likely not coincidence.[110]

V. REDEMPTION OF FAITH: THE FDA SHOULD IMPLEMENT PROCEDURES TO CONSISTENTLY MEET THE NINETY-DAY STATUTORY DEADLINE FOR ACTING ON ANDA SUITABILITY PETITIONS, OR CONGRESS SHOULD AMEND THE LAW WITH A MORE PRACTICAL DEADLINE

Despite the FDA's historical policy of sloth and lassitude in ruling on ANDA suitability petitions, leading to a loss of faith in the process itself, there is still hope that the FDA can redeem itself. But to do so, the FDA will need to make a concerted effort to promptly act on ANDA suitability petitions. Indeed, such an effort is already afoot at the FDA. In August 2013, the FDA published a Manual of Policies and Procedures (MaPP)[111] establishing the policies and procedures for responding to suitability petitions, and reiterating that "[u]nder 21 CFR 314.93(e), the Agency will approve or deny the petition no later than 90 days after the petition is submitted."[112] According to the MaPP:

> OGD's goal is to respond to suitability petitions in an efficient and effective manner. To meet this goal, a number of parties within the Center for Drug Evaluation and Research (CDER) and throughout the Agency must work in a coordinated manner. OGD, the office primarily responsible for responding to suitability petitions, has developed procedures for enhancing communication among parties involved in addressing the request(s) in the suitability petitions.[113]

Because the FDA's MaPP became effective only relatively recently, in August 2013, it is not yet clear what effect (if any) it has had on speeding up the FDA's review of new and long-pending ANDA suitability petitions. If, given the passage of time, the policies and procedures stated in the MaPP do not yield significant

110. Indeed, the personnel in the FDA's OGD tasked with reviewing ANDAs are the same personnel tasked with handling suitability petitions.

111. CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 86.

112. *Id.* at 1.

113. *Id.* at 2.

improvements in meeting the statutory ninety-day deadline, then perhaps Congress should amend the statute to reset the deadline to one that is more practical for the FDA to meet.

In other recent instances where Congress has required the FDA to respond to certain types of citizen petitions in 150 days, 180 days, and 270 days, the FDA has been quite successful in meeting those statutory deadlines. In 2007, the FDC Act was amended to require that the FDA respond, within 180 days, to certain citizen petitions and petitions for stays of action that request that the FDA take any form of action related to a pending ANDA or section 505(b)(2) NDA.[114] That 180-day deadline was reduced to 150 days in 2012.[115] Of the 116 petitions submitted to the FDA through fiscal year 2012 subject to the 180-day or 150-day deadline, the FDA has missed that deadline only twice.[116]

The FDC Act was also amended in 2012[117] to require that the FDA respond within 270 days to citizen petitions requesting that the FDA determine whether a particular RLD was withdrawn from sale for reasons of safety or effectiveness.[118] The FDA has thus far

114. *See* FDC Act § 505(q), 21 U.S.C. § 355(q) (2012). This section of the law was added by section 914 of the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 914, 121 Stat. 823, 953–57.

115. *See* Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 1135, 126 Stat. 993, 1123 (2012).

116. *See* FOOD & DRUG ADMIN., REPORT TO CONGRESS, FIFTH ANNUAL REPORT ON DELAYS IN APPROVALS OF APPLICATIONS RELATED TO CITIZEN PETITIONS AND PETITIONS FOR STAY OF AGENCY ACTION FOR FISCAL YEAR 2012, at 4 (2013), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM369780.pdf; *see also* Kurt R. Karst, *FDA's Fifth Annual Report to Congress on 505(q) Citizen Petitions: Something Old, Something New, Something Borrowed, FDA Is Still Blue*, FDA L. BLOG (Sept. 25, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/09/fdas-fifth-annual-report-to-congress-on-505q-citizen-petitions-something-old-something-new-something.html.

117. *See* FDC Act § 505(w), 21 U.S.C. § 355(w). This section of the law was added by section 1134 of the Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 1134, 126 Stat. 993, 1123 (2012).

118. The FDA may refuse to approve an ANDA if the Agency determines that the RLD was withdrawn from sale for reasons of safety or effectiveness. *See* FDC Act § 505(j)(4)(I), 21 U.S.C. § 355(j)(4)(I). In addition, the FDA can withdraw (or suspend) approval of an ANDA if the RLD is withdrawn from sale for reasons of safety or effectiveness. *See* FDC Act § 505(j)(6), 21 U.S.C. § 355(j)(6). The FDA acknowledged in the preamble to the Agency's July 1989 proposed regulations implementing the 1984 Hatch-Waxman Act that the law does not "specify procedures to be followed in determining whether a drug that is voluntarily

met that deadline for the relatively small number of petitions submitted pursuant to 21 C.F.R. § 314.161.

Clearly, the FDA can meet a statutory deadline for responding to a citizen petition when the Agency wants to do so, and when the Agency has sufficient time to do so. Perhaps the ninety-day deadline for approving or disapproving an ANDA suitability petition is insufficient for the FDA to complete its analysis and compose a decision. There might also be a mindset at the FDA that once the ninety-day period is breached, there is less impetus for the FDA to promptly rule on a suitability petition. That is, there may be a mindset that "a miss is a miss no matter how close to, or far off of, the mark you are." To address both of these issues, Congress should consider extending—perhaps as part of the next iteration of the Generic Drug User Fee Amendments of 2012 (GDUFA) that will be taken up in the coming years—the ninety-day response deadline to reflect deadlines that are more familiar to and attainable by the FDA, such as the 150-day, 180-day, or 270-day petition response deadlines imposed by Congress in recent years. An attainable deadline will give greater certainty to the ANDA suitability petition process, will reassure the generic drug industry that it is a viable and practical route to ANDA approval, and may lead to a renewed interest in submitting ANDA suitability petitions.[119]

withdrawn from sale by its manufacturer is withdrawn for safety or effectiveness reasons." Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,907 (proposed July 10, 1989). As such, the FDA took it upon itself to create such a procedure. The FDA's interpretation of the Hatch-Waxman Act is embodied in the Agency's regulations, which provide that "[a]ny person may petition under §§ 10.25(a) and 10.30 of this chapter for a determination whether a listed drug has been voluntarily withdrawn for safety or effectiveness reasons." 21 C.F.R. § 314.161(b) (2013).

