

FOOD AND DRUG LAW AND REGULATION

THIRD EDITION

EDITED BY
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CHAPTER 11
GENERIC DRUGS:
ANDAS, SECTION 505(b)(2) APPLICATIONS,
PATENTS, AND EXCLUSIVITIES

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Submission of a new drug application (NDA) under section 505(b)(1) following lengthy preclinical and clinical investigations, as discussed in Chapter 10, is not the only pathway to market for drugs. Indeed, there currently are two abbreviated pathways for traditional chemical drugs to reach the market: one for generic drugs, for which an abbreviated new drug application (ANDA) can be filed, and one for drugs approved under section 505(b)(2), for which an NDA must be filed but for which approval can be based in part on the safety and effectiveness of an already-approved drug.¹

The term “generic drug” generally applies to a drug that is the same as its counterpart brand product with respect to active ingredient(s), dosage form, strength, route of administration, and conditions of use.² FDA advises that generic drugs that contain the same active ingredients as the brand, and have the same labeling and are shown to be available to the treatment site at the same rate as the brand, may be therapeutically equivalent to the brand.³ Section 505(b)(2) applications may be submitted for new chemical entities or for modified versions of previously approved drugs. Section 505(b)(2) drugs differ from section 505(b)

* This is an updated version of a chapter originally written by William B. Schultz and Margaret M. Dotzel and updated by Lisa Barclay.

¹ On March 23, 2010, President Obama signed into law the Affordable Care Act, which contained the Biologics Price Competition and Innovation Act of 2009, which amends the Public Health Service Act (PHSA) and other statutes to create an abbreviated approval pathway for biological products shown to be highly similar (biosimilar) to, or interchangeable with, an FDA-licensed reference biological product. Section 351(k) of the PHSA (42 U.S.C. § 262(k)), which was added by the new legislation, allows a company to submit an application for licensure of a biosimilar or interchangeable biological product. Biosimilars are discussed more fully in Chapter 15.

² 21 C.F.R. § 314.92(a)(1).

³ See FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (34th ed. 2014) at vii (hereinafter the Orange Book). Virtually every state has adopted laws and/or regulations that govern the substitution of drug products. *Id.* at iv. Some take the approach of permitting substitution only for drugs on a specific list (the positive formulary approach). *Id.* Others require that substitution be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). *Id.*

(1) drugs because they may be approved based in part on the safety and effectiveness of an approved drug.

These abbreviated pathways to drug approval are important because they permit manufacturers to gain approval without having to repeat expensive clinical trials that have already been conducted by their brand counterparts.⁴ Because generic drug manufacturers are not required to repeat expensive clinical trials and because they generally market their products to drug suppliers and do not undertake significant advertising directed at physicians or consumers, generic drugs typically are sold at a fraction of the cost of brand products.⁵ Thus, generic drugs save consumers, healthcare providers, and state and federal governments billions of dollars per year.⁶

The History of Generic Drugs and Abbreviated Drug Applications

Although the Drug Price Competition and Patent Term Restoration Act of 1984, popularly known as the “Hatch-Waxman Amendments” or “Hatch-Waxman,” is credited with creating the approval pathway for generic drugs and is responsible for creating the modern-day generic drug industry, prior to 1984 FDA took important steps to facilitate the marketing of generic drugs.

The Earliest Generics

Prior to enactment of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938, there were few regulatory barriers to the market entry of drugs, including generic versions of brand products. After the 1938 act was enacted, however, a new drug could not be marketed unless its NDA demonstrating the drug’s safety became effective⁷ or the drug was generally recognized as safe (GRAS).⁸ With respect to the latter pathway, FDA adopted an informal practice whereby upon request it would inform an interested party whether a particular drug was GRAS or a new drug subject to a premarket application.⁹ Thus, a manufacturer could make its own determination that a particular drug was GRAS, or it could seek a letter

⁴ *Mova Pharmaceuticals Corp. v. Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998).

⁵ *United States v. Generix Drug Corp.*, 460 U.S. 453, 455 n.1 (1983). Generic drugs are discounted as much as 70 to 80 percent. See CONG. BUDGET OFF., HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY (July 1998), available at <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/6xx/doc655/pharm.pdf> [hereinafter the 1998 CBO Study]; see generally, David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 REVIEW OF ECON. & STAT. 37 (2005).

⁶ See, e.g., FEDERAL TRADE COMMISSION, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY (July 2002), at 9 (citing Congressional Budget Office studies to show, among other things, that in 1994, the availability of generic drugs saved consumers \$8 billion to \$10 billion) [hereinafter FTC Report].

⁷ The 1938 act provided that a new drug application (NDA) would automatically become effective within 60 days unless the agency affirmatively refused to approve the application. Pub. L. No. 75-717, 52 Stat. 1040 (codified at 21 U.S.C. § 301 *et seq.*) (1938). The requirement for affirmative approval by FDA was not added until the 1962 Drug Amendments, Pub. L. No. 87-781, 76 Stat. 780 (1962).

⁸ Pub. L. No. 75-717, 52 Stat. 1040 (codified at 21 U.S.C. § 301 *et seq.*).

⁹ See New Drug Status Opinions; Statement of Policy, 33 Fed. Reg. 7758 (Jan 23, 1968); see also Abbreviated New Drug Application Regulations; Proposed Rule, 54 Fed. Reg. 28,872 (July 10, 1989).

from FDA stating that fact. The practice of informing manufacturers about the status of their drugs was discontinued in 1968 and all “not new drug letters” were formally revoked by the agency at that time.¹⁰ Between 1938 and 1962, FDA considered drugs that were identical, similar, or related to drugs with effective applications to be covered by those approvals and allowed those drugs to be marketed without independent approval.¹¹

The DESI Review

In 1962, Congress passed the Kefauver-Harris Drug Amendment, which added as a condition for approval that a drug be effective. The 1962 amendments also required a retrospective evaluation of the efficacy of drugs that had been approved as safe between 1938 and 1962.¹² Under the Drug Efficacy Study Implementation (DESI) Review, which FDA established in 1968 to implement the 1962 amendments, the National Academy of Sciences appointed expert panels to review available data on all drugs first marketed between 1938 and 1962 to make recommendations as to their efficacy.¹³ FDA had approved generic versions of pre-1962 drugs without requiring independent evidence of safety or effectiveness if their manufacturers demonstrated that they were duplicates of drugs that the agency had determined had sufficient evidence of effectiveness to warrant continued approval and the manufacturer provided product quality information.¹⁴ To do so, the agency created a new form of NDA, known as the ANDA, for which approval was based on sameness of active ingredients and bioequivalence rather than on safety and efficacy data.¹⁵

The Paper NDA Policy

The DESI program and the abbreviated mechanism for approval of duplicates did not apply to drugs first marketed after 1962. Although FDA initially concluded that the FDCA did not provide authority for an abbreviated pathway for approval of these drugs, it did recognize that sound public policy would allow duplicates to enter the market without undertaking expensive and repetitive testing.¹⁶ Thus, FDA sought an alternate way to expand the ANDA policy to post-1962 drugs. Initially, it adopted the “paper NDA” policy. This policy permitted competing versions of approved new drugs to demonstrate safety and effectiveness on the basis of publicly available reports of well-controlled studies demonstrating the drug’s safety and efficacy.¹⁷ Although the paper NDA policy survived a court challenge,¹⁸ it did little to

¹⁰ *Id.*

¹¹ See FDA, Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guidance (June 2006).

¹² Pub. L. No. 87-781, 76 Stat. 780 (1962).

¹³ See 54 Fed. Reg. at 28,873.

¹⁴ See Abbreviated Applications; Proposed Rule, 34 Fed. Reg. 2673 (Feb 27, 1969); Abbreviated Applications; Final Rule, 35 Fed. Reg. 6574 (Apr. 24, 1970). See also 54 Fed. Reg. at 28,872-73.

¹⁵ *Id.* As discussed herein, many drugs came onto the market before 1962 without FDA approvals, most often because they were claimed to have been marketed prior to 1938 or to be identical, similar, or related to such a drug. These drugs were not subject to DESI. In response to concerns about these unapproved drugs, FDA developed a program known as the “Prescription Drug Wrap-Up,” which was designed to address the legal status of these drugs. See FDA, Guidance for FDA Staff and Industry: Marketed Unapproved Drugs—Compliance Policy Guide (June 2006).

¹⁶ Response to Petition Seeking Withdrawal of the Policy Described in the Agency’s “Paper” NDA Memorandum of July 31, 1978; Notice, 45 Fed. Reg. 82,052 (Dec. 12, 1980).

¹⁷ Publication of “Paper NDA” Memorandum; Notice, 46 Fed. Reg. 27,396 (May 19, 1981).

¹⁸ *Burroughs Wellcome Co. v. Schweiker*, 649 F.2d 221 (4th Cir. 1981); see also *Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982).

foster generic competition because adequate published studies were available for only a fraction of post-1962 drugs.¹⁹ In 1982, FDA announced that it was reconsidering its initial assessment of the scope of its authority and was contemplating changing its regulations to create an abbreviated pathway for post-1962 drugs similar to the DESI process for pre-1962 drugs.²⁰ FDA's efforts were overtaken by passage of the Hatch-Waxman Amendments in 1984, which eliminated the need for a regulatory change.

The Hatch-Waxman Amendments

At the same time that the generic drug industry was urging FDA and Congress to create an abbreviated pathway for generic drug approval, the brand drug industry was arguing that its companies were losing the effective period of their patent protection because of the length and complexity of the drug approval process. To address the brand industry concerns, Senator Orrin Hatch introduced a bill that would have provided for patent extensions where a company had lost patent time while testing its product and awaiting approval of its NDA. At approximately the same time, Congressman Henry Waxman introduced legislation to simplify the requirements for approval of generic drugs, modeled after the ANDA process that applied to pre-1962 drugs. Ultimately these bills were combined, and the Hatch-Waxman Act created two new abbreviated statutory pathways—ANDAs submitted under section 505(j), which were modeled after the ANDAs FDA had been accepting for DESI drugs; and NDAs submitted under section 505(b)(2), which under the law could be based in part on the agency's safety and efficacy finding for a different drug. The new statute also created a process for granting patent extensions to new drugs and incentives (in the form of exclusivity) both for research and for challenging patents.

Specifically, Hatch-Waxman established a process under section 505(j) pursuant to which duplicates of previously approved brand drugs could be approved on the basis of chemistry, manufacturing, and bioequivalence data without evidence from literature or clinical data to establish effectiveness and safety.²¹ Under these provisions, if an ANDA applicant establishes that its proposed drug product has the same active ingredient, strength, dosage form, route of administration, labeling, and conditions of use as the brand drug and that it is bioequivalent to that drug, the applicant may rely on the fact that FDA previously found the brand drug to be safe and effective.²² The legislation also permitted generic drug applicants to petition for permission to submit ANDAs for products that differ from the brand drug in any of four specified ways—dosage form, route of administration, strength, or active ingredients—where such changes do not require review of clinical data.²³ Such petitions are called “suitability petitions,” and under section 505(j) the applicant must show that the generic product is sufficiently similar to the approved product for which safety and effectiveness have already been established so that no additional evidence of safety and effectiveness need be submitted for review.²⁴

¹⁹ See 54 Fed. Reg. at 28,873-75.

²⁰ Abbreviated New Drug Applications for New Drugs Approved After October 10, 1962 for Human Use; Calendar of Federal Regs., 47 Fed. Reg. 1765, 1767 (Jan. 13, 1982).

²¹ Pub. L. No. 98-417, 98 Stat. 1585 (1984).

²² FDCA § 505(j), 21 U.S.C. § 355(j).

²³ FDCA § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C). A change in active ingredient is permitted only where one active ingredient is substituted for one of the active ingredients in a listed combination drug. 21 C.F.R. § 314.93(b). A change in active ingredient is therefore not permitted in a single active ingredient product.

²⁴ FDCA § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C).

One of the goals of the Hatch-Waxman Act was to get safe and effective generic substitutes on the market as quickly as possible after expiration of the underlying patent.²⁵ To achieve that objective, Congress created a statutory scheme pursuant to which FDA could tentatively approve an ANDA before the patent for the “pioneer” drug had expired with an effective date as of the patent’s expiration date.²⁶ Hatch-Waxman also overturned the holding of the 1984 decision of the Federal Circuit in *Roche v. Bolar*, which had prohibited testing on a patented drug before the expiration of the patent.²⁷ In addition, the law included a reward to the generic companies that contested the validity or infringement of brand patents, namely a 180-day period of “generic exclusivity,” during which the first generic to challenge the patent would be protected from competition by subsequently filed ANDAs challenging the same patent.

