

The 505(b)(2) Drug Approval Pathway

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ABSTRACT

Codified in 1984, the Section 505(b)(2) drug approval pathway lies part-way between the regular new drug approval pathway and the generic drug approval pathway, allowing changes in characteristics such as dose or dosage form and often requiring data beyond bioavailability studies. The number of 505(b)(2) approvals has increased dramatically and now annually exceeds the number of new drug approvals. Rising 505(b)(2) approvals can be explained by accumulating exclusivities and expedited approval programs that are unavailable to generic drugs, user fee funding aimed at reducing review times, new pediatric study requirements that cannot be fulfilled under the generic drug pathway, and heightened competition in the generic drug market. Based on an examination of all 505(b)(2) approvals from 1993 through the end of 2016, we found evidence suggesting the 505(b)(2) pathway is primarily serving to increase competition, including the historical background to the pathway's creation, the predominance of small or generic manufacturers as sponsors of 505(b)(2) applications, the frequency with which 505(b)(2) drug applicants fail to request or receive non-patent exclusivity, and the lack of identity between the 505(b)(2) applicant and the reference listed drug applicant.

INTRODUCTION

Since the 1962 Kefauver-Harris Drug Amendments Act, new drugs have been approved based on the submission of New Drug Applications (NDAs) containing reports of “adequate and well-controlled investigations” that establish each drug's safety and efficacy.¹ In the 1984 Hatch-Waxman Act,² Congress codified a second major pathway for the approval of new drugs, which involves the submission of an

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¹ Drug Amendments of 1962, Pub. L. No. 87-781, tit. 1, § 102(c), 78 Stat. 780, 781 (1962) (codified as amended at 21 U.S.C. § 355(d) (2018)).

² Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

Abbreviated New Drug Application (ANDA).³ The ANDA pathway facilitates the approval of generic copies of approved products designated as reference listed drugs (RLDs),⁴ based on more limited data from bioequivalence studies, and does not require data from full safety and efficacy trials that NDAs traditionally must include.⁵

The Hatch-Waxman Act also codified a third, lesser-known pathway. Named for the section of the Food, Drug, and Cosmetic Act (FDCA) in which it is found, the 505(b)(2) pathway serves as a midpoint between an ANDA and an NDA in terms of the volume of new evidence required to be generated and submitted. Like an NDA, it requires the submission of “full reports” of safety and efficacy investigations, but like an ANDA, it allows the applicant to rely in part on previous studies conducted by an unrelated party, such as another drug manufacturer, which could help to satisfy the requirement to submit full reports.⁶ Unlike an ANDA applicant, a 505(b)(2) applicant can rely not only on data associated with a previously approved RLD, but also on data from virtually any other source, such as the published literature.

Under the Hatch-Waxman Act, generic drug manufacturers sometimes have a choice between submitting a 505(b)(2) application or submitting a “suitability petition” that requests a Food and Drug Administration (FDA) determination as to whether a proposed drug modification would be suitable for submission as an ANDA.⁷ Both pathways allow manufacturers to obtain approval of drugs that differ from RLDs with respect to dose, dosage form, route of administration, or, in the case of combination products, active ingredient.⁸ Although the ANDA provisions offer an easier pathway to approval, they cannot be used if new studies (other than those needed to demonstrate the new drug will have the same therapeutic effect as the RLD) are

³ The ANDA pathway was created by regulation in 1970 but, until the Hatch-Waxman Act, applied only to pre-1962 drugs. See Jonathan J. Darrow, *Biosimilar Approvals and the BPCIA: Too Soon to Give Up*, HEALTH AFF. BLOG (2019), <https://www.healthaffairs.org/doi/10.1377/hblog20190718.722161/full/> [<https://perma.cc/MPL4-998X>].

⁴ 21 C.F.R. § 314.3 (2018). See also FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS ix (37th ed. 2017) (explaining the concepts of “reference listed drug” and “reference standard”) [hereinafter FOOD & DRUG ADMIN., THERAPEUTIC EQUIVALENCE EVALUATIONS (37th ed.)].