119. There are alternatives to amending the FDC Act's ANDA suitability petition provisions with a more practical deadline. For example, Congress could abolish the suitability petition procedures because the section 505(b)(2) NDA pathway already provides a route to obtain approval of an application for the types of changes permitted in a suitability petition, and without the need to first obtain the FDA's permission. Small generic drug companies that may use the suitability petition procedures might object to such a move because of the significant user fee payment that must accompany a section 505(b)(2) NDA submission (and annual product and establishment user fee payments), unless PDUFA is also amended to include a reduction or exemption from user fees. Congress could also amend the FDC Act to permit the submission of an ANDA for a petitioned change unless the FDA disapproves a petition within ninety days of submission. Such a

VI. CONCLUSION

Despite initial popularity, interest in the ANDA suitability petition has waned in recent years. This is likely the result of a confluence of factors; however, the FDA's inability to meet the statutory ninety-day deadline for approving or disapproving a suitability petition has resulted in a loss of faith in the petition process. The petitioned ANDA remains a viable route for many generic drug applicants to obtain approval of a drug product without having to conduct expensive and time-consuming clinical studies, but to renew trust and reinvigorate interest in the petitioned ANDA, change is necessary. Recently, the FDA indicated that it is committed to acting promptly on suitability petitions. If the FDA's renewed interest in meeting the statutory ninety-day deadline is unsuccessful, then Congress should consider amending the FDC Act with a more practical deadline.

change would effectively remove the condition precedent currently in the statute and create greater urgency for FDA to review and act on a suitability petition in a timely manner.

APPENDIX

Table 1: ANDA Suitability Petition Submissions by Year (1984–2013)

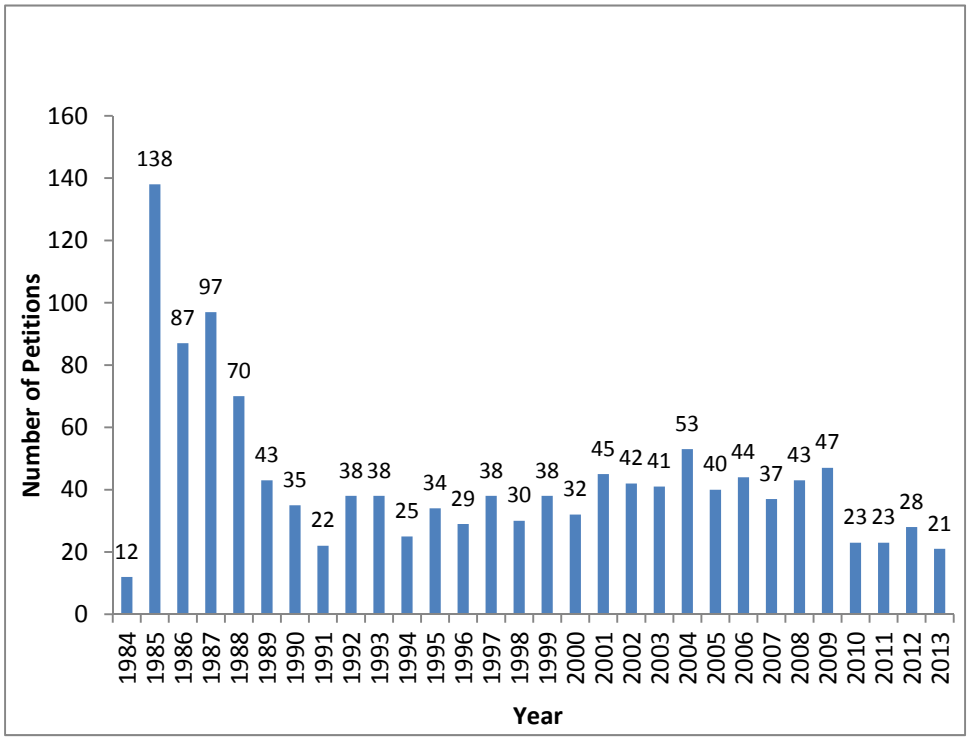

Table 2: ANDA Suitability Petition Approvals by Year (1984–2013)

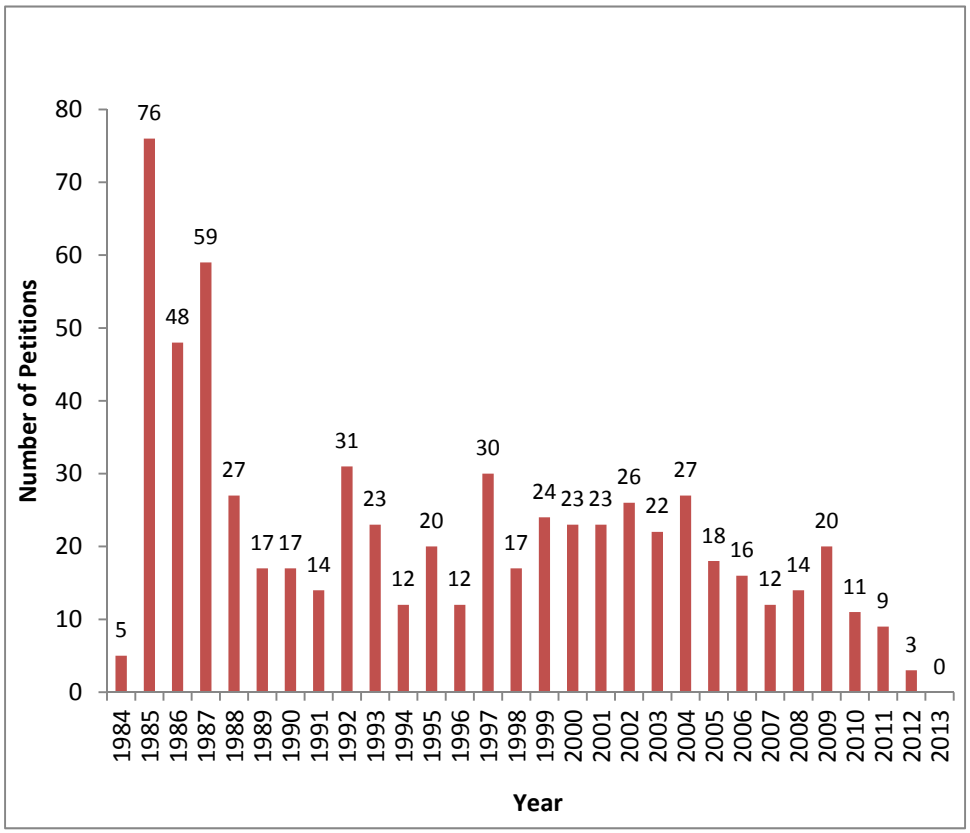

Table 3: ANDA Suitability Petition Denials by Year (1984–2013)