The second abbreviated pathway created by Hatch-Waxman was a new type of NDA, the 505(b)(2) application. Section 505(b)(2) permits an applicant to rely on investigations not conducted by or for the applicant and for which the applicant has not obtained a right of reference. Although, as discussed in greater detail below, it has been argued that this provision was intended only to codify FDA’s “paper NDA” policy, since 1984 FDA has concluded, based on the provision’s language, that Congress intended a much broader application, namely to permit companies to rely on the agency’s previous findings of safety and effectiveness for a drug if that finding is useful in reducing the data required to establish safety and effectiveness of the applicant’s product. Section 505(b)(2) basically covers drugs that are not duplicates of already-approved drugs but for which a full NDA would require testing that would be duplicative and unnecessary. The patent extension provisions and exclusivities awarded to innovator products that apply to ANDAs also apply to 505(b)(2) applications.²⁸

The Post Hatch-Waxman Years

The Hatch-Waxman Amendments dramatically increased the entry of generic drugs into the market. Today, generic drugs comprise 69 percent of all prescriptions dispensed, up from 19 percent in 1984, when the law was passed.²⁹ At the same time, generic medicines account for only 16 percent of all dollars spent on prescription drugs.³⁰ Despite the success

²⁵ See H.R. REP. NO. 98-857, Part II at 8-9 (Aug. 1, 1984), 1984 U.S.C.C.A.N. 2686, 2692-3; see also *Mead Johnson Pharmaceutical Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988) (“The purpose of [the Drug Price Competition and Patent Term Restoration Act] was to increase competition in the drug industry by facilitating the approval of generic copies of drugs.”).

²⁶ See H.R. REP. NO. 98-857, Part I at 27 (June 21, 1984) (“The Committee recognizes that some ANDA’s will be submitted and ready for approval before the patent on the listed drug has expired.”).

²⁷ *Roche v. Bolar*, 733 F.2d 858 (Fed. Cir. 1984), cert. denied, 469 U.S. 856 (1984). The House Judiciary Committee rejected an amendment to the act that would have limited generic drug manufacturers’ ability to conduct bioequivalency tests before the pioneer drug’s patent expired to the last year of exclusivity because the amendment would have resulted in delays after the expiration of the patent before the generic drug could go on the market, in contradiction of the policy objective of “getting safe and effective generic substitutes on the market as quickly as possible after the expiration of the patent.” H.R. REP. NO. 98-857, Part II at 8-9.

²⁸ See FDCA § 505(c)(3), 21 U.S.C. § 355(c)(3).

²⁹ See “Facts at a Glance,” Generic Pharmaceutical Industry Ass’n., available at <http://gpha.hfwebdev.com/about-gpha/about-generics/facts> (last visited Sept. 17, 2014) [hereinafter GPhA Facts at a Glance]; see also the 1998 CBO Study, *supra* note 5 at ix; FTC Report, *supra* note 6 at i.

³⁰ GPhA Facts at a Glance, *supra* note 29.

of the law, FDA's generic program got off to a difficult start. In addition, some aspects of the law led to controversial practices and strategies, which resulted in additional legislation. The significant issues and statutory changes designed to address those issues will be discussed throughout this chapter.

The first controversy grew out of what is now referred to as “the generic drug scandal.” Following the passage of Hatch-Waxman, an investigation by the Subcommittee on Oversight of the House Committee on Energy and Commerce revealed that a number of generic companies were paying unlawful gratuities to FDA reviewers with the hope of receiving expedited or favorable consideration of their ANDAs. Others were submitting fraudulent data. Congress responded by referring some of the individuals whom it investigated for criminal prosecution and enacting the Generic Drug Enforcement Act of 1992.³¹ That act provides for debarment of firms or individuals convicted of fraud and other crimes in the course of the ANDA process, and it authorizes FDA to impose civil money penalties for ANDA fraud.³²

Since 1984, the courts and FDA have addressed a number of Hatch-Waxman issues. In response to allegations that certain provisions of Hatch-Waxman were being misused, in 2003, Congress included amendments to Hatch-Waxman in the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA).³³ These provisions were designed to close some legal loopholes that continued to delay generic drug approval. In 2007, as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress added additional new requirements related to ANDAs and generic drug approvals.³⁴ The specifics of these laws and the issues they sought to address are discussed in further detail below.

The ANDA Approval Process

ANDA Applications

As stated above, a generic drug typically is the same as the brand drug product with respect to active ingredient, dosage form, strength, route of administration, and intended use.³⁵ A company seeking to market a generic version of a brand-name drug first must submit an ANDA to FDA that includes:

- (a) information showing that the proposed conditions of use previously have been approved for a drug that FDA has approved for safety and efficacy (hereinafter referred to as the “reference listed drug” or “RLD”);³⁶

³¹ Pub. L. No. 102-292, 106 Stat. 149 (codified at 21 U.S.C. §§ 335a-335c).

³² See 21 U.S.C. § 335a-335c.

³³ Pub. L. No. 108-173, 117 Stat. 2066 (2003).

³⁴ Pub. L. No. 110-85, 121 Stat. 823 (2007).

³⁵ 21 C.F.R. § 314.92(a)(1).

³⁶ FDCA § 505(j)(2)(A)(i), 21 U.S.C. § 355(j)(2)(A)(i).

- (b) proof that the active ingredient(s) is (are) the same as the active ingredient(s) in the RLD;³⁷
- (c) information showing that the route of administration, dosage form, and strength are the same as those for the RLD;³⁸
- (d) information to show that the drug is bioequivalent to the RLD;³⁹
- (e) information to show that the proposed labeling of the generic is the same as the labeling for the RLD except for changes required because of differences approved pursuant to the suitability petition process, discussed below, or because of differences related to different manufacturers;⁴⁰
- (f) the basic technical information required in an NDA (e.g., chemistry, manufacturing data);⁴¹ and
- (g) a certification that describes the applicant's belief regarding the status of each patent that claims the RLD.⁴²

Reference Listed Drug—Orange Book Listing/Delisting

A reference listed drug is a drug identified by FDA in its list of approved drugs (the Orange Book) as a drug product upon which an ANDA applicant can rely in seeking approval.⁴³ A listing in the Orange Book means that the drug has been approved and not withdrawn from the market based upon safety or efficacy concerns.⁴⁴ Although FDA rarely withdraws an approval for a drug, manufacturers occasionally remove a drug voluntarily. In such cases, FDA must determine whether the drug was withdrawn for reasons of safety or effectiveness before approving any ANDA that references such drug or before permitting the continued marketing of any ANDA that has already been approved.⁴⁵ A firm that seeks to use a reference drug that is not designated as an RLD may submit a citizen petition to FDA seeking to have the agency designate its preferred listed drug as an RLD.⁴⁶ An interested person may also petition FDA to make such a determination.⁴⁷

Suitability Petition

As noted above, although a generic drug generally must be the same as the brand drug product with respect to active ingredient, dosage form, strength, route of administration, and intended use,⁴⁸ Hatch-Waxman permits a generic applicant to petition FDA for permission to file an ANDA for a drug that has a different active ingredient, route of administration, dosage

³⁷ FDCA § 505(j)(2)(A)(ii), 21 U.S.C. § 355(j)(2)(A)(ii). The statute permits the use of a different active ingredient in a multiple-active-ingredient drug product provided the difference has been approved in a "suitability petition," which is discussed in further detail below.

³⁸ FDCA § 505(j)(2)(A)(iii), 21 U.S.C. § 355(j)(2)(A)(iii). The statute also permits differences here pursuant to an approved suitability petition.

³⁹ FDCA § 505(j)(2)(A)(iv), 21 U.S.C. § 355(j)(2)(A)(iv).

⁴⁰ FDCA § 505(j)(2)(A)(v), 21 U.S.C. § 355(j)(2)(A)(v).

⁴¹ FDCA § 505(j)(2)(A)(vi), 21 U.S.C. § 355(j)(2)(A)(vi).

⁴² FDCA § 505(j)(2)(A)(vii), (viii), 21 U.S.C. § 355(j)(2)(A)(vii), (viii).

⁴³ 21 C.F.R. §§ 314.3(b), 314.94(a)(3).

⁴⁴ 21 U.S.C. §§ 355(j)(7)(C); 21 C.F.R. § 314.3(b).

⁴⁵ 21 C.F.R. § 314.161.

⁴⁶ See *id.* §§ 10.25(a), 10.30, 314.94(a)(3).

⁴⁷ *Id.*

⁴⁸ 21 C.F.R. § 314.92(a)(1).

form or strength.⁴⁹ FDA is directed to approve such a petition (called a suitability petition) unless it finds that 1) investigations must be conducted to show safety and effectiveness; or 2) the drug with a different active ingredient cannot be evaluated for approval on the basis of information that is required in an ANDA.⁵⁰ An applicant may not submit an ANDA for a drug subject to a suitability petition until after FDA has granted the petition. Because of the time involved in FDA reviewing the petition and the significant backlog, many applicants forgo this route and instead submit a 505(b)(2) filing.

Bioequivalence

In order to rely on FDA's previous finding that the RLD is safe and effective, the ANDA applicant must show that its proposed product is bioequivalent to the RLD.⁵¹ Bioequivalence is the foundation of generic drug approval. A generic will be found to be bioequivalent if:

- the rate and extent of the drug's absorption into the body (i.e., bioavailability) is not significantly different from the RLD when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses;⁵² or
- the extent of absorption of the drug into the body does not show a significant difference from the extent of absorption of the RLD when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the RLD in the rate of absorption is intentional, is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.⁵³

An ANDA submitted based on a suitability petition may be approved on the basis of a showing that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug and that the new drug can be expected to have the same therapeutic effect.⁵⁴

Same Labeling

Historically, as mentioned above, the Hatch-Waxman Amendments provided an avenue for generic drug manufacturers to submit more streamlined drug applications that no longer required expensive and lengthy clinical trials for generic drug products. Instead, the generic drug manufacturer had to prove that the drug was the same as the branded drug with regard to active ingredients, dosage form, strength, and route of administration, except for differences approved by FDA under a suitability petition.⁵⁵ This sameness requirement is the hallmark of the Hatch-Waxman Amendments.

⁴⁹ FDCA § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C); 21 C.F.R. § 314.93.

⁵⁰ FDCA § 505(j)(2)(C), 21 U.S.C. § 355(j)(2)(C). Different active ingredients are allowed only for combination drugs in which at least one active ingredient is the same as the RLD and the second is approved in a similar drug.

⁵¹ FDCA § 505(j)(4)(F), 21 U.S.C. § 355(j)(4)(F); *Pfizer Inc. v. Shalala*, 182 F.3d 975, 977 (D.C. Cir. 1999).

⁵² FDCA § 505(j)(8)(B)(i), 21 U.S.C. § 355(j)(8)(B)(i).

⁵³ FDCA § 505(j)(8)(B)(ii), 21 U.S.C. § 355(j)(8)(B)(ii).

⁵⁴ FDCA § 505(j)(4)(F), 21 U.S.C. § 355(j)(4)(F).

⁵⁵ 21 U.S.C. § 355(j)(2)(A)(i)-(iv).

Likewise, the FDCA requires a generic drug's labeling to be the same as the RLD unless changes are required because of differences approved under a suitability petition or because the generic and the RLD are produced or distributed by different manufacturers.⁵⁶ FDA's regulations have interpreted the law to permit changes in a generic drug's labeling in a variety of circumstances, including for differences in expiration dates, formulations, bioavailability, or pharmacokinetics; because of labeling revisions made to comply with current FDA labeling guidelines; and because aspects of the RLD's labeling are protected by patent or by exclusivity (discussed below) and such differences do not render the generic drug less safe and effective than the RLD for all of the remaining, non-protected conditions of use.⁵⁷

Brand companies have mounted several unsuccessful judicial challenges to FDA's regulations. For example, in one case, a brand company challenged the approval of an ANDA that included a label warning regarding an inactive ingredient (sulfite) found in the generic product but not in the brand.⁵⁸ The court rejected the challenge on the grounds that the changes were permitted based on differences in formulation and in order to comply with current FDA labeling guidelines and guidance on sulfite warnings.⁵⁹

Equally unsuccessful court challenges were mounted against the part of the regulation that permits differences in labels that exclude protected information. For example, two companies argued that permitting a generic to be approved without the protected information undercuts their exclusivity or protection because a physician can prescribe the generic product for the protected indication. The courts rejected this argument.⁶⁰

Brand manufacturers also have argued in administrative proceedings that the labeling change for which they were granted exclusivity or patent protection was so critical to the safe and effective use of the drug that no generic could be approved without it, and thus no generic could be approved until the three-year exclusivity or the patent had expired. FDA has generally rejected this argument and allowed the generics to carve out the protected information and market the drug without it.⁶¹ In the one instance in which FDA determined

⁵⁶ FDCA § 505(j)(2)(A)(v), 21 U.S.C. § 355(j)(2)(A)(v).

⁵⁷ 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7).

⁵⁸ *Zeneca v. Shalala*, 213 F.3d 161 (4th Cir. 2000).

⁵⁹ *Id.*

⁶⁰ *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996) (holding that a generic drug manufacturer may omit labeling protected by the three-year exclusivity because the exclusivity would otherwise prevent the approved ANDA from entering the market at all during the three-year period and would expand the scope of the exclusivity beyond that intended by Congress); *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, 288 F.3d 141, 148 n.3 (4th Cir. 2002) (agreeing with the D.C. Circuit's holding in *Bristol-Myers*).