⁵ See 98 Stat. at 1585–86.

⁶ See *id.* § 103, 98 Stat. at 1593 (codified as amended at 21 U.S.C. § 355(b)(2)) (stating that 505(b)(2) applications are “submitted under paragraph [505(b)(1)]”). See also CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., REFERENCING APPROVED DRUG PRODUCTS IN ANDA SUBMISSIONS 2 (2017) (“A 505(b)(2) application is an NDA that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant . . .”).

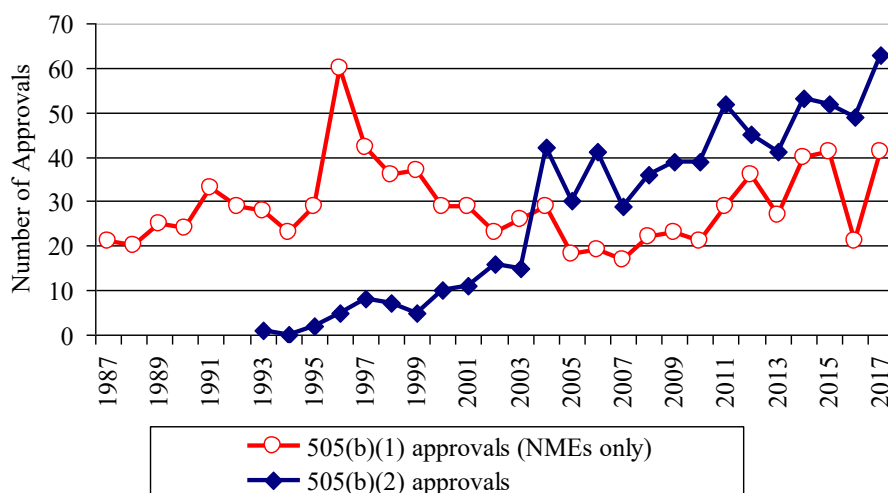
⁷ Pub. L. No. 98-417, tit. 1, § 101, 98 Stat. 1585, 1587 (1984) (codified as amended at 21 U.S.C. § 355(j)(2)(C)). An antecedent suitability petition procedure was codified in FDA regulations prior to the Hatch-Waxman Act. See Abbreviated New Drug Applications; Related Drug Amendments, 48 Fed. Reg. 2751 (Jan. 21, 1983) (“The rule also establishes a petition procedure whereby prospective applicants may ask FDA to determine whether an abbreviated new drug application is suitable for similar or related products.”).

⁸ See 21 C.F.R. §§ 314.92–314.93 (2017) (ANDAs and suitability petitions); 21 C.F.R. § 314.54 (noting a 505(b)(2) application is for a “drug product that represents a modification of a listed drug” such as “a new dosage form”).

essential to establish safety and efficacy.⁹ If a manufacturer seeking to obtain approval via the ANDA pathway submits a suitability petition and it is denied, then the manufacturer can then submit a 505(b)(2) application, which would generally need to contain additional data, such as bridging studies, that, along with data from investigations not conducted by or for the applicant, establish the drug's safety and effectiveness.¹⁰

In the years following the enactment of the Hatch-Waxman Act, use of the ANDA pathway surged, while the 505(b)(2) pathway remained little used.¹¹ But beginning in the 1990s, the number of 505(b)(2) approvals began to increase, first slowly, then sharply in 2004. In that year, the number of 505(b)(2) approvals exceeded the number of new molecular entities (NME) approved under 505(b)(1) for the first time. Since then, 505(b)(2) approvals have continued to increase, and now annually exceed the number of NMEs approved under 505(b)(1), with more than forty new approvals per year (Figure 1).

Figure 1: Approvals of NMEs and 505(b)(2) Applications, 1987–2017¹²



⁹ See CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., GUIDANCE: DETERMINING WHETHER TO SUBMIT AN ANDA OR A 505(B)(2) APPLICATION 3 (2019) [hereinafter CDER, ANDA vs. 505(B)(2) DRAFT GUIDANCE].