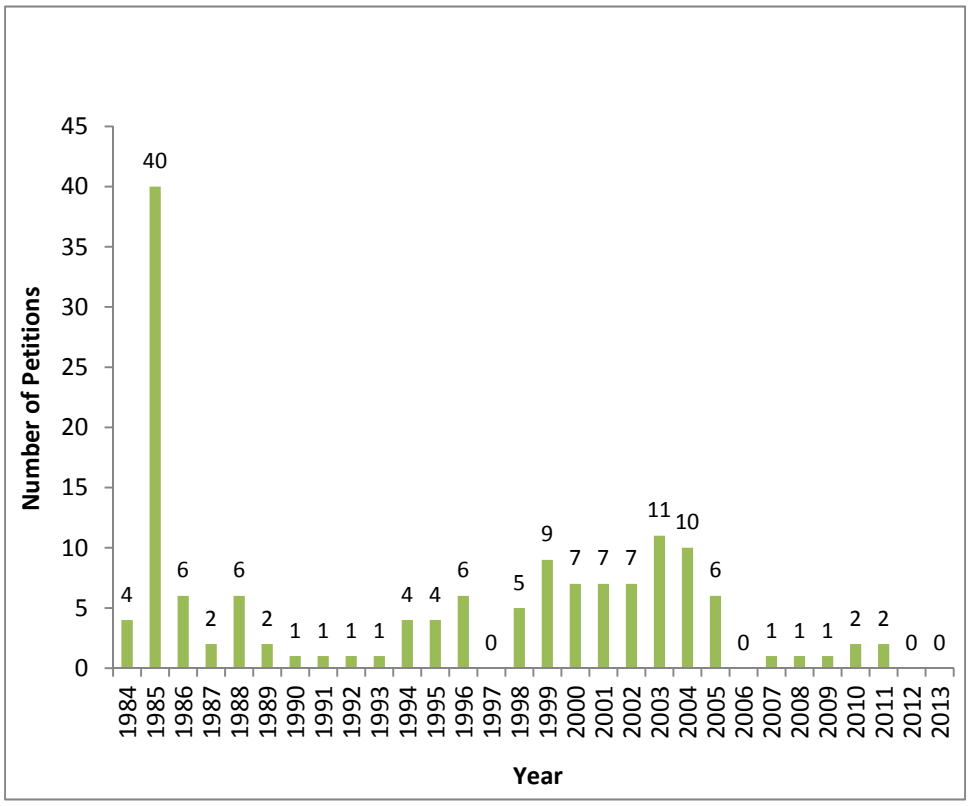

Table 4: ANDA Suitability Petition Withdrawals by Year
(1984–2013)

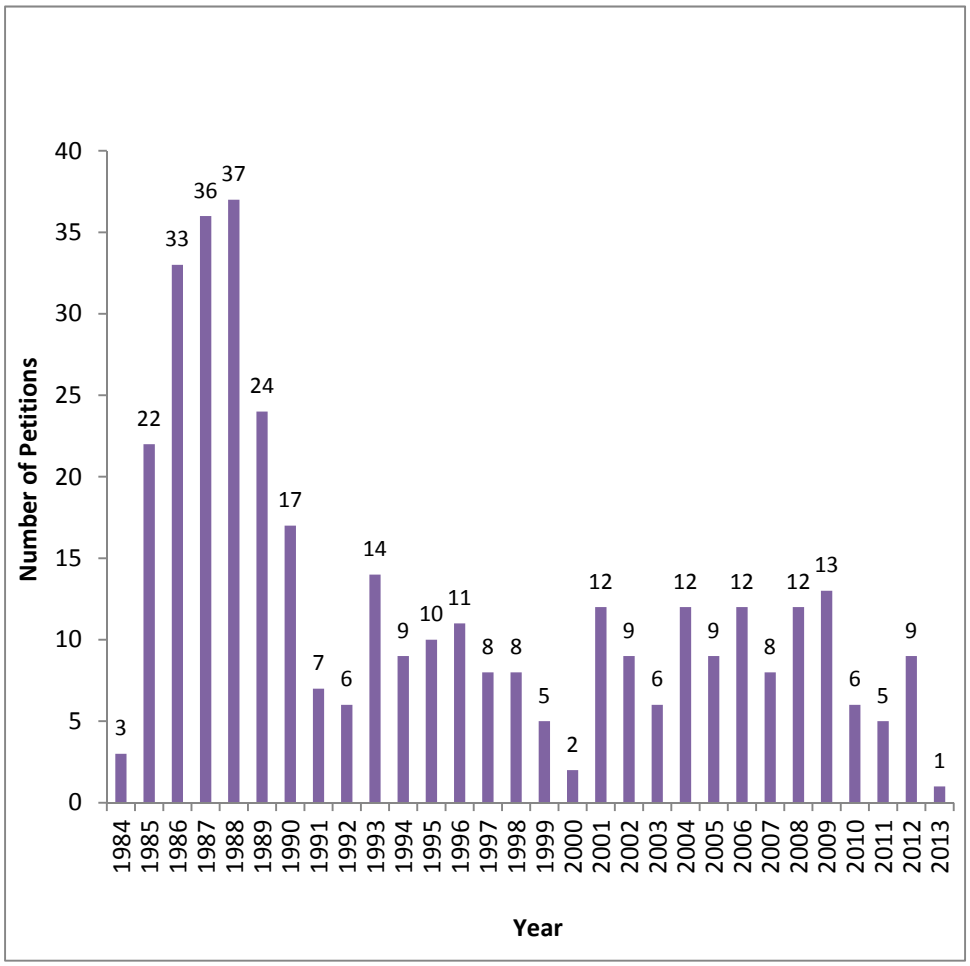

Table 5: Pending ANDA Suitability Petitions by Year (2001–2013)