⁶¹ *See, e.g.*, Letter from Steven K. Galson, Director, CDER, to Edward John Allere and Theodore Sullivan, Buchanan Ingersoll P.C., Docket No. 2005P-0383 (Dec. 1, 2006) (rejected Savient's argument that omission of protected geriatric use information was inconsistent with FDA's regulations and would render the generic less safe because the generic's label would lack important dosing and safety information for use in geriatric patients that comprise a significant portion of the patient population); Letter from Steven K. Galson, Acting Director, CDER, to David M. Fox, Esq., Hogan and Hartson, Docket No. 2003P-0321 (Apr. 6, 2004) (denied Citizen Petition asking FDA to refrain from approving generic ribavirin with labels that omit protected information regarding the use of ribavirin with PEG-Intron® arguing that generics with labeling for only the non-protected use (ribavirin used in combination with INTRON A®) would result in medication errors for patients prescribed generic ribavirin for use in combination with PEG-Intron® because appropriate dosage information would be missing); Letter from Janet Woodcock, Director, CDER, to Marcy MacDonald, Associate Director, Regulatory Affairs, Apotex Corp., Deborah A. Jaskot, Executive Director, Regulatory

that the protected information could not be omitted from the generic labeling and thus a generic could not be approved until the three-year period expired, FDA found that the protected labeling was critical prescribing information that all physicians should receive to appropriately determine treatment for all indications.⁶²

The same labeling requirement has become an impediment in failure-to-warn claims brought by private citizens under state law against generic drug manufacturers. The United States Supreme Court in *PLIVA, Inc. v. Mensing*,⁶³ held that federal laws and regulations preempted state failure-to-warn claims because it would be impossible for generic manufacturers to fulfill their state-law duties to warn without violating the federal-law requirement that the labeling be the same as the approved brand drug.

For instance, FDA's regulations expressly require the same labeling and do not authorize divergent product warnings. FDA has specifically stated:

Except for labeling differences under section 505(j)(2)(v) of the act, the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. *Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart.*⁶⁴

Mensing established that FDA's interpretations of these types of regulations are "controlling unless plainly erroneous or inconsistent with the regulations or where there is another reason to doubt that these views reflect FDA's fair and considerate judgments."⁶⁵

Until recently, FDA has stood its ground with respect to these "sameness" labeling requirements. However, just as it has permitted branded drug manufacturers to make certain changes to their labels prior to receiving FDA approval,⁶⁶ FDA has proposed new rules that would "allow[] generic drug makers to use the same process as brand drug manufacturers to update safety information in the product labeling."⁶⁷ In an effort to "speed the dissemination of new safety information about generic drugs," generic drug manufacturers would be

Affairs, Teva Pharmaceuticals, USA, and James F. Hurst, Esq., Winston and Strawn, Docket Nos. 2001P-0495, 2002P-0191, 2002P-0252 (June 11, 2002) (permitted generic applicants to omit from their labeling protected information regarding a 25-mg 16-day titration schedule; rejected brand argument that omission of the protected titration dosing information would decrease efficacy because slower titration increases tolerability); Letter from Janet Woodcock, Director, CDER, to Terry G. Mahn, Esq., Fish and Richardson, PC., Docket No. 2002P-0469 (May 21, 2003) (rejected argument that omission of pediatric information would prevent FDA from ensuring that generics are labeled for safe use in the pediatric population because section 11 of the Best Pharmaceuticals for Children Act would authorize it to include any necessary warnings or precautions in the labeling of the generic).

⁶² See Letter from Steven K. Galson, Acting Director, CDER to Michael S. Labson and Elizabeth M. Walsh, Counsel for Wyeth Pharmaceuticals, Docket No. 2003P-0518 (Sept. 20, 2004).

⁶³ 79 U.S.L.W. 4606 (2011).

⁶⁴ *Krelic v. Mutual Pharms. Co., Inc.*, C.A. No. GD-08-024513, 161 P.L.J. 329, 332 (emphasis added).

⁶⁵ *Id.* (citing *Mensing*, 131 S. Ct. at 2575).

⁶⁶ *Wyeth v. Levine*, 555 U.S. 555, 568 (2009).

⁶⁷ Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, 78 Fed. Reg. 67,985 (Nov. 13, 2013), available at <https://www.federalregister.gov/articles/2013/11/13/2013-26799/supplemental-applications-proposing-labeling-changes-for-approved-drugs-and-biological-products> (last visited Dec. 29, 2014); see also FDA News Release, FDA takes action to speed safety information on generic

permitted to “independently update product labeling . . . with newly-acquired safety information before FDA’s review of the change.”⁶⁸ FDA’s ultimate decision on these proposed labeling changes could affect both the branded and generic drug label, making sure that the branded and generic drug labeling information ultimately stay the “same” as each other.⁶⁹

Fundamentally, it is unlikely FDA has legal authority to implement these changes. FDA takes the position that the FDCA and the Public Health Service Act provide it with the authority to regulate drug labeling.⁷⁰ For example, FDA points to FDCA section 502, which “allows it to consider a drug misbranded if it bears inadequate directions for use or insufficient warnings.”⁷¹ Similarly, FDA points to FDCA section 701, which allows it to “regulate CBE supplements and their use.”⁷² However, one commentator points out that “[t]he ‘sameness’ requirement that underlies preemption is in the statute, and is unique to generic drugs.”⁷³ As such, FDA may be precluded by the statute from making such rules.⁷⁴ Ultimately, the promulgation of the proposed rule could upset the “delicate balance of rights and responsibilities of the brand and generic industry.”⁷⁵ If nothing else, it would “change the entire regulatory and liability landscape for generic drug manufacturers.”⁷⁶

Patent Protection and Exclusivity

Today drug patents have a life of 20 years from the date of first filing of the patent application.⁷⁷ Because the U.S. Patent and Trademark Office (PTO) typically takes about one year to issue a patent, the new patent term generally lasts 19 years from the date of issuance. Nevertheless, because patents usually are obtained before a drug has been studied and approved for marketing, the effective patent term of the product is usually significantly less than the 19 or 20 years afforded under the law.

In 1984, when Congress passed Hatch-Waxman, it extended the patent life for drugs to compensate patent holders for time lost while developing their products and awaiting FDA approval. Under this law, approved drug products are eligible for a one-time patent extension of up to five years.⁷⁸ The extension period is calculated on the basis of length of time required to study and gain approval of the patented product. The total post-approval patent protection period may not exceed 14 years (e.g., if there are still 12 years left on the

drugs (Nov. 8, 2013), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm374171.htm> (last visited Dec. 29, 2014).

⁶⁸ *Id.*

⁶⁹ *Id.*

⁷⁰ Alexander Gaffney, *Experts: FDA’s Generic Drug Labeling Rule Likely Illegal*, Regulatory Affairs Professionals Society (Nov. 15, 2013), available at <http://www.raps.org/regulatoryDetail.aspx?id=9655> (last visited Sept. 18, 2014).

⁷¹ *Id.*

⁷² *Id.*

⁷³ *Id.*

⁷⁴ *Id.*

⁷⁵ *Id.*

⁷⁶ Jennifer M. Thomas, *FDA Proposes a Rule That Would Undercut Generic Drug Preemption*, FDA Law Blog (Nov. 12, 2013), available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/11/fda-proposes-a-rule-that-would-undercut-generic-preemption.html (last visited Sept. 18, 2014).

⁷⁷ 35 U.S.C. § 154. Prior to June 8, 1995, the effective date of the Uruguay Rounds Agreement, patents had 17 years of patent life from the date the patent was issued.

⁷⁸ *Id.* § 156(d)(5)(E).

patent post-approval, the extension will be only two years; if there are 14 years left on the patent, no extension will be granted).⁷⁹

Hatch-Waxman also made drug products approved under section 505 of the FDCA eligible for five years of new drug product exclusivity (also called NCE (new chemical entity) exclusivity), and/or three years of exclusivity for certain applications that include clinical data under the same provision of the FDCA.⁸⁰

With regard to the NCE exclusivity, if there is no patent protection, the generic application may not be submitted until five years after the brand is approved, which means that the five-year exclusivity is effectively extended by the time it takes the generic to get approved. (This typically takes more than one year; the median approval time in 2007 was 18.9 months.) If the brand has a patent and the generic challenges the patent (on the grounds that it is not valid, not enforceable, or not infringed), the generic may submit an application four years after approval of the brand, but a timely patent suit by the brand will bar approval for an additional 30 months beyond what would have been the end of the five-year exclusivity period (unless the patent challenge is successful). Under the statute, if the brand files a timely patent suit, it gets a minimum of seven and one-half years of exclusivity.⁸¹ The period will be shortened if before the expiration of the seven-and-one-half-year period, a district court rules that the patent is invalid or was not infringed. (Note: if the brand has a patent that is not challenged and the patent runs longer than the five years of NCE exclusivity, the exclusivity will expire before the patent and provide no additional market protection other than that afforded by a valid patent.)

The three-year period of exclusivity is available for a product that is not an NCE if clinical data is needed to obtain approval of the product.⁸² To qualify for this type of exclusivity, a supplement to an application approved under section 505(b) must contain reports of new clinical investigations other than bioavailability studies.⁸³ This type of exclusivity is granted, for example, for changes to an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration, or conditions of use if clinical investigations were essential to approval of the application or supplemental application containing those changes. In contrast to the five-year exclusivity, which prevents even the submission of an ANDA for four or five years, depending on the circumstances, the three-year exclusivity does not delay submission of an ANDA; it delays only the ANDA's approval. This means that an ANDA can be submitted during the period of exclusivity and be ready for final approval as soon as the period expires. Moreover, a generic may be able to avoid the exclusivity by relying on the original formulation of the RLD. For example, if the exclusivity is based

⁷⁹ *Id.* § 156. The law defines drug product to mean the active ingredient of a new drug including any salt or ester of the active ingredient. *Id.* § 156(f). There has been litigation over the precise meaning of drug product. *See, e.g.,* Pfizer v. Dr. Reddy's Labs, Ltd., 359 F.3d 1361 (Fed. Cir. 2004); Glaxo v. Quigg, 894 F.2d 392 (Fed. Cir. 1990); Photocure ASA v. Kappos, 603 F.3d 1372 (Fed. Cir. 2010); Ortho-McNeil Pharm. v. Lupin, 603 F.3d 1377 (Fed. Cir. 2010).

⁸⁰ FDCA §§ 505(c)(3)(E), (j)(5)(F), 21 U.S.C. §§ 355(c)(3)(E), (j)(5)(F); *see also* 21 C.F.R. § 314.108.

⁸¹ FDCA § 505(j)(5)(F), 21 U.S.C. § 355(j)(5)(F). Thus, if a generic applicant challenges a brand patent in an ANDA filed four years after approval and the brand files suit, the 30-month period becomes a 42-month period during which an ANDA may not be approved. The 42-month period begins to run on the date that is four years after the date of approval of the brand RLD.

⁸² FDCA § 505(j)(5)(F)(iv), 21 U.S.C. § 355(j)(5)(F)(iv).

⁸³ *Id.*

on a formulation change, a generic can market the original formulation. Similarly, if the exclusivity is for a new use, the generic can market without the new use on its label. In some circumstances, however, the three-year exclusivity has the effect of blocking generics. For example, when the three-year exclusivity is granted in connection with a switch from prescription to over-the-counter (OTC) status, a generic cannot be approved until the expiration of the three years because the OTC status is protected by the three-year exclusivity.

Historically, FDA has interpreted the term NCE to be “a drug product that does not contain a previously approved active moiety.”⁸⁴ According to FDA’s Exclusivity Summary checklist for a fixed-combination product, if “*any one* of the active moieties in the drug product’ has been previously approved,” the three-year exclusivity checklist applies and the drug product is not eligible for the five-year NCE exclusivity.⁸⁵ In other words, if “the combination contains one never-before-approved active moiety and one previously approved active moiety,” it does not meet the criteria for five-year NCE exclusivity.⁸⁶ However, under FDA’s “umbrella policy,” if the drug product is eligible for five-year NCE exclusivity, then “drug products subsequently developed that contain the same active moiety would also benefit from the original product’s 5-year NCE exclusivity until the exclusivity period for the original product expired.”⁸⁷

FDA recognizes that fixed-combination drug products “can simplify regimens to allow easier distribution and improved patient adherence,” as well as provide “real clinical benefits, including potential increases in efficacy . . . reductions in adverse events and the development of resistance to antimicrobial treatments.”⁸⁸ In order to incentivize the development of fixed-combination products, FDA has issued a Final Guidance for Industry that recognizes the term “drug” in these provisions to mean “drug substance” or “active ingredient.”⁸⁹ Under this definition, the “5-year NCE exclusivity determination will be made for each drug substance in a drug product, not for the drug product as a whole.”⁹⁰ Therefore, a drug product would be “eligible for a 5-year NCE exclusivity, provided that it contains a drug substance that meets the definition of *new chemical entity*, regardless of whether that drug substance is approved alone or in a fixed combination.”⁹¹ This change is applied prospectively and, therefore, does not apply to any products that have already been approved.⁹²

⁸⁴ See, e.g., Letter from Janet Woodcock, M.D., Director, CDER, to David M. Fox, Hogan Lovells US LLP, Theodore M. Sullivan and Edward J. Allera, Buchanan Ingersoll & Rooney PC, and Joy J. Liu, Ropes & Gray LLP, Docket Nos. 2013-P-0058, 2013-P-0119, 2013-P-0471 (Feb. 21, 2014) (denied Citizen’s Petitions requesting FDA change its interpretation of the five-year NCE exclusivity provisions and regulations of implementation related to fixed-combination drug products); FDA Response to Citizens Petitions dated Feb. 21, 2014, at p. 6, available at http://www.duanemorris.com/site/static/Citizen_Petition_Denial_Response_from_FDA_CDER.pdf.

⁸⁵ *Id.* at 7 (emphasis in original).

⁸⁶ *Id.*

⁸⁷ *Id.* at 8.

⁸⁸ *Id.* at 15.

⁸⁹ FDA, Guidance for Industry: New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products (Oct. 2014) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf>.

⁹⁰ *Id.* at 8.