¹⁰ See *id.* at 5.

¹¹ See PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 1012 n.1 (4th ed. 2014) (“For the decade following its enactment, section 505(b)(2) was rarely used.”). See also William W. Vodra, *Paper NDAs and Real Problems*, 39 FOOD DRUG COSMETIC L.J. 356, 357 (1984) (noting that only fifty-seven paper NDAs had been approved in the program’s “first five-and-a-half years of life”).

¹² Data were compiled from various FDA sources, including data received following a Freedom of Information Act request. See generally Jonathan J. Darrow & Aaron S. Kesselheim, *Drug Development and FDA Approval, 1938–2013*, 370 NEW ENG. J. MED. 2465 (2014) (online interactive graphic displaying NME information). The 691 approvals under 505(b)(2) illustrated in Figure 1 include thirty NMEs; to avoid double counting, these NMEs were subtracted from compiled NME counts to arrive at the 505(b)(1) data illustrated.

This Article investigates the causes and effects of the increase in the use of the 505(b)(2) pathway, the types of products being approved under the pathway, how it is being used by both generic and brand-name manufacturers, and what increasing utilization may mean for competition and pricing. We also examine the frequency with which 505(b)(2) applications have benefited from FDA's special programs (fast-track, priority review, breakthrough therapy, or accelerated approval) or been awarded seven-year orphan drug exclusivity, five-year NME exclusivity, or three-year new clinical investigation exclusivity, and the extent to which patent exclusivities have extended beyond the end of these non-patent exclusivities. Finally, we investigate the extent to which 505(b)(2) products have been deemed by FDA to be therapeutically equivalent to other products, thereby allowing substitution by pharmacists and potentially reducing prices.

I. METHODS

We obtained a list of all drugs approved or tentatively approved under the 505(b)(2) pathway between January 1, 1993 and December 31, 2016 from FDA by a request under the Freedom of Information Act (FOIA).¹³ This list contains application numbers, brand names, generic names, applicant names, and approval or tentative approval dates. As with new drugs approved under section 505(b)(1), FDA categorizes drugs approved under 505(b)(2) by classification code (e.g., 1=new molecular entity; 3=new formulation; 4=new combination, etc.).¹⁴ Classification codes for each drug were obtained from the 2016 electronic version of FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Tentative approval status was obtained from an electronic version of FDA's Orange Book downloaded in September 2018.¹⁵

We reviewed the Orange Book of the year following the year of each drug's approval to extract: the applicant name at the time of approval (if different from the applicant indicated in the list obtained by FOIA request, which generally indicates the current owner of the product); the RLD status of each drug; the number of patents per drug; the expiration date of the last expiring patent; any non-patent exclusivity; non-patent exclusivity expiration dates; and therapeutic equivalence codes. To determine the extent to which additional equivalence codes were present as time elapsed, we also examined these codes for each drug using the 2017 Orange Book.

Unique applicants were determined based upon applicant name, using author judgment when necessary. For example, Dr. Reddy's Laboratories Ltd. was considered to be the same applicant as Dr. Reddy's Laboratories Inc., and Endo Pharmaceuticals Inc. was considered to be the same applicant as Endo Pharms. Inc. Applicants appearing to represent different subunits or affiliates of the same pharmaceutical company were also grouped as a single applicant, whether or not they were legally

¹³ FDA was unable to fulfill a FOIA request for 505(b)(2) applications approved between 1984 and 1992 by the time this Article went to press, stating "FDA has only been identifying applications in its database as being approved under section 505(b)(2) of the Act since 1993; therefore, we are having issues compiling responsive data for the dates noted in your request." Email from Diderot Nicolas, FDA, to Jonathan J. Darrow, Nov. 7, 2018 (on file with Jonathan J. Darrow).