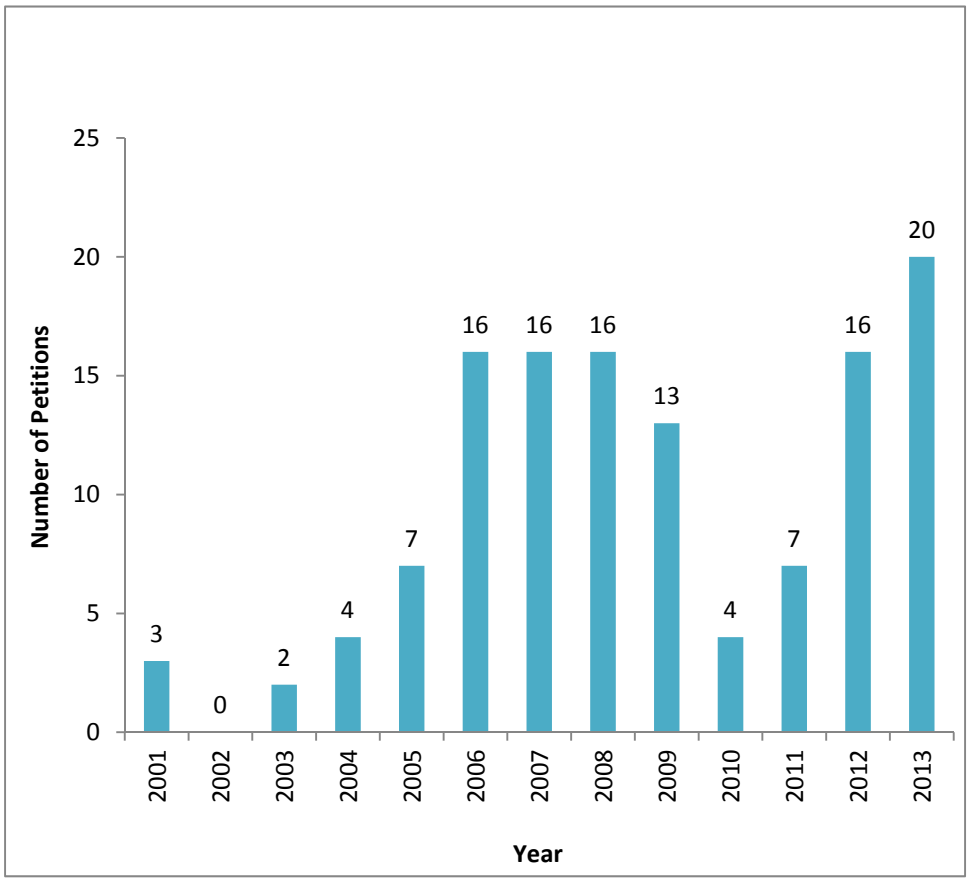

Table 6: ANDA Suitability Petition Approvals, Denials, Withdrawals, and Pending by Year (1984–2013)

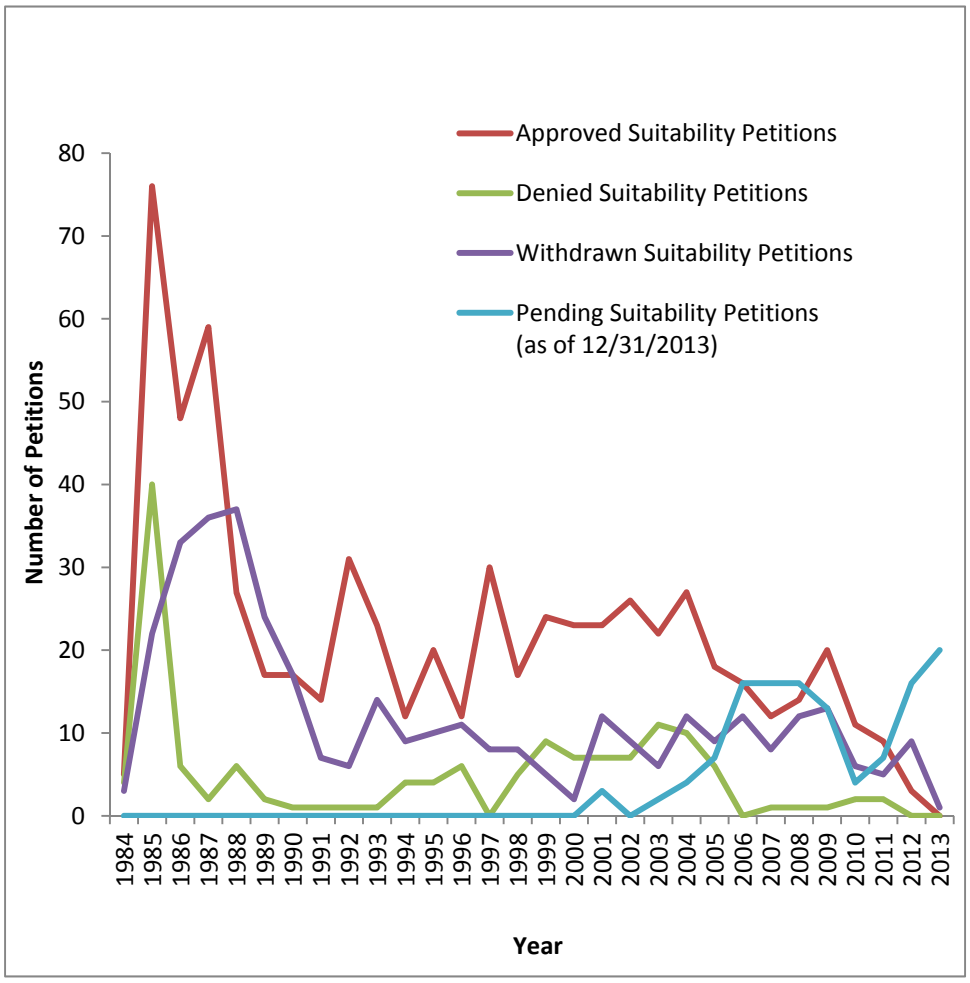

Table 7: Average Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Excluding Pending Petitions