⁹¹ *Id.* at 2.

⁹² *Id.* at 1.

Another type of exclusivity that is available is orphan drug exclusivity. The first sponsor to gain approval of a drug product that qualifies for orphan designation under section 526 of the FDCA will receive a seven-year period of marketing exclusivity under section 527 of the FDCA.⁹³ An orphan drug is a drug for a disease or condition that affects fewer than 200,000 persons.⁹⁴ This exclusivity applies only to the indication for which the drug has been designated and approved, permitting other applications for the same drug for a new use to be approved. The exclusivity applies broadly, however, to any application for the same drug, which is defined in the regulations generally to mean a drug that contains the same active moiety or the same principal molecular structural features for the same indication.⁹⁵ This means that orphan exclusivity will block even the submission of a full NDA for the same product for the protected indication. The one exception is when the sponsor of a drug that is otherwise the same as one that already has orphan-drug approval for the same rare disease or condition can show that its drug is clinically superior.⁹⁶

In 1997, as part of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress created a new type of exclusivity, pediatric exclusivity, which awards an additional six months of exclusivity for conducting pediatric studies.⁹⁷ In order to qualify for the exclusivity, FDA must request a pediatric study, the study must be conducted in accordance with the request, and FDA must accept the study. Even if the study does not result in a pediatric indication, if it was conducted in accordance with the request, exclusivity will be granted.⁹⁸ Pediatric exclusivity attaches to any exclusivity and patent protection listed in the Orange Book for any drug product containing the same active moiety as the drug studied and for which the party submitting the study holds the approved new drug application.⁹⁹ When a qualifying pediatric study is conducted prior to approval, pediatric exclusivity will attach to any exclusivity or patent protection listed in the Orange Book upon approval of that unapproved drug.¹⁰⁰

Patent Listing and Certification

Because an ANDA may generally not be approved until all of the brand patents and relevant exclusivities have expired or have been successfully challenged, an ANDA applicant must include as part of its application a certification with respect to each patent that “claims” the RLD.¹⁰¹

Information as to which patents may be infringed if a generic is marketed is provided by the holder of the approval for the referenced listed drug, which, in its original NDA submission, must identify each patent that it believes “claims” the drug for which approval is sought.¹⁰² Once an NDA is approved, FDA is required to “make available to the public” a list containing,

⁹³ See 21 U.S.C. §§ 360bb, 360cc.

⁹⁴ FDCA § 526, 21 U.S.C. § 360bb.

⁹⁵ 21 C.F.R. § 316.3(b)(13).

⁹⁶ *Id.* See also 21 C.F.R. §§ 316.24, 316.25.

⁹⁷ See generally FDCA § 505A, 21 U.S.C. § 355a.

⁹⁸ *Id.*

⁹⁹ FDCA §§ 505A(a), (c), 21 U.S.C. §§ 355a(a), (c).

¹⁰⁰ *Id.*

¹⁰¹ FDCA § 505(j)(2)(A)(vii), 21 U.S.C. § 355(j)(2)(A)(vii).

¹⁰² FDCA §§ 505(b)(1), (c)(2), 21 U.S.C. §§ 355(b)(1), (c)(2). Process patents and patents that claim a method of use that is not in the NDA may not be submitted. 21 C.F.R. § 314.53(b).

among other things, patent information pertaining to approved drug products.¹⁰³ During the initial Hatch-Waxman rulemaking process, FDA identified the Orange Book, which was already in existence at the time Hatch-Waxman was enacted, as the publication that would be used to meet this statutory obligation.¹⁰⁴ The Orange Book thus provides publicly available, frequently updated information on the patents to which ANDA applicants must certify.¹⁰⁵ Patents listed in the Orange Book generally are referred to as “listed patents.”

If an NDA holder is awarded a patent that it believes claims its product after the NDA has already been approved, the NDA holder must submit to FDA supplemental information on the newly issued patent. The holder of an approved NDA has 30 days after issuance of a patent by PTO to submit new patent information to FDA.¹⁰⁶

The statute provides that “[u]pon the submission of [post-approval] patent information, the Secretary *shall* publish it.”¹⁰⁷ With respect to post-approval patents submitted to FDA by an NDA holder, however, the agency will not publish the patent in the Orange Book until the agency determines that the patent submission is substantially complete and contains the information indicating that the patent is eligible for listing; i.e., that the patent “claims” the approved drug.¹⁰⁸ FDA bolstered these requirements in 2003, in response to concerns that NDA holders were submitting eleventh-hour patents to FDA that were ineligible for listing in an effort to delay improperly the onset of generic competition.¹⁰⁹ While FDA does not generally consider as part of its review of patent submissions the substantive patent law question of whether the patent in fact claims the approved drug, it does consider whether the

¹⁰³ FDCA § 505(j)(7)(A), 21 U.S.C. § 355(j)(7)(A).

¹⁰⁴ 54 Fed. Reg. at 28,876 (“As a general rule, FDA intends to use the list [i.e., the Orange Book] and its supplemental updates as the primary means of announcing information regarding patent status [and] exclusivity . . .”). See also *Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions*; Final Rule, 59 Fed. Reg. 50,338, 50,338 (Oct. 3, 1994) (noting that FDA publishes “patent information in its approved drug products list”—i.e., the Orange Book); 21 C.F.R. §§ 314.3, 314.53(e) (defining the Orange Book as “the list” and noting that FDA will publish in “the list” patent information that is required to be submitted to FDA by an NDA applicant or holder).

¹⁰⁵ See *Ranbaxy Labs., Ltd., v. Leavitt*, 459 F. Supp. 2d 1, 9-10 (D.D.C. 2006), *aff'd*, 469 F.3d 120 (D.C. Cir. 2006) (“NDA patent information appears in the Orange Book because Congress included in [Hatch-Waxman] a provision requiring the publication of such information to facilitate the new ANDA process.”); *Merck & Co., Inc. v. Mediplan Health Consulting, Inc.*, 434 F. Supp. 2d 257, 264 (S.D.N.Y. 2006) (describing the Orange Book as “a catalogue that informs the public of [a] patent’s existence”). Until 2005, the Orange Book was available both in “hard copy” and in an electronic format, the latter appearing on FDA’s website. The “hard copy” Orange Book was traditionally updated on a monthly basis. 21 C.F.R. § 314.53(e). Before FDA began to update patent information daily via the Electronic Orange Book (EOB), patent information not yet published in the Orange Book was made available to the public by FDA’s Freedom of Information staff. *Id.* Today the Orange Book is only available electronically at www.fda.gov/cder/ob, and patent information contained in the EOB is updated daily. FDA, *Frequently Asked Questions about the Orange Book*, available at <http://www.fda.gov/Drugs/InformationOnDrugs/ucm114166.htm>.

¹⁰⁶ FDCA § 505(c)(2), 21 U.S.C. § 355(c)(2).

¹⁰⁷ *Id.* (emphasis added).

¹⁰⁸ 21 C.F.R. § 314.53(c)(1); *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*; Final Rule, 68 Fed. Reg. 36,676, 36,687 (June 18, 2003).

¹⁰⁹ See generally FTC Report, *supra* note 6 at iii-v (detailing concerns about post-approval patents).

NDA holder has provided the requisite “complete” documentation under FDA regulations in support of an Orange Book listing.¹¹⁰

An ANDA applicant that must certify to a patent claiming the RLD may submit to FDA one of four types of certifications with respect to that patent: a “paragraph I” certification asserting that patent information (for the relevant patent) has not been filed,¹¹¹ a “paragraph II” certification asserting that the relevant patent has expired,¹¹² a “paragraph III” certification stating that the relevant patent will expire on a date certain,¹¹³ or a “paragraph IV” certification asserting that the patent is invalid, unenforceable or will not be infringed by the drug for which ANDA approval is sought.¹¹⁴ With respect to any patent that has been listed in the Orange Book before the filing of the ANDA, the ANDA applicant’s certification must appear in the original ANDA. With respect to patents added by the NDA holder after the submission of the ANDA, the ANDA holder must file a supplement to its application containing the appropriate certification, unless the patent was not listed in a timely manner.¹¹⁵ Where the ANDA applicant has filed a paragraph III certification including the patent expiration date, the ANDA will not be approved until all of the paragraph III listed patents have expired. An ANDA applicant may convert its certification if it chooses to do so. For example, an applicant can convert from a paragraph III to paragraph IV certification or vice versa based on changes in circumstances or strategy.

If an ANDA applicant wishes to challenge the validity or enforceability of the patent or to assert that the patent will not be infringed by the product in the ANDA, the applicant must submit a paragraph IV certification to FDA. Although some applicants have served “preemptive” notice letters, FDA’s position, with support from the courts, is that the applicant also must provide notice to the NDA holder and patent owner stating that the application has been submitted and explaining the factual and legal basis for the applicant’s opinion that the patent is invalid, not infringed, or not enforceable, once the applicant received notice of “acceptance” of the ANDA filing from FDA.¹¹⁶ Upon notification from the ANDA applicant that it has submitted to FDA a paragraph IV certification challenging the NDA holder’s patent, the NDA holder may commence patent infringement litigation against the ANDA applicant—a process that the framers of Hatch-Waxman had intended would lead to the swift resolution of brand-generic patent disputes.¹¹⁷ By commencing such litigation within 45 days of receiving the notice, the patent holder can trigger a 30-month stay of FDA

¹¹⁰ 21 C.F.R. § 314.53(c)(1) (“We will not accept the patent information unless it is complete and submitted on the appropriate forms . . .”).

¹¹¹ FDCA § 505(j)(2)(A)(vii)(I), 21 U.S.C. § 355(j)(2)(A)(vii)(I).

¹¹² FDCA § 505(j)(2)(A)(vii)(II), 21 U.S.C. § 355(j)(2)(A)(vii)(II).

¹¹³ FDCA § 505(j)(2)(A)(vii)(III), 21 U.S.C. § 355(j)(2)(A)(vii)(III).

¹¹⁴ FDCA § 505(j)(2)(A)(vii)(IV), 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

¹¹⁵ FDCA § 505(j)(2)(A)(vii), 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. §§ 314.94(a)(12)(i), (vi). If the patent was not submitted to FDA within the statutory time frame (30 days from issuance), FDA regulations permit ANDA applicants to disregard the new patent listing and to avoid amending the ANDA with regard to the late-listed patent. 21 C.F.R. § 314.94(a)(12)(vi).

¹¹⁶ FDCA §§ 505(b)(2), (j)(2)(B), 21 U.S.C. §§ 355(b)(2), (j)(2)(B); *See* SB Pharmco Puerto Rico, Inc. v. Mutual Pharm. Co., 552 F. Supp. 2d 500 (E.D. Pa. 2008); *Merck & Cie v. Watson Pharms., Inc.*, C.A. No. 12-161-RGA (D. Del. Sept. 25, 2012); and *Otsuka Pharm. Co. v. Par Pharm., Inc.*, C.A. No. 13-1979 (RGA) (D. Del. Mar. 10, 2014). If FDA has already “accepted” the ANDA for filing, then the applicant must send the notice letter at the same time as the amended certification to FDA.

¹¹⁷ *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1338 (Fed. Cir. 2003) (paragraph IV process a “streamlined mechanism” created to “facilitate judicial resolution” of patent infringement claims). *See also In re Barr Labs.*,

approval of the ANDA.¹¹⁸ As discussed below, under certain conditions, the 30-month stay of approval may be terminated, shortened, or even extended.¹¹⁹

Further, where an ANDA applicant believes that patent information in the Orange Book needs to be corrected or deleted, an applicant may assert a counterclaim under section 505(j)(5)(C)(ii)(I) of the FDCA.¹²⁰ Such a counterclaim is known as a “delisting” counterclaim. According to the United States Supreme Court, a delisting counterclaim may be employed “to force correction of a use code that inaccurately describes the brand’s patent as covering a particular method of using the drug in question.”¹²¹

Extension or Termination of the 30-Month Stay

The 30-month stay of approval that is triggered by the timely filing of a patent infringement suit can be terminated, and approval of an ANDA may be made effective as of:

- the date that the district court enters judgment reflecting its decision that the patent at issue is invalid or not infringed; or
- the date of a settlement order or consent decree signed and entered by the district court stating that the patent that is the subject of the certification is invalid or not infringed; or
- if the district court decides that the patent has been infringed and this decision is reversed on appeal, the date on which the court of appeals decides that the patent is invalid or not infringed or the date of a settlement order or consent decree that is signed and entered by the court of appeals stating that the patent is invalid or not infringed.¹²²

The court may shorten or lengthen the 30-month period if either party fails to cooperate in expediting the litigation.¹²³ The 30-month stay will be extended if the court grants a preliminary injunction prior to the end of the 30-month stay prohibiting the ANDA

Inc., 930 F.2d 72, 76 (D.C. Cir. 1991) (purpose of Hatch-Waxman was “to get generic drugs into the hands of patients at reasonable prices—fast”).

¹¹⁸ FDCA §§ 505(c)(3)(C), (j)(5)(B), 21 U.S.C. §§ 355(c)(3)(C), (j)(5)(B).

¹¹⁹ *Id.*

¹²⁰ 21 U.S.C. § 355(j)(5)(C)(ii)(I).

¹²¹ *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 80 U.S.L.W. 4324, 4327 (2012).