¹⁴ See CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MAPP No. 5018.2, NDA CLASSIFICATION CODES (effective Nov. 4, 2015) [hereinafter CDER, NDA CLASSIFICATION CODES].

¹⁵ 21 C.F.R. § 314.3 (2018) (defining "tentative approval").

distinct entities. Thus, Teva Branded Pharmaceutical Products R&D Inc., Teva Parenteral Medicines Inc., Teva Pharmaceuticals USA Inc, and Teva Pharms. were collectively considered to be a single applicant.

We classified applicants as generic or brand-name, which we defined as those having more than 1.5 times as many ANDAs than NDAs, or more than 1.5 times as many NDAs than ANDAs, respectively, based on products listed in the 2016 Orange Book. If applicants were not listed in the 2016 Orange Book, we consulted the 2010 Orange Book, as it is the earliest Orange Book that distinguishes ANDAs from NDAs.

Requests for exclusivity are recorded in each drug's administrative and correspondence documents, which are part of the FDA review package that is available for most drugs from the drugs@FDA website or by FOIA request. We determined exclusivity grants by reference to the Orange Book of the year following each drug's approval. Each drug product was assigned a single exclusivity type. For products awarded multiple non-patent exclusivities, the last-expiring exclusivity was considered to define that product's exclusivity type. Any patent exclusivity and the date of expiration of the last-expiring patent were also extracted from the Orange Book of the year following each drug's approval. In some cases, patents may be added to the Orange Book in subsequent years, and these additions were not captured in our data.

We also reviewed administrative and correspondence documents from each drug's FDA-approval package to determine whether drugs received orphan drug designation, fast-track designation, breakthrough designation, accelerated approval, or priority review, and whether the applicant requested non-patent exclusivity. When approval documents were unavailable from either the FDA website or under FOIA, we extracted priority review status and orphan drug designation from the drugs@FDA database. We cross-checked fast-track, accelerated approval, and breakthrough statuses with FDA's lists of drugs approved under these programs.

II. RESULTS

Between January 1, 1993 and December 31, 2016, FDA approved or tentatively approved 628 drug products under the 505(b)(2) pathway (different doses approved under a single NDA were counted as one product even though FDA assigns different product numbers, under each NDA, to each dose).¹⁶ Tentatively approved drugs are not listed in the Orange Book until the approval becomes final. Sixty-three drugs (ten percent) were not listed in the Orange Book of the year following approval and continued to have tentative approvals as of September 2018, indicating the approval could not be made effective due to unexpired non-patent exclusivity of a reference product. An additional twelve drugs were not listed in the Orange Book of the year following approval, including six (one percent of 628) that later received final approval. Altogether, seventy-five (twelve percent) of 628 drugs were not listed in the Orange Book of the year following approval (or were listed as "discontinued").¹⁷ Of

¹⁶ See FOOD & DRUG ADMIN., THERAPEUTIC EQUIVALENCE EVALUATIONS (37th ed.), *supra* note 4, at 2.2.

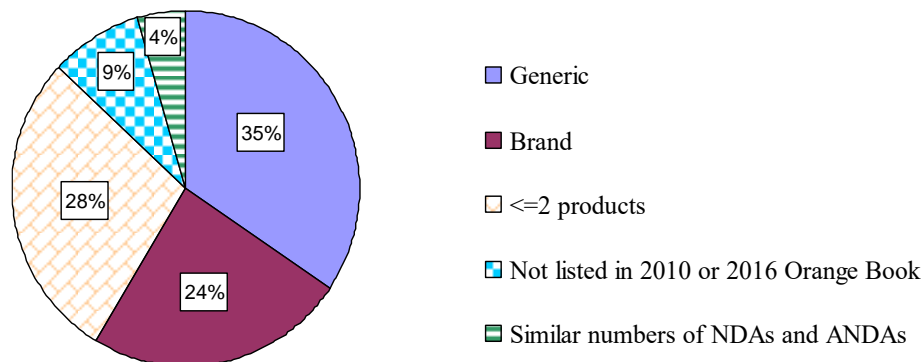
¹⁷ Among the 505(b)(2) products not listed in the Orange Book in the year following each drug's approval were fifty-four antivirals for the treatment or prophylaxis of HIV/AIDS. By 2014, at least twenty-six 505(b)(2) products had already been approved under the President's Emergency Plan for AIDS Relief.