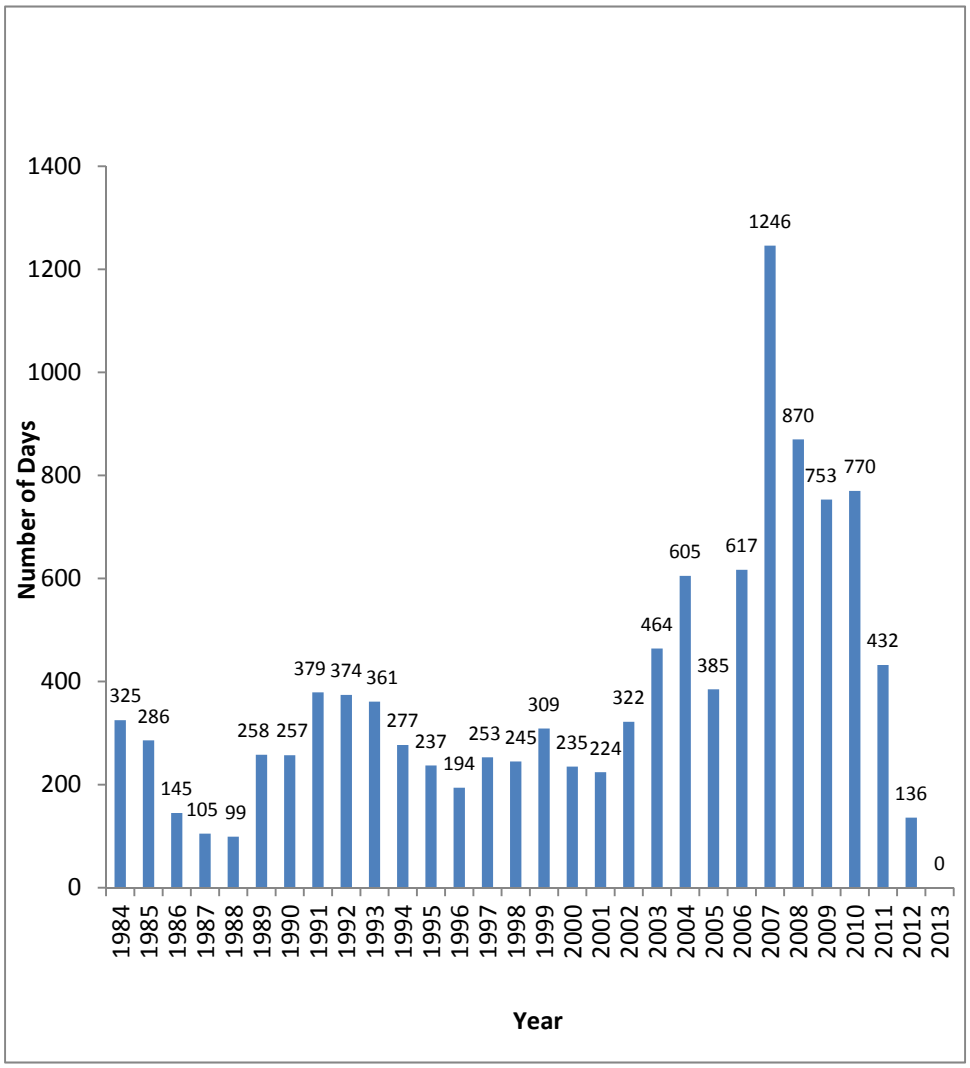

Table 8: Median Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Excluding Pending Petitions

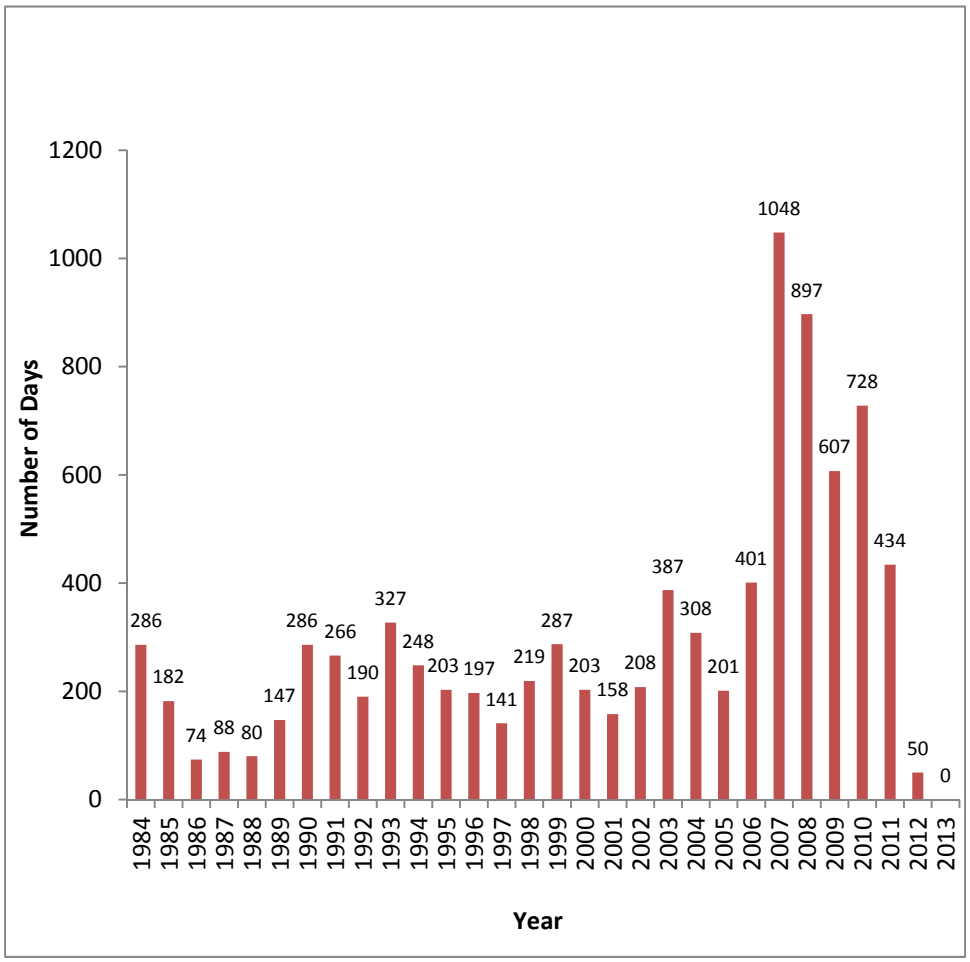

Table 9: Average and Median Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Excluding Pending Petitions

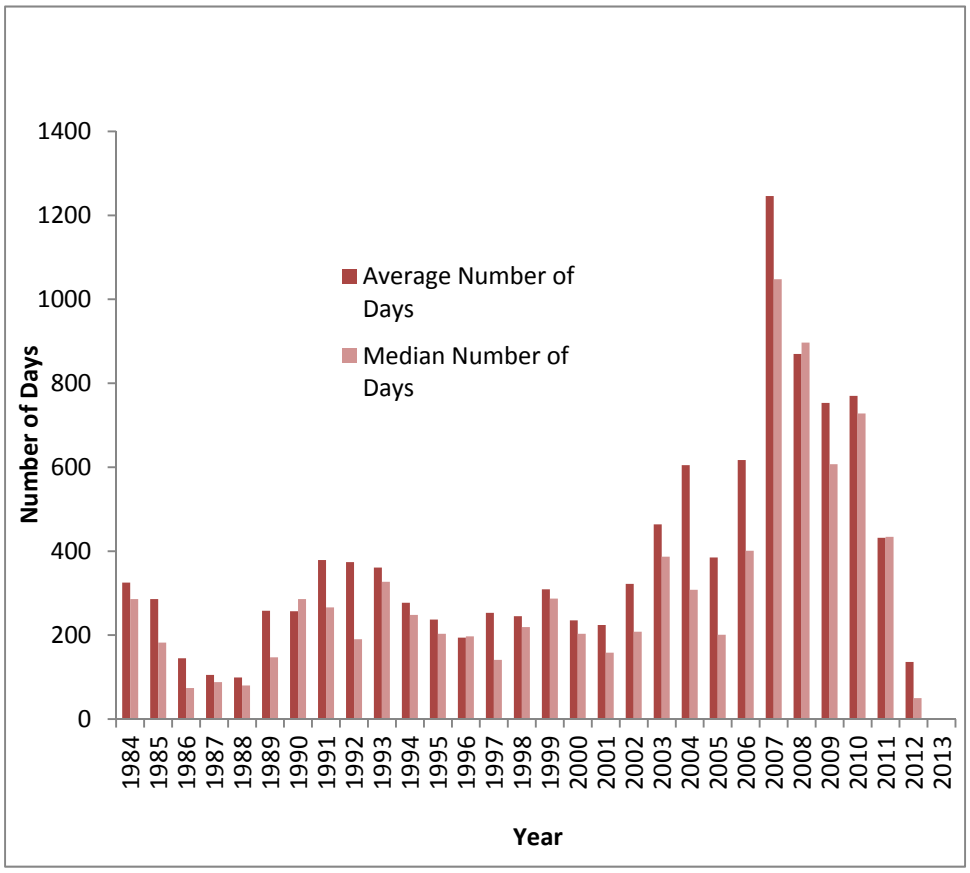

Table 10: Average Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Including Pending Petitions