¹²² FDCA §§ 505(c)(3)(C), (j)(5)(B)(iii), 21 U.S.C. §§ 355(c)(3)(C), (j)(5)(B)(iii); FDA’s Draft Guidance for Industry on Listed Drugs, 30-Month Stays, and Approval of Abbreviated New Drug Applications and 505(b)(2) Applications Under Hatch-Waxman, as Amended by the Medicare Prescription Drug Improvements and Modernization Act of 2003—Questions and Answers [hereinafter FDA Draft MMA Guidance]. In its initial regulations implementing Hatch-Waxman, FDA interpreted “court” to mean “the court that enters final judgment from which no appeal can be or has been taken,” which is a final decision by a federal circuit court of appeals. *Abbreviated New Drug Application Regulations: Patent and Exclusivity Provisions*; Final Rule, 59 Fed. Reg. 50,338, 50,352-50,354 (Oct. 3, 1994). This interpretation was challenged and the court ruled that the 30-month stay expires upon a district court decision finding a patent invalid, unenforceable, or not infringed. *TorPharm, Inc. v. Shalala*, No. 97-1925, 1997 U.S. Dist. LEXIS 21983 (D.D.C. Sept. 15, 1997), *appeal withdrawn and remanded*, 1998 U.S. App. LEXIS 4681 (D.C. Cir. Feb. 5, 1998); *vacated* No. 97-1925 (D.C.C. Apr. 9, 1998). FDA subsequently issued a guidance adopting the *TorPharm* court’s decision and defined “court” to mean the first court to render a decision finding the patent at issue invalid, unenforceable, or not infringed. See FDA, *Guidance for Industry on Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act* (March 2000). When Congress amended the law as part of MMA, it specifically described the circumstances under which the 30-month stay would terminate. MMA, Title XI, section 1101(a)(2).

¹²³ FDCA §§ 505(c)(3)(C), (j)(5)(B)(iii), 21 U.S.C. §§ 355(c)(3)(C), (j)(5)(B)(iii).

applicant from marketing the drug until the court decides the issues of patent validity and infringement.¹²⁴

If the district court hearing the infringement suit decides that the patent at issue is infringed and this decision is not appealed or is affirmed on appeal, the ANDA will not be approved prior to the patent's expiration and any extension or exclusivity that remains.¹²⁵

Multiple 30-Month Stays

As discussed above, Hatch-Waxman provided for a 30-month stay of FDA approval of an ANDA if a brand company files suit for patent infringement within 45 days of receiving notice of the ANDA's paragraph IV certification. Pursuant to FDA's initial interpretation of the act, multiple 30-month stays were possible. For example, an ANDA application that already had been subject to one 30-month stay based on a paragraph IV certification to a patent listed before the ANDA was filed could be subject to additional 30-month stays if the applicant filed a subsequent paragraph IV certification to a patent listed after the application's submission and that subsequent certification triggered another timely filed patent infringement suit.¹²⁶ A 2002 FTC report found that after 1998 there was a substantial increase in the number of patents being submitted to FDA after an ANDA had been filed and that these later-listed patents were resulting in multiple 30-month stays and additional delays to generic approval.¹²⁷ Even more disturbing was the finding that most of these late-listed patents ultimately were found to be invalid or not infringed. FTC concluded that some brand companies were filing questionable patents and delaying generic approval.¹²⁸

In June 2003, FDA issued regulations that permitted only one 30-month stay per ANDA.¹²⁹ Several months later, Congress passed the MMA, which amended Hatch-Waxman to preclude most multiple 30-month stays for applications with paragraph IV certifications to patents submitted to FDA after August 13, 2003 (the effective date).¹³⁰ Specifically, MMA precludes 30-month stays for patents submitted to FDA after the date an ANDA is submitted.¹³¹ There is still the possibility of multiple 30-month stays with regard to patents that were submitted before the ANDA, if the ANDA applicant amends one of its patent certifications. For example, if an ANDA applicant converts a paragraph III certification to a patent that was submitted to FDA before the ANDA was filed, then a second 30-month stay

¹²⁴ *Id.*

¹²⁵ *Id.*, FDA Draft MMA Guidance, *supra* note 122.

¹²⁶ See Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming the Drug Is Invalid or Will Not Be Infringed; Proposed Rule, 67 Fed. Reg. 65,448, 65,454-55 (Oct. 24, 2002); FDA Draft MMA Guidance, *supra* note 122.

¹²⁷ FTC Report, *supra* note 6 at iii-iv, 36 and 45.

¹²⁸ *Id.*

¹²⁹ 68 Fed. Reg. 36,676.

¹³⁰ MMA, tit. XI, §§ 1101(a)(2)(A)(ii)(I), 1101(b).

¹³¹ *Id.* See also FDA Draft MMA Guidance, *supra* note 122. Following passage of MMA, FDA revoked its regulatory provision regarding 30-month stays on the basis that it was superseded by the MMA provision. Application of 30-Month Stays on Approval of Abbreviated New Drug Applications and Certain New Drug Applications Containing a Certification Certifying That a Patent Claiming the Drug is Invalid or Will Not Be Infringed; Technical Amendment, 69 Fed. Reg. 11,309 (Mar. 10, 2004).

is possible. Thus, after the MMA, the possibility of multiple 30-month stays is largely within the control of the applicant.¹³²

180-Day Generic Drug Exclusivity

As an incentive for generic companies to initiate challenges, through paragraph IV certifications, to suspect brand company patents, Hatch-Waxman awards 180 days of market exclusivity to the generic applicant that is the first to submit a substantially complete ANDA containing a paragraph IV certification with respect to a patent that the NDA holder asserts claims the referenced brand drug. During this period no other ANDA with a paragraph IV certification for the same drug can be approved. Hatch-Waxman exclusivity is an extremely valuable incentive for generic companies to bring paragraph IV challenges to brand company patents. The success rate of generic company paragraph IV challenges has been quite high,¹³³ and numerous generic companies have earned significant profits as a result of exclusivity awards arising out of these challenges.¹³⁴ Because of the considerable value of Hatch-Waxman exclusivity, ANDA applicants aggressively vie for the position of “first-filer” of paragraph IV certifications in cases in which such certifications are deemed appropriate.

For example, until FDA issued a guidance clarifying that any ANDA applicant that submitted a paragraph IV certification on the first day that such certifications are appropriate would be entitled to a share of exclusivity, representatives of ANDA applicants lined up outside FDA for days or even weeks in advance in an effort to be the first paragraph IV filer with respect to a particular patent.¹³⁵ In 2003, FDA put an end to this practice by declaring that two or more same-day paragraph IV certifications to the same patent will share exclusivity.¹³⁶

Another example of ANDA applicants aggressively vying for the position of first-filer relates to a practice that has been adopted when the Patent and Trademark Office grants a patent application that arguably covers a drug for which FDA has approved an NDA but for which no patents are listed in the Orange Book and the exclusivity period has expired. If the

¹³² See FDA Draft MMA Guidance, *supra* note 122.

¹³³ See FTC Report, *supra* note 6 at 16 (noting that paragraph IV challenges leading to actual patent litigation have resulted in victory for the generic company in 73 percent of cases). Of course, the generic company also effectively prevails when no lawsuit is filed.

¹³⁴ Mylan Pharms., Inc., 454 F.3d at 273 (“The 180-day exclusivity period . . . is a significant boon to the recipient.”).

¹³⁵ See FDA, Guidance for Industry: 180-Day Exclusivity When Multiple ANDAs Are Submitted on the Same Day (July 2003) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072851.pdf>.

¹³⁶ *Id.* FDA also has addressed the situation in which different ANDA applicants were first to submit patent challenges as to *different* listed patents such that each applicant ends up blocking the other applicant[s] with its exclusivity creating an “exclusivity standoff” in which no application can be approved. Under these circumstances, FDA has adopted the shared exclusivity approach. Pursuant to this approach, when different applicants have submitted first paragraph IV ANDAs for different listed patents, resulting in mutually blocking exclusivities, each is eligible to share a single 180-day period of exclusivity. The eligible first paragraph IV ANDAs cannot block each other. The 180 days will begin to run for all eligible ANDAs sharing in the exclusivity when it begins to run for any one of the eligible ANDAs. See, e.g., Letter from Gary Buehler, Director, FDA Office of Generic Drugs to Marcy Macdonald, U.S. Agent for Torpharm (July 30, 2003) (Re: Shared Exclusivity for Paroxetine Hydrochloride Tablets, ANDA 75-356); Letter from Gary Buehler, Director, FDA Office of Generic Drugs to Diane Servello, Andrx Pharmaceuticals, Inc. (Nov. 16, 2001) (Re: Shared Exclusivity for Omeprazole, ANDA 75-347).

NDA holder then asks FDA to list the newly issued patent, the ANDA applicant who is the first to certify against that patent receives the 180-day exclusivity. These types of patents are commonly known as “pop-up” patents. Although the ANDA holder can determine that a patent has been issued by the PTO, it cannot know when the NDA holder will actually submit the patent to FDA. FDA ultimately lists the patent in the Orange Book but this presumably happens some time after it has been submitted. In an effort to ensure that they are first filers, generic companies have adopted the practice of submitting to FDA daily paragraph IV certifications to a relevant patent once the patent has been issued by the PTO, stopping these daily submissions only after the patent is actually listed by FDA in the Orange Book. This approach is based on the generic companies’ assumption that one of its paragraph IV certifications, though it does not know which one, will reach FDA on the first day that the certifications will be deemed effective by FDA and will therefore give rise to partial or full generic exclusivity.

Once a first filer has been identified by FDA, subsequent ANDA applicants cannot be approved until the 180-day period has expired.¹³⁷ A big question that both FDA and the courts have struggled with over the years is when the 180-day period actually begins; i.e., what triggers the start of the 180-day period. The answer to the question is of critical importance to those other ANDA applicants waiting to get on the market. The sooner the 180-day period begins, the sooner they can get on the market. As discussed below, the answer to the question has changed several times, and Congress sought to clarify the issue in the MMA.

Prior to the MMA, the FDCA provided that the 180-day exclusivity period was triggered by the earlier of the first commercial marketing of the generic drug for which the first ANDA was submitted or the first court decision holding the patent that was the subject of the paragraph IV certification invalid or not infringed.¹³⁸ Although FDA had interpreted “court decision” to mean the final decision from which no appeal can be or has been taken,¹³⁹ the D.C. district court overruled that interpretation and held that the “court decision” that could begin the running of the 180-day period may be the decision of the district court that the patent at issue is unenforceable or will not be infringed, even if the decision is appealed.¹⁴⁰ The rationale for FDA’s initial interpretation was that the generic exclusivity would be significantly devalued if the generic manufacturer had to market at the risk of being subject to treble damages if the appeals court ruled in favor of the patent holder, and that Congress could not have intended this result.¹⁴¹ Nevertheless, FDA adopted the D.C. district court’s position.¹⁴² The practical effect of that interpretation was that many generics chose not to market at risk and lost the benefit of the 180-day exclusivity, which ran during the pendency of an appeal.¹⁴³

¹³⁷ FDCA § 505(j)(5)(B)(iv), 21 U.S.C. § 355(j)(5)(B)(iv).

¹³⁸ See *Mylan Pharmaceuticals, Inc. v. Shalala*, 81 F. Supp. 2d 30, 33 (D.D.C. 2000).

¹³⁹ 59 Fed. Reg. at 50,354-55.

¹⁴⁰ *Mylan Pharmaceuticals, Inc.*, 81 F. Supp. 2d 30.

¹⁴¹ 59 Fed. Reg. at 50,354-55.

¹⁴² FDA, Guidance for Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act (Mar. 2000) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072868.pdf>.

¹⁴³ In cases where there was no court decision and the first applicant did not begin commercial marketing, there could be prolonged or indefinite delays in the beginning of the running of the 180-day period and thus delays in the approval of any other ANDAs with an end result of no generic competition. The FTC

The MMA revised the precise conditions under which FDA can approve subsequent ANDAs. For paragraph IV ANDAs filed after the date of enactment of MMA (December 8, 2003), a court decision will no longer trigger the period of 180-day exclusivity. Instead, as discussed below, a court decision can be a forfeiture event. For ANDAs with paragraph IV certifications filed before December 8, 2003, a court decision can still trigger exclusivity. If the exclusivity was not already triggered before December 8, 2003, the triggering court decision is one from which no appeal has been or can be taken, other than a petition to the Supreme Court for a writ of certiorari.¹⁴⁴

Although post-MMA court decisions no longer trigger the running of the 180-day exclusivity period, the law added provisions to ensure that first filers cannot block subsequent ANDA approvals by delaying the commercial marketing of their product.¹⁴⁵ Specifically, MMA sought to address the potential for blocking generic competition by adding provisions pursuant to which the first to file can forfeit its right to 180 days of exclusivity. The MMA added six possible forfeiture events.¹⁴⁶ With the exception of the fifth forfeiture event (regarding agreements that violate the antitrust laws), these forfeiture events apply only to ANDAs filed after the effective date of the MMA (December 8, 2003) certifying to patents for which no paragraph IV certification had been made in any ANDA before December 8, 2003. The collusive agreement forfeiture provision applies to ANDAs filed after December 8, 2003, regardless of when the first paragraph IV certification was made for the RLD.