the remaining 553 products that were listed in the Orange Book of the year following each drug's approval, 451 (eighty-two percent) were immediately designated by FDA as RLDs. After our study period, sixty-three 505(b)(2) applications were approved in 2017.¹⁸

A. Applicant Identity

Products approved under 505(b)(2) were sponsored by 318 unique applicants, none of which was associated with more than sixteen (2.5 percent of 628) products. Of 628 products, 217 (thirty-five percent) were associated with generic manufacturers, and 151 (twenty-four percent) with brand-name manufacturers (Figure 2). Another 178 (twenty-eight percent) products were associated with manufacturers not classified as either brand or generic because the manufacturer was associated with two products or fewer, excluding its 505(b)(2) products. Twenty-eight (four percent) products were associated with applicants that fell between our definition of brand and generic manufacturers, having similar numbers of ANDA and NDA products. Another fifty-four (nine percent) products were associated with manufacturers that were not listed in either the 2016 or 2010 Orange Books, which may occur, for example, if a manufacturer is acquired, changes its name, or ceases operations, or if all of a manufacturer's applications continue to bear tentative approval status. Top applicants are listed in Figure 3.

Figure 2: 505(b)(2) Applicant Type



See Sheetal Agarwal et al., *Overview of Recently Approved 505(b)(2) New Drug Applications (2010-2012): Role of Clinical Pharmacology*, 54 J. CLINICAL PHARMACOLOGY 1330, 1331 (2014).

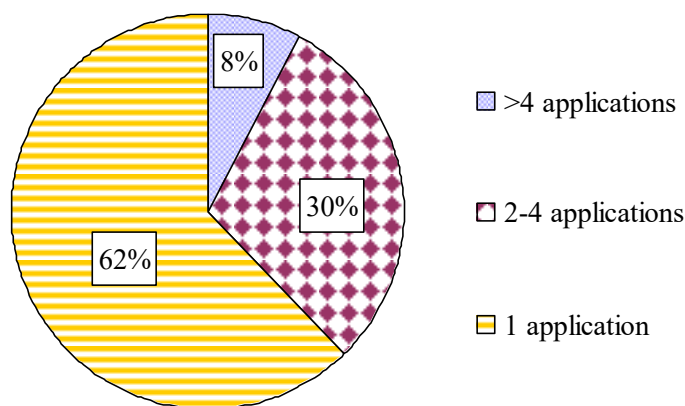
¹⁸ Jennifer King, *505(b)(2) Approvals for 2017: What Were They and Who Developed Them?*, CAMARGO BLOG, (Jan. 24, 2018), <https://camargopharma.com/2018/01/505b2-approvals-for-2017-what-were-they-and-who-developed-them/> [<https://perma.cc/X9PD-CBZS>].

Figure 3: Top 505(b)(2) Applicants

Applicant Name	Applicant Type	No. Applications (%)
Mylan	Generic	16 (2.5)
Cipla	Generic	12 (1.9)
Teva	Generic	11 (1.8)
Fresenius	Generic	10 (1.6)
Novartis	Brand	10 (1.6)
Alcon	Generic	9 (1.4)
Aurobindo	Generic	9 (1.4)
Baxter	Brand	9 (1.4)
Hospira	Generic	8 (1.3)
B Braun Medical	Brand	7 (1.1)
Galderma	Brand	7 (1.1)
Roxane	Generic	7 (1.1)
Sandoz	Generic	7 (1.1)
Strides	Generic	7 (1.1)

More than sixty percent of applicants (after the consolidation as described above) were associated with only a single 505(b)(2) application, and approximately ninety-two percent of applicants were associated with four or fewer 505(b)(2) applications (Figure 4).