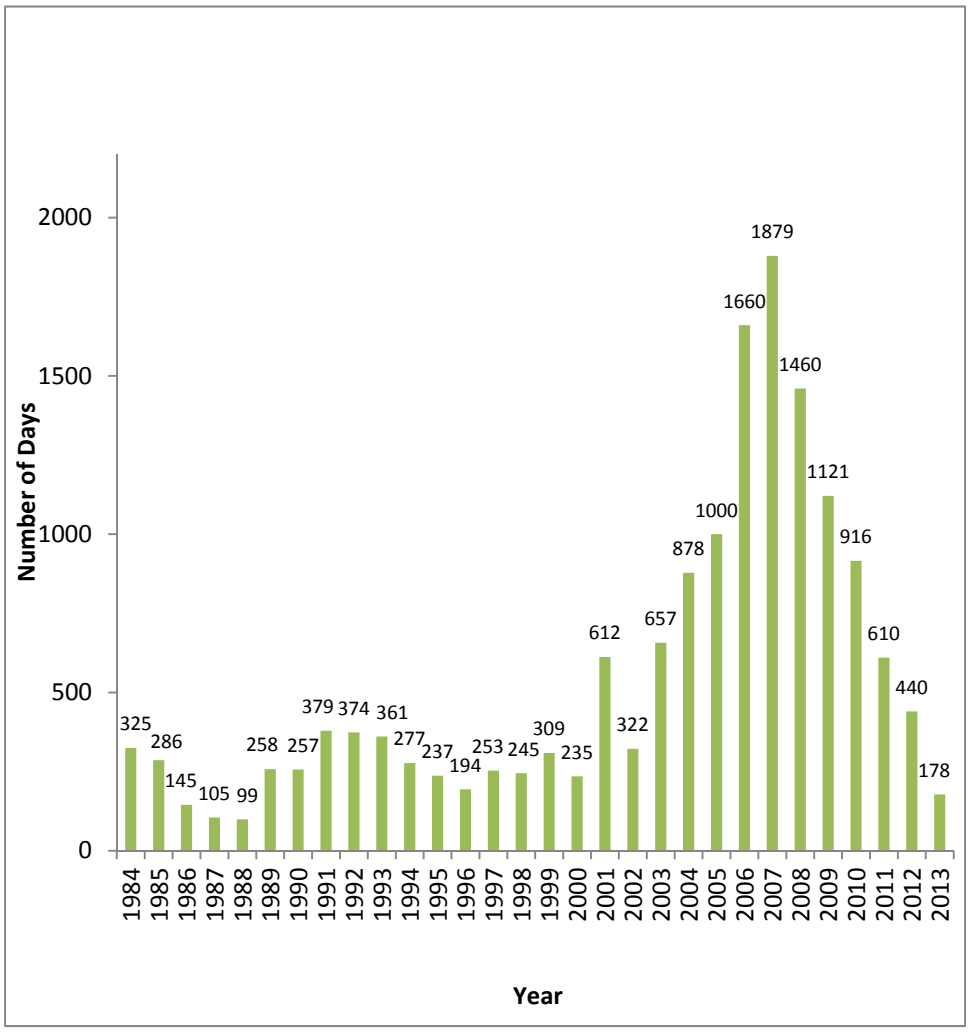

Table 11: Median Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Including Pending Petitions

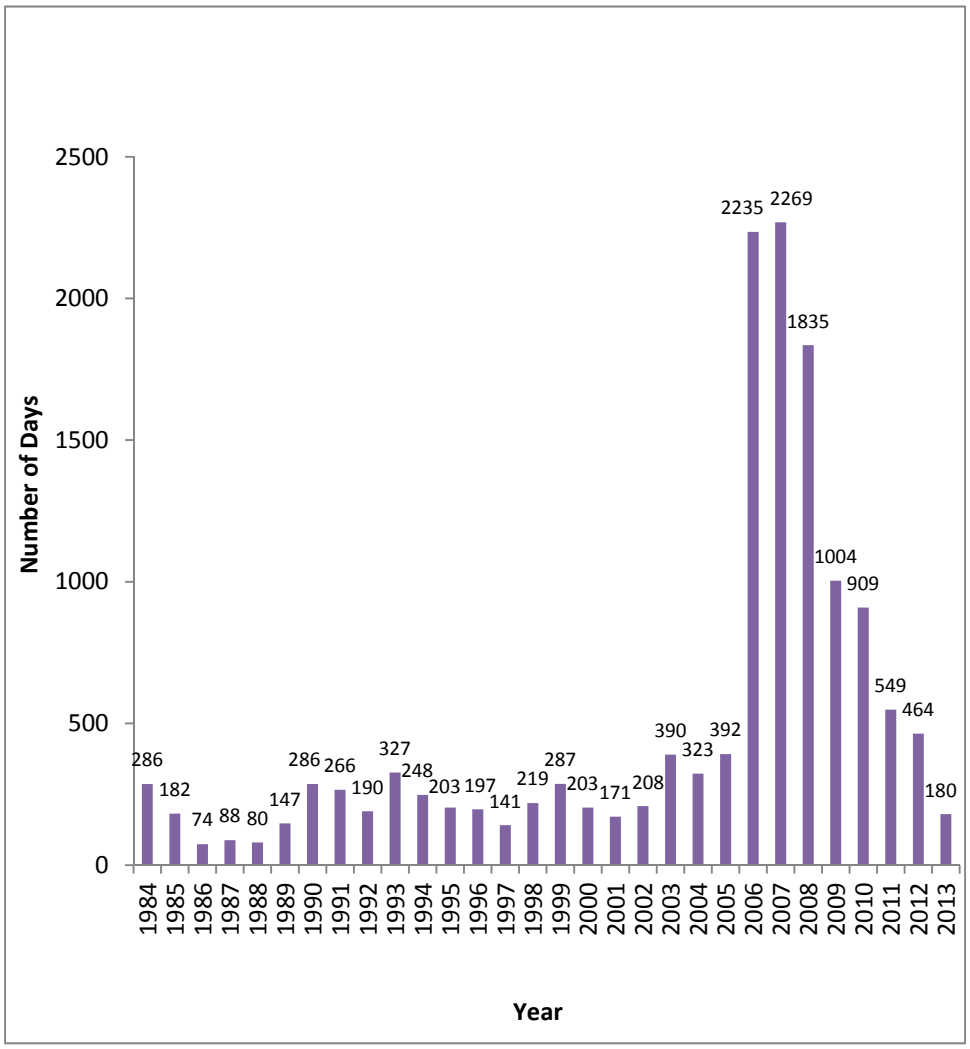

Table 12: Average and Median Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Including Pending Petitions