Under the first forfeiture event, a first applicant will forfeit its 180 days if it fails to market its product by the later of (aa) 75 days after approval of the first ANDA or 30 months after the submission of the first ANDA, whichever is earlier, or (bb) the date that is 75 days after at least one of the following occurs: a court enters a final decision that the patent is invalid or not infringed, a court signs a settlement order or consent decree entering final judgment that includes a finding that the patent is invalid or not infringed, or the patent information for the listed drug is withdrawn by the NDA holder.¹⁴⁷ In a decision regarding Teva's eligibility for 180-day exclusivity in connection with its ANDA for granisetron hydrochloride, FDA determined that a failure-to-market forfeiture event could not occur if none of the events in the second subpart (bb) has occurred.¹⁴⁸ In a subsequent decision, FDA determined that the first filer, Cobalt Pharmaceuticals, did forfeit its 180-day exclusivity by failing to market by the later of (aa) September 22, 2007 (which was 30 months after it submitted its ANDA) or (bb) April 16, 2007 (which was the date that the NDA holder requested that the patent information be withdrawn from the Orange Book).¹⁴⁹

report found instances of brand companies and first generic applicants entering agreements pursuant to which the generic agreed not to go to market. See FTC Report, *supra* note 6 at vii. As discussed below, MMA added provisions aimed at addressing this problem. See MMA, tit. XI, § 1102(b)(3).

¹⁴⁴ See MMA, tit. XI, § 1102(b)(3) (defining, for this purpose, "decision of a court" as used in section 505(j)(5)(B)(iv) of the act).

¹⁴⁵ As stated above, under the pre-MMA exclusivity provision, in a situation where there was not a court decision and the first applicant did not begin commercial marketing, there could be prolonged or indefinite delays in the beginning of the running of the 180-day period and thus delays in the approval of any other ANDAs during which there would be no generic competition.

¹⁴⁶ FDCA § 505(j)(5)(D), 21 U.S.C. § 355(j)(5)(D).

¹⁴⁷ FDCA § 505(j)(5)(D)(i)(I), 21 U.S.C. § 355(j)(5)(D)(i)(I).

¹⁴⁸ See Letter from Gary Buehler, Director, FDA Office of Generic Drugs to Marc A. Goshko, Teva North America, Docket No. 2007N-0389 (Jan. 17, 2008).

¹⁴⁹ See Letter from Gary Buehler, Director, FDA Office of Generic Drugs to William A. Rakoczy, Esq., Docket No. 2007N-0445 (May 8, 2008). Following that decision FDA approved Roxane's ANDAs for acarbose.

The second potential forfeiture event is the first applicant's withdrawal of its ANDA.¹⁵⁰ FDA can consider the ANDA withdrawn if it determines that the application does not meet the requirements for approval.¹⁵¹ If the first applicant changes its paragraph IV certification (by withdrawing or amending its certification for all patents with respect to which it submitted a certification qualifying it for the 180 days), it will forfeit the 180-day exclusivity.¹⁵² Under the fourth forfeiture event, a first applicant forfeits its 180 days of exclusivity if it fails to obtain tentative approval within 30 months of filing its application, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application was filed.¹⁵³

A first applicant will forfeit its 180-day exclusivity if it enters into an agreement with the brand company that is found to violate antitrust law.¹⁵⁴ FDA recently was asked to find that Cobalt Pharmaceuticals was not entitled to 180-day exclusivity because it had entered into a settlement with the brand company, King Pharmaceuticals. FDA denied the request on the grounds that there was no final, unappealable order finding that the terms of the agreement violate antitrust law, as required by the law.¹⁵⁵ Finally, the 180-day exclusivity period will be lost if the qualifying patents expire.¹⁵⁶

Because the 180-day exclusivity is so valuable and there are so many different and complicated factors at play when it comes to determining whether it has been forfeited, FDA has been interpreting the application of these forfeiture events on a case-by-case basis and has been establishing dockets for the purpose of soliciting comment from all interested parties as potential forfeiture issues arise.¹⁵⁷

FDA has had the opportunity to address some of the issues raised by these new provisions, but it has yet to see or address all possible scenarios. For example, FDA has addressed the question of whether a forfeiture event occurs if an applicant fails to market its product due to the fact that it was blocked from approval by an unexpired patent or period of exclusivity. In that instance, FDA found that the first ANDA applicant, Hi-Tech, had forfeited its 180-day exclusivity for a generic form of COSOPT® ophthalmic solution because the statute's "failure to market" forfeiture provision does not contain any qualifying language that would stay or toll the forfeiture provision due to circumstances outside of the applicant's control. Of

Cobalt unsuccessfully sought to stop the marketing of Roxane's products, but the D.C. district court declined to issue a temporary restraining order on the grounds that FDA's decision was likely to be upheld. *Cobalt Laboratories v. FDA*, No. 08CV798 (D.D.C.). Subsequently, Cobalt voluntarily dismissed the case.

¹⁵⁰ FDCA § 505(j)(5)(D)(i)(II), 21 U.S.C. § 355(j)(5)(D)(i)(II).

¹⁵¹ *Id.*

¹⁵² FDCA § 505(j)(5)(D)(i)(III), 21 U.S.C. § 355(j)(5)(D)(i)(III).

¹⁵³ FDCA § 505(j)(5)(D)(i)(IV), 21 U.S.C. § 355(j)(5)(D)(i)(IV).

¹⁵⁴ FDCA § 505(j)(5)(D)(i)(V), 21 U.S.C. § 355(j)(5)(D)(i)(V).

¹⁵⁵ See Letter from Gary Buehler, Director, FDA Office of Generic Drugs to Carmen M. Shepard and Kate C. Beardsley, Buc and Beardsley, Docket No. 2007N-0382 (Jan. 29, 2008). FDA also rejected the argument that a subsequent ANDA applicant should be permitted to change its paragraph IV certification after a final court decision finding the patent invalid and thus avoid being blocked by Cobalt's 180-day exclusivity. FDA requires unexpired patents to remain in the Orange Book until the end of the patent term or the end of the 180-day exclusivity, whichever occurs first so that the protection offered by the 180-day exclusivity cannot be undermined by changes from paragraph IV certifications. 21 C.F.R. § 314.94(a)(12)(viii). See also 59 Fed. Reg. 50,338, 50,348 (Oct. 3, 1994).

¹⁵⁶ 21 U.S.C. § 355(j)(5)(D)(i)(VI).

¹⁵⁷ See, e.g., Docket Nos. 2007N-0382, 2007N-0389, 2007N-0417.

course, the interpretation and impact of these forfeiture provisions will continue to evolve over time.

Authorized Generics

The term “authorized generic” is generally used to describe an instance when an NDA holder, in the face of pending generic competition, markets a generic version of its own product.¹⁵⁸ Prior FDA approval is not needed for the NDA holder to market an authorized generic because the product has already been approved under the NDA. Moreover, because generic drug 180-day exclusivity only blocks approval of ANDAs for which paragraph IV certifications have been submitted, the courts have held that it does not block an authorized generic (which is really another version of the drug approved in the NDA) from entering the market.¹⁵⁹

The marketing of authorized generics has been controversial. Although the brand industry argues that the additional competition lowers generic drug prices, generic manufacturers argue that in some cases the decreased profits caused by the marketing of authorized generics will deter generic manufacturers from challenging patents.¹⁶⁰ The generic companies also argue that the marketing of authorized generics is inconsistent with congressional intent because it devalues the exclusivity Congress gave to generic companies willing to challenge questionable patents.¹⁶¹

In 2006 and 2007, following requests from several Senators and Congressman Waxman, the Federal Trade Commission (FTC) announced that it would conduct a study on the short- and long-term competitive effects of authorized generics.¹⁶² FDAAA includes a provision that requires FDA to compile and update quarterly a database of authorized generics and to provide that information to FTC and the Centers for Medicare and Medicaid Services.¹⁶³ The provision is intended to assist FTC’s study on the impact of authorized generics.

Declaratory Judgment Actions

The MMA added a provision to the ANDA statutory provisions expressly authorizing declaratory judgment actions.¹⁶⁴ This new subparagraph, entitled “Civil Action to Obtain Patent Certainty,” provides that an ANDA applicant may bring a civil action for a declaratory judgment that the patent at issue is invalid or will not be infringed by the ANDA applicant if the patentee or NDA holder does not bring an infringement action within 45 days after receiving notice of a paragraph IV certification.¹⁶⁵ The MMA also amended the companion patent statute to provide that in a civil action to obtain patent certainty, federal courts

¹⁵⁸ See *Mylan Pharmaceuticals, Inc. v. FDA*, 454 F.3d 270 (4th Cir. 2006); *Teva Pharm. Indus. v. FDA*, 410 F.3d 51 (D.C. Cir. 2005).

¹⁵⁹ See *Mylan Pharmaceuticals, Inc.*, 454 F.3d at 276; *Teva Pharm. Indus.*, 410 F.3d at 55.

¹⁶⁰ See Federal Trade Commission Information Collection Notice, 72 Fed. Reg. 25,304, 25,305 (May 4, 2007) and Federal Trade Commission Information Collection Notice, 71 Fed. Reg. 16,779, 16,780 (Apr. 4, 2006).

¹⁶¹ 72 Fed. Reg. at 25,305; 71 Fed. Reg. at 16,780.

¹⁶² See 72 Fed. Reg. at 25,305 (referring to Letters from Senators Grassley, Leahy, and Rockefeller and Representative Henry Waxman to Chairman Deborah Platt Majoras); 71 Fed. Reg. 16,779.

¹⁶³ FDAAA, tit. IX, § 920; 21 U.S.C. § 355(t).

¹⁶⁴ MMA, tit. XI, § 1101.

¹⁶⁵ FDCA § 505(j)(5)(C), 21 U.S.C. § 355(j)(5)(C).

“shall, to the extent consistent with the Constitution, have subject matter jurisdiction for a declaratory judgment action.”¹⁶⁶ According to the legislative history of the MMA, Congress added this provision to level the playing field. Hatch-Waxman provided that patent owners and NDA holders may bring patent infringement suits against an ANDA applicant immediately upon receiving notice that the applicant is challenging the patent. The MMA provision simply clarifies that the generic applicant may also seek prompt resolution of these patent issues by bringing a declaratory judgment action if not sued within 45 days.¹⁶⁷

Since enactment of the MMA, generic companies have filed lawsuits that test the limits of the new declaratory judgment provision. The Supreme Court addressed the issue in *MedImmune, Inc. v. Genentech, Inc.*, where the Court rejected the federal circuit’s longstanding “reasonable apprehension of suit” test, holding that “Article III jurisdiction may be met where the patentee takes a position that puts the declaratory judgment plaintiff in the position of either pursuing arguably illegal behavior or abandoning that which claims a right to do.”¹⁶⁸ The dispute must be “definite and concrete, touching the legal relations of parties having adverse legal interests” and “be real and substantial.”¹⁶⁹

The federal circuit subsequently opined that the *MedImmune* decision had changed the landscape, in a decision that requires a declaratory judgment plaintiff to satisfy only Article III of the Constitution by showing under all of the circumstances an actual or imminent injury caused by the defendant that can be redressed by judicial relief and that is of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.¹⁷⁰ The Federal Circuit cited the MMA legislative history in which Congress states: “[W]e fully expect that in almost all situations where a generic applicant has challenged a patent by filing a paragraph IV certification and not been sued for patent infringement, a claim by the generic applicant seeking declaratory judgment will give rise to a justiciable case or controversy under the Constitution. The only circumstance in which a case or controversy might not exist is in the rare instance when a patent owner or brand company has given the generic a covenant not to sue or otherwise formally acknowledged that the generic applicant drug does not infringe.”¹⁷¹ Additional cases that have been decided since *MedImmune* and *Teva* illustrate that the determination is fact-specific and the courts will determine jurisdiction on a case-by-case basis.¹⁷²

¹⁶⁶ 35 U.S.C. § 271(e)(5).

¹⁶⁷ 149 CONG. REC. S15,885 (Nov. 25, 2003) (remarks of Senator Kennedy, ranking member of the Senate Committee on Health, Education, Labor, and Pensions).

¹⁶⁸ *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007).

¹⁶⁹ *Id.*

¹⁷⁰ *Teva Pharmaceuticals USA, Inc. v. Novartis Pharmaceuticals Corp.* 482 F.3d 1330 (Fed. Cir. 2007).

¹⁷¹ *Id.* at 1343.

¹⁷² See, e.g., *Pfizer Inc. v. Ranbaxy Laboratories Ltd.*, 525 F. Supp. 2d 680 (D. Del. 2007); *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, No. 06-1020, 2007 U.S. Dist. LEXIS 75967 (D.N.J. Oct. 11, 2007); *Rite Aid Corp. v. Purdue Pharma, L.P.*, No. 06-15304, 2007 U.S. Dist. LEXIS 61583 (S.D.N.Y. Aug. 21, 2007).