Figure 4: Number of 505(b)(2) Applications per Applicant

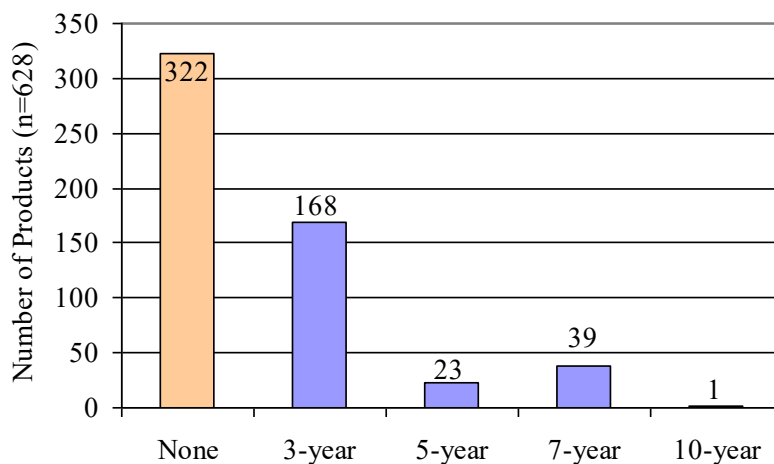


Of the 628 products approved or tentatively approved under the 505(b)(2) pathway, fifty-six (nine percent) relied in part on existing data of a sponsor that was the same as the 505(b)(2) applicant (in addition to relying on the data of at least one unrelated third party), while 432 (sixty-nine percent) relied on existing data only of unrelated third parties. For the remaining 140 (twenty-two percent) products, we were unable to identify RLD information for the 505(b)(2) product, for example, because the 505(b)(2) application relied on published literature rather than an RLD.

B. Non-Patent Exclusivity

Non-patent exclusivity can be requested by 505(b)(2) applicants or granted by FDA absent a request. Using the FDA website or by FOIA request, we were able to obtain associated documentation for 490 of the 628 drugs. Of these, 201 (forty-one percent of 490) applicants requested non-patent exclusivity, 155 (seventy-seven percent of 201) of which received it. Based on the Orange Book of the year following each drug's approval, we determined that an additional seventy-six applicants were awarded exclusivity without documentation regarding the presence or absence of a request, resulting in 231 (forty-two percent of the 553 drugs listed in the Orange Book in the year following the drug's approval) total awards of exclusivity. These included 168 (thirty percent) drugs that received three-year exclusivity for submissions requiring new clinical data (such as for new dosage forms or new combinations),¹⁹ thirty-nine (seven percent) that received seven-year exclusivity under the Orphan Drug Act,²⁰ twenty-three (four percent) that received five-year new chemical entity exclusivity,²¹ and one (0.2 percent) that received five-year exclusivity under the Generating Antibiotic Incentives Now Act which was added to its five-year new chemical entity exclusivity (Figure 5).²²

Figure 5: Exclusivity Awarded to 505(b)(2) Applicants*



* Ten-year exclusivity was awarded for ceftolozane/tazobactam (Zerbaxa, NDA 206829), and included five-year new chemical entity exclusivity plus five-year

¹⁹ Two products received non-standard durations of new clinical investigation exclusivity: NDA 022157 (2.3 years) and NDA 205636 (2.9 years).

²⁰ Four products received non-standard durations of exclusivity under the Orphan Drug Act: NDA 203324 (7.2 years), NDA 203922 (5.9 years), NDA 203923 (5.9 years), and NDA 022278 (2.8 years).

²¹ Four products received non-standard durations of new chemical entity exclusivity: NDA 204353 (3.6 years), NDA 206111 (3.9 years), NDA 202331 (4.2 years), and NDA 022044 (4.5 years).

²² See Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, tit. IV, § 801, 126 Stat. 993, 1077 (2012).