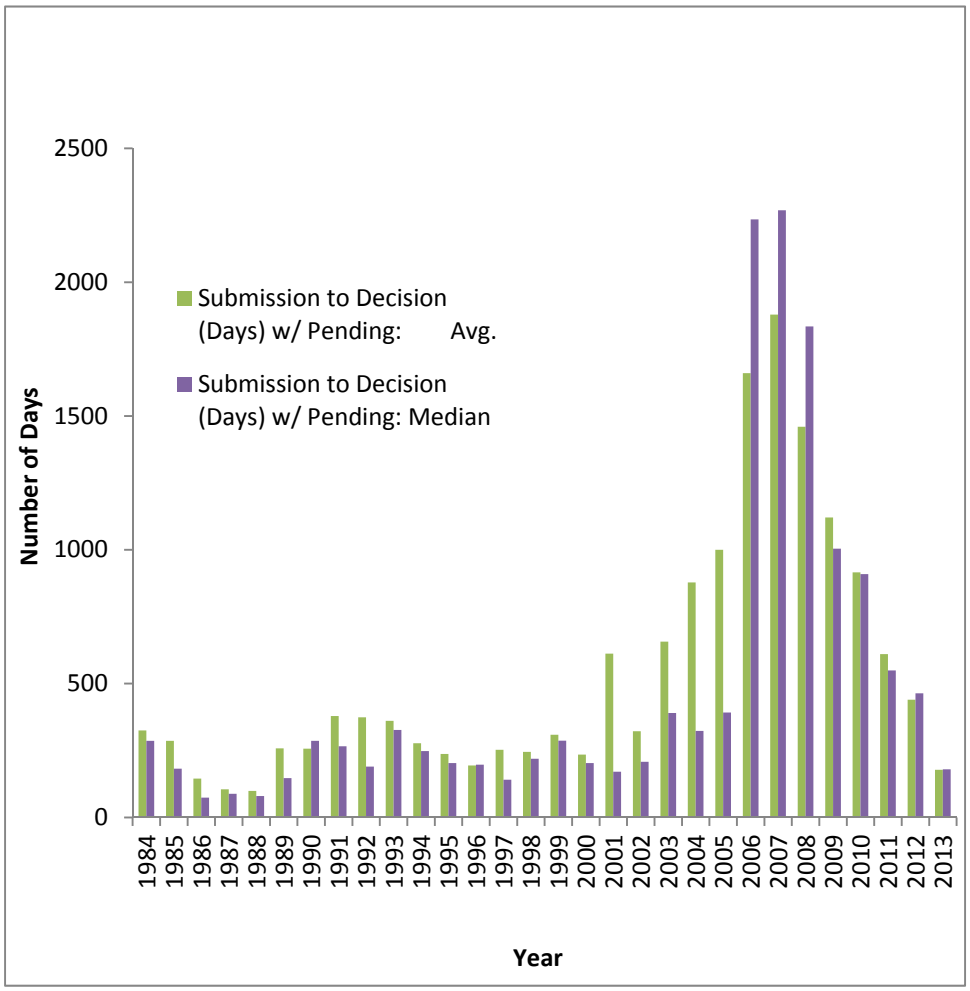

Table 13: ANDA Suitability Petition Submission & Action by Year (1984–2013)—Excluding Pending Petitions

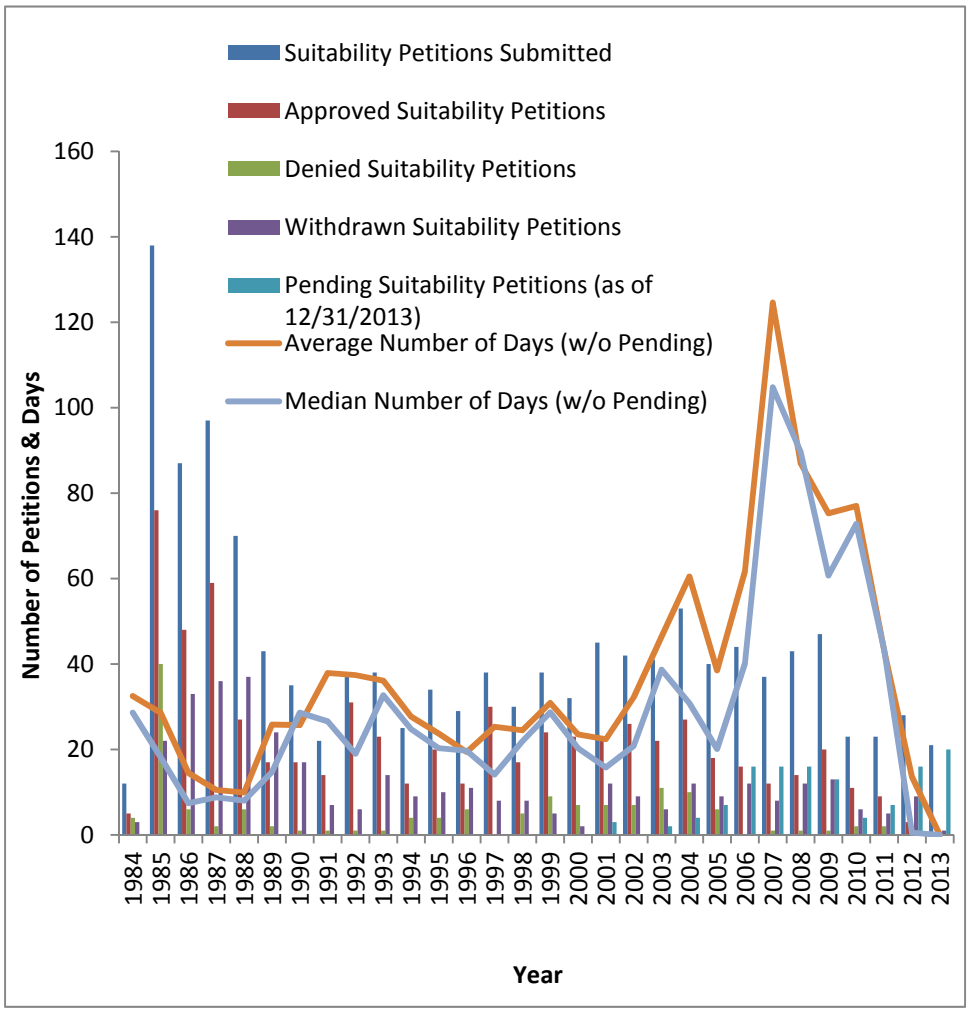

Table 14: ANDA Suitability Petition Submission and Action by Year (1984–2013) — Including Pending Petitions