Antitrust Issues Raised By Settlements between Brand and Generic Companies

A relatively recent trend in the generics arena has been patent litigation settlements between a brand company and a generic company. In the late 1990s, FTC challenged several such agreements as being anticompetitive, and their use diminished.¹⁷³

In 2003, the MMA included a provision that requires pharmaceutical companies to file certain agreements with FTC and the Department of Justice.¹⁷⁴ On June 17, 2013, the United States Supreme Court weighed in with its opinion in *FTC v. Actavis, Inc.*¹⁷⁵ In *Actavis, Inc.*, the FTC filed an antitrust complaint against a brand-name manufacturer of AndroGel, alleging that the manufacturer's reverse payment settlement agreements with certain generic drug manufacturers were unlawful agreements not to compete in violation of the Federal Trade Commission Act.¹⁷⁶ The Eleventh Circuit dismissed the FTC's complaint, and the United States Supreme Court reversed, finding that, while reverse payment settlement agreements are not per se lawful, in some instances they may violate antitrust laws.¹⁷⁷ Specifically, the Court held that:

[A] reverse payment, where large and unjustified, can bring with it the risk of significant anticompetitive effects; one who makes such a payment may be unable to explain and to justify it; such a firm or individual may well possess market power derived from the patent; a court, by examining the size of the payment, may well be able to assess its likely anticompetitive effects along with its potential justifications without litigating the validity of the patent; and parties may well find ways to settle patent disputes without the use of reverse payments.¹⁷⁸

Citizen Petitions Challenging ANDA Approvals

FDA regulations provide that any person (including a corporation) may file a "Citizen Petition" with the agency seeking FDA action or inaction on any issue before FDA.¹⁷⁹ The origin of Citizen Petitions is rooted in genuine concerns for the health and safety of the

¹⁷³ See Prepared Statement of the Federal Trade Commission Before the Subcommittee on Commerce, Trade, and Consumer Protection, Committee on Energy and Commerce, United States House of Representatives on Protecting Consumer Access to Generic Drugs: The Benefits of a Legislative Solution to Anticompetitive Patent Settlements in the Pharmaceutical Industry (May 2, 2007) [hereinafter FTC May 2007 House Testimony], available at http://www.ftc.gov/sites/default/files/documents/public_statements/prepared-statement-federal-trade-commission-protecting-consumer-access-generic-drugs-benefits/p85991020protecting_consume_20access_testimony.pdf; Prepared Statement of the Federal Trade Commission Before the Committee on The Judiciary of the United States Senate on Anticompetitive Patent Settlements in the Pharmaceutical Industry: The Benefits of a Legislative Solution (Jan. 17, 2007) [hereinafter FTC January 2007 Senate Testimony], available at http://www.ftc.gov/speeches/leibowitz/070117anticompetitivepatentsettlements_senate.pdf.

¹⁷⁴ MMA, tit. XI, § 1112.

¹⁷⁵ 133 S. Ct. 2223 (2013).

¹⁷⁶ *FTC v. Watson Pharms., Inc.*, 677 F.3d 1298, 1304-05 (11th Cir. 2012), rev'd 81 U.S.L.W. 4455 (2013).

¹⁷⁷ *Id.* at 2227.

¹⁷⁸ *Id.* at 2237.

¹⁷⁹ 21 C.F.R. §§ 10.25, 10.30.

American people. Citizen Petitions, which may be filed by a citizen or corporation, are a means of requesting administrative action by FDA.

Both FDA and FTC have found, however, that brand companies sometimes use the Citizen Petition process to delay generic drug approvals and thereby prolong the life-cycle of brand-manufacturer's drugs.¹⁸⁰ Some commentators argue that the process is "susceptible to systemic abuse . . . It is no coincidence that brand companies often file these petitions at the eleventh hour before generic entry and that the vast majority of citizen petitions are denied."¹⁸¹ As a result of these tactics of delay, American purchasers have lost billions of dollars of cost savings from generic drugs.¹⁸² With such extraordinary profits on the line, Citizen Petitions have become part of an arsenal used to protect drug manufacturers' profit and exclusivity in the marketplace.

In FDAAA, in an attempt to curb the baseless claims of some Citizen Petitions, Congress added a provision that is intended to counter the tactic of delaying generic approval by filing last-minute Citizen Petitions. The amendment to the FDCA prohibits FDA from delaying the approval of a generic drug while it is preparing a response to a Citizen Petition, unless there is a fairly rigorous certification that the petition raises a public health issue.¹⁸³ It is not clear, however, that this provision will solve the Citizen Petition problem. Today, FDA has authority to approve a generic drug while a related Citizen Petition is pending, but often, in anticipation of litigation, at the direction of the agency's Chief Counsel's office, the agency delays approval while it is preparing a response. It is difficult to show why a generic approval is being delayed and therefore it will be difficult to monitor the implementation of this well-intentioned provision. Moreover, some brand companies have begun to file challenges to ANDA approval in their NDA file. Because information in the NDA file is confidential, ANDA applicants have no opportunity to respond to the brand arguments unless FDA itself raises the issue.

Further congressional legislation increased FDA's responsibility and burden. For instance, the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) section 1135 shortened FDA's timeframe for responding to petitions from 180 days to 150 days.

In 2013, about 32 Citizen Petitions with 505(q) certifications were submitted to FDA for consideration. Out of the 32 petitions 17 were denied, six were denied in part/granted in part, five received interim responses, three were withdrawn, and one remains pending.

¹⁸⁰ FTC Report, *supra* note 6 at 65-68; See Citizen Petition Needs Reforming, FDA Chief Counsel Says, DRUG INDUSTRY DAILY, Sept. 21, 2005 (noting comments of FDA Chief Counsel Sheldon Bradshaw at the Annual Meeting of the Generic Pharmaceutical Manufacturers Association (Sept. 19, 2005) that he has "seen firsthand that many [citizen] petitions seem totally without merit" and that "[s]ometimes, stakeholders try to use the [citizen petition] mechanism to unnecessarily delay approval of a competitor's products").

¹⁸¹ Jon Leibowitz, Fed. Trade Comm'n, text based on speech given to Generic Pharmaceutical Annual Policy Conference, entitled "How Settlements Make Strange Bedfellows: Or How the Federal Trade Commission has Managed to Unite the Entire Pharmaceutical Industry" (Sept. 29, 2006), available at <http://www.ftc.gov/public-statements/2006/09/how-settlements-make-strange-bedfellows-or-how-federal-trade-commission>.

¹⁸² See *The Generic Drug Maze: Speeding Access to Affordable Life-Saving Drugs: Hearing Before the Special Committee on Aging*, 109th Cong. (2006) (statement of Gordon H. Smith, Sen. of the United States).

¹⁸³ FDCA § 505(q), 21 U.S.C. § 355(q).

FDAAA

Although FDAAA included a number of provisions that affect ANDAs, as discussed earlier in this chapter, the principal focus of the legislation was on brand products. Thus, for example, the user fee provisions extended by the law apply only to new drug and biologic applications, and not to abbreviated new drug applications.¹⁸⁴ The most significant provisions of FDAAA (other than the extension of user fees) establish a program to regulate and evaluate the safety of new drugs after they have been approved. The legislation provided FDA with new enforcement authorities, including the authority to order label changes and some additional authority with respect to drug advertising and provided substantial funding for the agency. There is also authority to require applicants to conduct postmarket and other studies of drug safety after a drug has been approved.¹⁸⁵

Generic drugs are exempt from most of the new drug safety obligations except the obligation to conform to new labeling and the obligation to comply with restricted distribution plans (where FDA for example restricts the sale of drugs to particular specialties or requires drug registries).¹⁸⁶ With regard to the restricted distribution requirements, the law requires the generic and brand to use a single shared system unless the burden of doing so outweighs the benefit or some aspect of the plan is subject to patent or trade secret protection and the generic has been unable to obtain a license to use the protected aspect of the plan.¹⁸⁷

Generic Drug User Fees

The Generic Drug User Fee Amendments of 2012 (GDUFA) were signed into law on July 9, 2012, in an effort “to speed access to safe and effective generic drugs to the public and reduce costs to industry.”¹⁸⁸ A failure to pay a required fee may result in a refusal to receive an ANDA, any supplement to an ANDA, or in a drug being deemed misbranded.¹⁸⁹ Some of the required fees include a backlog fee, Drug Master File (DMF) fee, ANDA fee, Active Pharmaceutical Ingredient (API) fee, Prior Approval Supplement (PAS) fees, and facilities fees.¹⁹⁰

Under GDUFA, facilities are determined based on a self-identification process, which is required for 1) facilities that manufacture, or intend to manufacture, human generic drug APIs and/or final dosage forms (FDFs); 2) sites that package the FDF; 3) sites that are identified in a generic drug submission that subdivide the contents of the primary container/closure system; 4) bioequivalence/bioavailability sites that conduct clinical, bioanalytical, and/or in

¹⁸⁴ Applications under section 505(b)(2) are also subject to user fees.

¹⁸⁵ FDCA §§ 505(o), (p), 505-1, 21 U.S.C. §§ 355(o), (p), 355-1.

¹⁸⁶ FDCA § 505-1(i), 21 U.S.C. § 355-1(i).

¹⁸⁷ *Id.*

¹⁸⁸ Generic Drug User Fee Amendments of 2012, Pub. L. No. 112-144, tit. III (July 9, 2012), available at <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>.

¹⁸⁹ See generally FDA, Draft Guidance for Industry: Generic Drug User Fee Amendments of 2012: Questions and Answers (Sept. 2013), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316671.pdf>.

¹⁹⁰ See <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>.

vitro testing; and 5) sites that perform testing of one or more attributes/characteristics of the FDF or API.¹⁹¹

FDA has also issued guidance regarding PASs under GDUFA. These PASs and amendments to PASs for ANDAs are submitted under section 505(j) of the FDCA.¹⁹² FDA may refuse to receive a PAS for:

- failure to pay the application fee within 20 calendar days of submission;
- reference to a drug master file (DMF) that is not on the public available for reference list;
- reference to a facility on the facility arrears list;
- the applicant is the owner or is affiliated with the owner of a facility on the facility arrears list; or
- the applicant is on or affiliated with an entity on the backlog arrears list.¹⁹³

FDA has also issued guidance regarding amendments and easily correctable deficiencies under GDUFA.¹⁹⁴ Such amendments fall into the following categories: solicited, unsolicited, and administrative. A solicited amendment is a submission made in response “to a complete response letter (CR) issued by FDA.”¹⁹⁵ An unsolicited or “gratuitous” amendment is one that is submitted “on the applicant’s own initiative and not in response to FDA’s CR letter.”¹⁹⁶ By

¹⁹¹ Generic Drug User Fee Amendments of 2012, Pub. L. No. 112-144, tit. III, pt. 7 (July 9, 2012); *see also* FDA, Draft Guidance for Industry: Self-Identification of Generic Drug Facilities, Sites, and Organizations (Aug. 2012), at 3-4, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316672.pdf>.

¹⁹² 21 U.S.C. 355(j); FDA, Draft Guidance for Industry: ANDA Submissions—Prior Approval Supplements Under GDUFA (July 2014), at 1, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404441.pdf>.

¹⁹³ *Id.* at 6-7.

¹⁹⁴ FDA, Draft Guidance for Industry: ANDA Submissions—Amendments and Easily Correctable Deficiencies Under GDUFA (July 2014), at 1, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404440.pdf>.

¹⁹⁵ *Id.* at 4. These amendments are classified as either Tier 1 or Tier 3 and either as a major amendment, a minor amendment, or an easily correctable deficiency (ECD). *Id.* A major amendment “contain[s] a substantial amount of new data or new information not previously submitted to or reviewed by FDA, requiring . . . a substantial expenditure of FDA resources.” *Id.* The first solicited major amendment is classified as Tier 1; any subsequent major amendment is classified as Tier 3. *Id.* A minor amendment, on the other hand, “requires . . . fewer FDA resources than are necessary to review a major amendment but more than are necessary to review the information submitted in response to an ECD.” *Id.* For instance, a minor amendment may address missing information but not require any new studies to be performed. *Id.* The first through fifth solicited minor amendments are classified as Tier 1; any subsequent minor amendment is classified as Tier 3. *Id.* Finally, ECDs “require[. . .] a modest expenditure of FDA resources.” *Id.* They can be responded to quickly because the applicant should already have the necessary information. ECDs generally relate to requests for clarification, requests for postapproval commitments, or final resolution of technical issues. *Id.*

¹⁹⁶ *Id.* at 5. These amendments are classified as either delaying or nondelaying. *Id.* All delaying amendments are Tier 1 and all nondelaying amendments are Tier 2. *Id.* at 5-6. A delaying amendment “address[es] actions by a third party that would cause delay or impede application review or approval timing and that were not a factor at the time of submission.” *Id.* at 5. A nondelaying amendment “contain[s] information that is not requested by FDA and is not the result of changes to the RLD or USP monograph, changes to the RLD labeling, a REMS and REMS modification, or generic approval requirements reflected in citizen petition responses issued by FDA.” *Id.* at 6.

contrast, an administrative amendment is “routine in nature and do[es] not require scientific review.”¹⁹⁷

Section 505(b)(2) Applications

A section 505(b)(2) application is an NDA for which one or more of the investigations relied upon by the applicant for approval come from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.¹⁹⁸ A section 505(b)(2) application is similar to a full NDA in that it must satisfy the same requirements for safety and effectiveness. It is similar to an ANDA because it may rely on FDA’s finding that the drug it references is safe and effective to support its own safety and effectiveness. A section 505(b)(2) NDA, however, can be for a drug that has substantial differences from the listed drug it references. The application must support those differences with appropriate safety and effectiveness information. The basic idea is that FDA will rely on its approval of the brand reference product to the extent it is scientifically relevant. This approach saves both agency and industry resources and prevents unnecessary delay. The section 505(b)(2) process fills a gap between the full NDA and the ANDA.