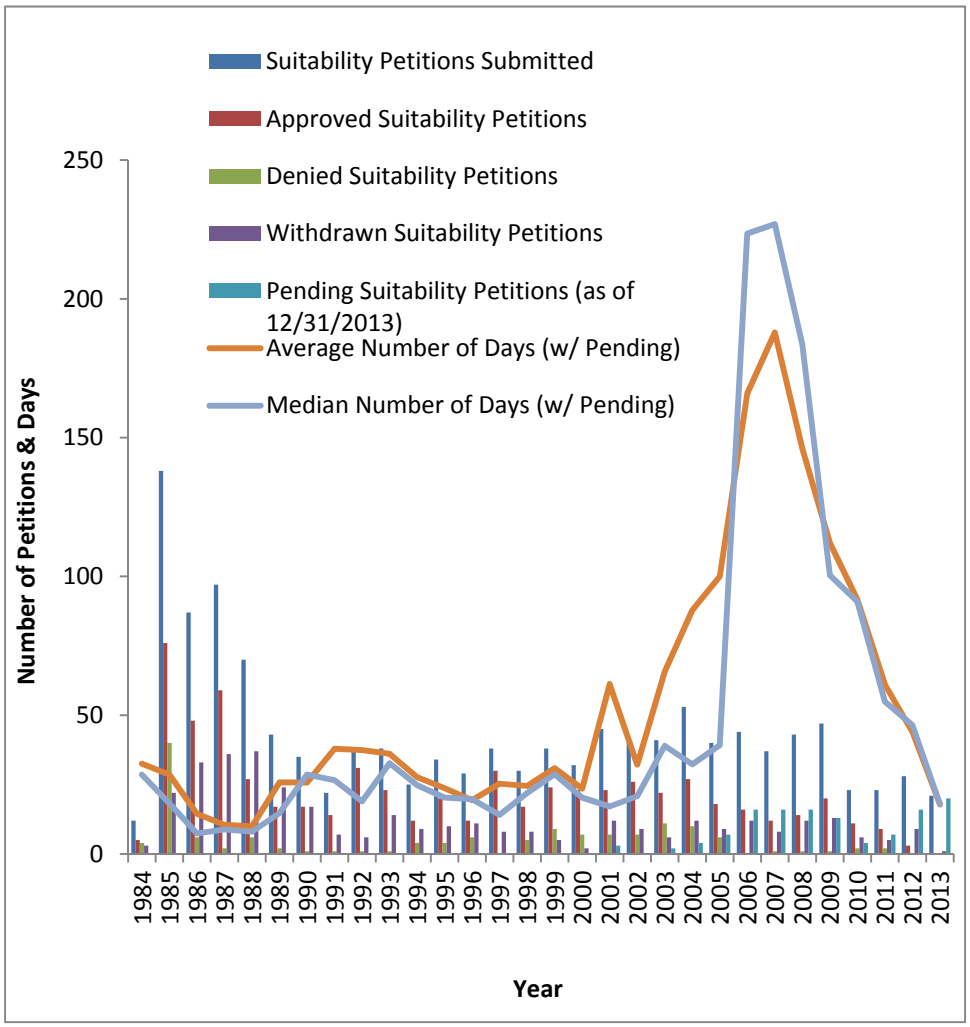

Table 15: ANDA Suitability Petition Submissions by Year (1984–2013)—Trend

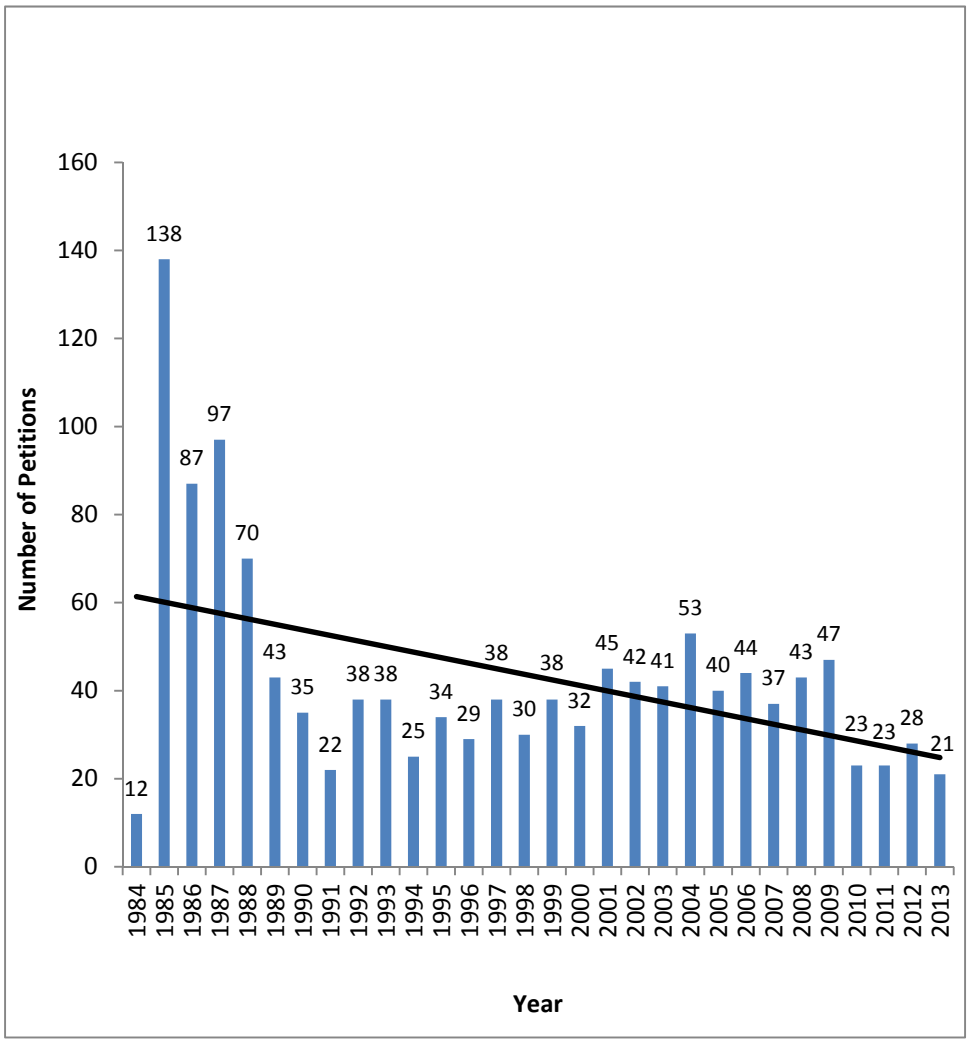

Table 16: Average & Median Number of Days to FDA Decision (Approval or Denial) by Year (1984–2013)—Excluding Pending Petitions—Trend