A section 505(b)(2) applicant may rely on published literature or on the agency’s previous finding of safety and effectiveness for an approved drug. A section 505(b)(2) NDA may be submitted for a new chemical entity (NCE) when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. A section 505(b)(2) NDA may also be submitted for changes to a previously approved drug product that would not be permitted under section 505(j) because approval would require the review of clinical data. An application submitted pursuant to section 505(b)(2) is appropriate even when new clinical data are not required for approval and the application also could have been submitted in an ANDA based on a suitability petition.¹⁹⁹ This use of section 505(b)(2) for changes to previously approved drugs encourages innovation without requiring duplicate work. Like section 505(j), it reflects the principle that it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug.²⁰⁰

Some examples of changes to approved drugs that would be submitted as section 505(b)(2) applications include formulation changes, a new dosing regimen, a change in the active ingredient (for example a different salt, ester, or racemate), a new molecular entity, a combination product for which the active ingredients were approved individually, a new

¹⁹⁷ *Id.* at 6. These types of amendments include “[r]equests for final approval with no scientific changes to the ANDA, patent amendments, and general correspondence submitted by applicants.” *Id.*

¹⁹⁸ FDCA § 505(b)(2), 21 U.S.C. § 355(b)(2). If the applicant obtains a right of reference to the raw data underlying the relevant studies, it may be submitted as a full NDA under section 505(b)(1) of the FDCA.

¹⁹⁹ See 57 Fed. Reg. 17,950 (Apr. 28, 1992). Applications submitted pursuant to section 505(b)(2) are subject to user fees. 21 U.S.C. §§ 379g, 379h. This also means that such applications will be reviewed in accordance with FDA’s user fee goals.

²⁰⁰ See FDA, Draft Guidance for Industry: Applications Covered by Section 505(b)(2) (Oct. 1999).

indication, and a switch from prescription to OTC.²⁰¹ A section 505(b)(2) application would also be appropriate for drug products with active ingredients derived from animal or botanic sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug. Applications for drug products with rates and/or extents of absorption that are different from the listed drug (but are not less than the listed drug) also could be appropriately submitted as a section 505(b)(2) application.²⁰²

Changes in dosage form, strength, or route of administration and substitution of an active ingredient in a combination product might have to be submitted in a section 505(b)(2) application if they require studies beyond those permitted in an ANDA. As noted above, if they require only review of bioavailability or bioequivalence studies of data from limited confirmatory testing, they can be submitted either in a section 505(b)(2) application or a ANDA based on an approved suitability petition.²⁰³

An application that is a duplicate of an RLD and eligible for approval under section 505(j) cannot be submitted as a section 505(b)(2) application. Likewise, if the product's only difference from the RLD is the extent to which its active ingredient is absorbed or otherwise made available to the site of action is less than the RLD or if the product's only difference from the RLD is that the rate at which its active ingredient is absorbed or otherwise made available to the site of action is unintentionally less than that of the RLD, a section 505(b)(2) application is not appropriate.²⁰⁴

After FDA issued its 1999 guidance on section 505(b)(2) applications, several brand-name companies filed citizen petitions challenging the agency's interpretation of section 505(b)(2) that permits a section 505(b)(2) applicant to rely on the agency's finding of safety and effectiveness for another approved product.²⁰⁵ Specifically, they argued that section 505(b)(2) permitted sponsors to rely only on studies in published literature. FDA has rejected these challenges and has taken the position, based on the language of the statute, that section 505(b)(2) is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug.²⁰⁶

As with ANDAs, the filing or approval of a section 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include the patent certifications described in the statute and must provide notice of such certifications to the NDA holder and patent owner.²⁰⁷ A section 505(b)(2) NDA is eligible for all exclusivities that may be awarded to a full NDA, including the five-

²⁰¹ *See id.*

²⁰² *Id.*

²⁰³ *Id.*

²⁰⁴ *Id.*

²⁰⁵ *See* Docket Nos. 2001P-0323; 2002P-0447 and 2003P-0408.

²⁰⁶ *See* Letter from Janet Woodcock, Director FDA Center for Drugs to Katherine M. Sanzo and Lawrence S. Ganslaw, Morgan, Lewis & Bockius, LLP, Jeffrey B. Chasnow, Pfizer, Inc., Stephen E. Lawton and Gillian R. Woollett, Biotechnology Industry Organization, and William R. Rakoczy, Lord, Bissell & Brook LLP, Docket Nos. 2001P-0323, 2002P-0447 and 2003P-0408 (Oct. 14, 2003).

²⁰⁷ FDCA §§ 505(b)(2), (b)(3), 21 U.S.C. §§ 355(b)(2), (b)(3).

year exclusivity for an NCE; the three-year exclusivity based on new clinical investigations, other than bioavailability or bioequivalence studies, essential to approval of the application and conducted or sponsored by the applicant; orphan drug exclusivity; and pediatric exclusivity.²⁰⁸ A section 505(b)(2) NDA can neither be awarded 180-day exclusivity nor have its approval delayed by such exclusivity.²⁰⁹

Antibiotics

Until 1997, antibiotics were not approved under section 505 of the FDCA and thus were not subject to the Hatch-Waxman provisions. In 1997, FDAMA repealed section 507 of the FDCA, under which antibiotics had been approved for marketing.²¹⁰ Antibiotics, including generic antibiotics, subsequently were approved under section 505, in NDAs and ANDAs. Because generic antibiotics previously had not been subject to the Hatch-Waxman exclusivity and patent certification provisions, FDAMA excluded from those provisions antibiotics for which the active moiety of the RLD was approved prior to enactment of FDAMA.²¹¹ Thus, under FDAMA, “old antibiotics” approved in NDAs were not entitled to Hatch-Waxman exclusivity, and thus, old antibiotics approved in ANDAs were not blocked by such exclusivity.²¹² Applications for antibiotics filed after 1997 are subject to the Hatch-Waxman exclusivity and patent certification provisions.

Then, on October 8, 2008, Congress passed the Qualifying Individual Program Supplemental Funding Act of 2008 (the QI Act) and amended the FDCA to add new section 505(v) to extend Hatch-Waxman benefits to antibiotics approved prior to enactment of FDAMA in 1997.

Enantiomer Exclusivity

Enantiomers are stereoisomers of a chiral compound that are mirror images of each other. Enantiomers can be either left-handed or right-handed. A racemic mixture is one that has equal amounts of left- and right-handed enantiomers. In implementing Hatch-Waxman, FDA did not consider single enantiomers of approved racemates to be active ingredients eligible for Hatch-Waxman five-year new chemical entity exclusivity.²¹³ In 2007, FDA amended the FDCA to provide that NDA applicants for a non-racemic drug containing as an active ingredient a single enantiomer that is contained in a racemic drug approved in

²⁰⁸ FDCA §§ 505(c)(3)(E), (j)(5)(F), 21 U.S.C. §§ 355(c)(3)(E), (j)(5)(F); FDCA § 527, 21 U.S.C. § 360cc; FDCA § 505A, 21 U.S.C. § 355a.

²⁰⁹ FDCA § 505(c)(3)(E), (j)(5)(B), 21 U.S.C. § 355(c)(3)(E), (j)(5)(B).

²¹⁰ Pub. L. No. 105-115, § 125; 111 Stat. at 2326-27.

²¹¹ Pub. L. No. 105-115, § 125(d); 111 Stat. at 2326-27.

²¹² See FDA, Guidance for Industry and Reviewers: Repeal of Section 507 of the Federal Food Drug and Cosmetic Act (May 1998), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080566.pdf>.

²¹³ See 54 Fed. Reg. 28,872, 28,898 (July 10, 1989). FDA requested comment on whether granting a five-year period of exclusivity to single enantiomers of approved racemates was advisable, but never initiated a rule-making to do so. See 62 Fed. Reg. 2167 (Jan. 15, 1997).

another application under section 505(b) can elect to have the single enantiomer an active ingredient that is different than the ingredient contained in the approved racemic drug if the following conditions are met:

- the single enantiomer has not previously been approved except in the approved racemic drug;
- the application includes full reports of new clinical investigations (other than bioavailability studies) necessary for approval and conducted or sponsored by the applicant; and
- the enantiomer is not for a condition of use in a therapeutic category in which the approved racemic drug has been approved or for which any other enantiomer of the racemic drug has been approved.²¹⁴

If the enantiomer is not considered to be the same active ingredient, then it would be eligible for five years of exclusivity. If the enantiomer NDA applicant elects to receive this exclusivity, however, the enantiomer drug cannot be approved for any condition of use in the therapeutic category in which the racemic drug is approved until 10 years after the enantiomer has been approved.²¹⁵ The provision applies only to applicants submitted after enactment of FDAAA and it expires in 2012.²¹⁶

Reorganization of the Office of Generic Drugs

On December 10, 2013 FDA announced that FDA's Center for Drug Evaluation and Research (CDER) approved plans to reorganize the Office of Generic Drugs (OGD) into a "super office."²¹⁷ OGD now reports directly to the director of CDER and will be structured into four separate sub-offices: the Office of Research and Standards, the Office of Bioequivalence, the Office of Regulatory Operations, and the Office of Generic Drug Policy.²¹⁸ The restructuring was announced as a measure designed to "lead to greater efficiency and more consistency across review components" and "to expedite the availability of safe, effective, and high-quality generic drugs to patients."²¹⁹ In large part, the restructuring was motivated by FDA's desire to meet the challenges posed by the passage of GDUFA.²²⁰

The Office of Generic Drug Policy includes the Division of Legal and Regulatory Support, which is expected to focus its efforts on handling and resolving Hatch-Waxman disputes.²²¹

²¹⁴ FDCA § 505(u), 21 U.S.C. § 355(u), added by FDAAA § 1113.

²¹⁵ *Id.*

²¹⁶ *Id.*

²¹⁷ U.S. Food & Drug Admin., Office of Generic Drugs Reorganization: *Development and Approval Process (Drugs)* (last updated July 21, 2014), available at <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandgenerics/ucm378126.htm>.

²¹⁸ *Id.*

²¹⁹ *Id.*

²²⁰ Bob Pollock, *OGD Elevation to Super Office in CDER* (Sept. 10, 2012), available at <http://www.lachmanconsultants.com/ogd-elevation-to-super-office-in-cder.asp>.

²²¹ Kurt R. Karst, *Office of Generic Drugs "Super Office" Becomes a Reality: New "Office of Generic Drug Policy" Will Handle Hatch-Waxman Issues*, FDA Law Blog (Dec. 25, 2013), available at <http://www.fdalawblog.net/>

Prior to the reorganization, certain issues, such as 180-day exclusivity, were handled in a less focused manner and this division should “bring greater clarity (and speed?) to FDA’s decisions and decision-making process,” not unlike the CDER Exclusivity Board does for five- and three-year exclusivity disputes.²²² It has been further predicted that the restructuring should lead to a wave of new hiring in the OGD, which has proven to be accurate.²²³

In fact, improving the ANDA process appeared to be part of a larger strategy to meet GDUFA metrics in the future.²²⁴ FDA provided further guidance on the content and format of ANDAs, including a closer look at “enhanced refuse-to-receive standards, the establishment of a public docket . . . to receive input and suggestions on ways to improve ANDA quality and on how to best communicate those suggestions to the generic drug industry.”²²⁵ The guidance was intended to be an accessible document containing much of OGD’s advice for submissions, with links to other OGD documents. Again, this move was logical considering that high-quality ANDAs should be easier to review, thus making it easier for the OGD to meet its GDUFA performance goals.²²⁶

OGD’s Acting Director also announced that starting on February 1, 2014, “OGD’s CC officers will conduct a complete inventory of all the original ANDAs in our queue, and provide each applicant with an update regarding the status of its ANDAs.”²²⁷ This effort would extend to ANDAs submitted prior to GDUFA; it also covers ANDAs submitted in Fiscal Years 2013 and 2014, despite the lack of FDA performance goals regarding review and action on those ANDAs.²²⁸ FDA Law Blog reported on a form-version of the correspondence that the OGD expects to send out in connection with this initiative.²²⁹

fda_law_blog_hyman_phelps/2013/12/office-of-generic-drugs-super-office-becomes-a-reliability-new-office-of-generic-drug-policy-will-handle.html.

²²² *Id.*

²²³ *Id.*

²²⁴ Kurt R. Karst, *Improving the Yield on ANDA Submissions: FDA Wants to Hear Industry’s Concerns and Provide Guidance on How to Build a Better ANDA*, FDA Law Blog (Jan. 22, 2014), available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/01/improving-the-yield-on-anda-submissions-fda-wants-to-hear-industrys-concerns-and-provide-guidance-on-.html.

²²⁵ Kurt R. Karst, *Gentlemen, We Can Rebuild the ANDA – Better, Stronger, Faster: FDA Issues Guidance on Quality ANDA Submissions*, FDA Law Blog (June 12, 2014), available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/06/gentlemen-we-can-rebuild-the-anda-better-stronger-faster-fda-issues-guidance-on-quality-anda-submiss.html.

²²⁶ *Id.*

²²⁷ Kurt R. Karst, *FDA’s Office of Generic Drugs Says “We Hear You, and We’re Willing to Bite the Bullet” in a Massive Effort to Address Post-GDUFA Stakeholder Transparency Concerns*, FDA Law Blog (Jan. 31, 2014), available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/01/fdas-office-of-generic-drugs-says-we-hear-you-and-were-willing-to-bite-the-bullet-in-a-massive-effor.html.

²²⁸ *Id.*

²²⁹ See Kurt R. Karst, *The Rollout: FDA’s Mission Critical ANDA Undertaking*, FDA Law Blog (Feb. 12, 2014), available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/02/the-rollout-fdas-mission-critical-anda-undertaking.html.