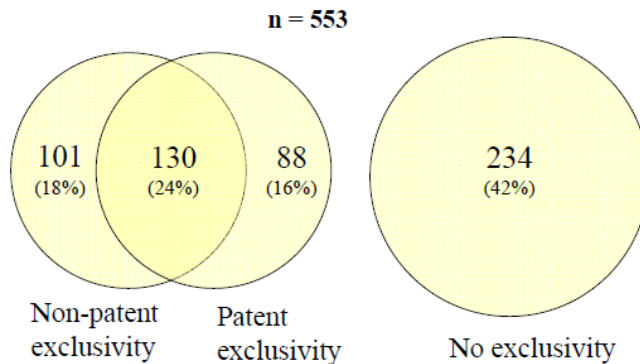
qualified infectious disease product exclusivity.

C. Patent Exclusivity

Two hundred eighteen (thirty-nine percent of 553) 505(b)(2) products had at least one associated patent listed in the Orange Book by the year following approval (median: 2; interquartile range: 1–4; max: 23). Twenty-seven (five percent of 553) last-expiring patents bore a drug substance code (with or without a drug product or use code), 136 (twenty-five percent) bore a drug product code (with or without a use code), but not a drug substance code, forty-four (eight percent) bore a use code with no drug substance or drug product code, and ten (two percent) bore no code.

Patent and non-patent exclusivity overlapped incompletely: ninety-one (sixteen percent) products had patent exclusivity but no non-patent exclusivity, while 101 (eighteen percent) products had non-patent exclusivity but no patent exclusivity. Altogether, 319 products (fifty-eight percent of 553) had either patent- or non-patent exclusivity, while 234 (forty-two percent) products had no patent or non-patent exclusivity (Figure 6). Of the 130 (twenty-four percent) products that had both patent and non-patent exclusivity, 124 (ninety-five percent) had at least one patent with an expiration date that extended beyond the end of the last expiring non-patent exclusivity. Of these 124 products, the average period by which patent exclusivity extended beyond non-patent exclusivity was 8.5 years.

Figure 6: Patent and Non-Patent Exclusivity of 505(b)(2) Products



D. Therapeutic Equivalence

If a prescription drug product of a given strength, dosage form, and route of administration is available from more than one source, FDA will list a therapeutic equivalence code in the Orange Book.²³ As described in the Orange Book of the year following each drug's approval, twenty-eight (five percent) of 553 products bore an "A"-type therapeutic equivalence code, indicating that the 505(b)(2) product was

²³ See FOOD & DRUG ADMIN., THERAPEUTIC EQUIVALENCE EVALUATIONS (37th ed.), *supra* note 4, at 2-1; see also CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., ASSESSING USER FEES UNDER THE PRESCRIPTION DRUG USER FEE AMENDMENTS OF 2017 9 (2018) ("FDA publishes its conclusions regarding therapeutic equivalence in the Orange Book.").

designated as therapeutically equivalent to at least one other product, while twenty-four (four percent) bore “B”-type codes, indicating that at least one other product was considered to be pharmaceutically equivalent²⁴ but not therapeutically equivalent (i.e., pharmaceutically equivalent products that are demonstrated or deemed to be bioequivalent to each other) to the 505(b)(2) product.²⁵ By the time of the 2017 Orange Book, 127 (twenty-three percent) of 551 products bore A codes, while seventeen (three percent) bore B codes.²⁶

A and B codes are subcategorized by second-character designations. AB-rated products, for example, are those of various dosage forms for which bioequivalence has been demonstrated by *in vivo* and/or *in vitro* methodology.²⁷ A-rated products for which bioequivalence is presumed (without the need for bioequivalence testing) or demonstrated by the use of an *in vitro* dissolution standard are designated as AA, AN, AO, AP, or AT, depending on the dosage form.²⁸ B-rated products are those for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, and are rated as B*, BC, BD, BE, BN, BP, BR, BS, BT, or BX, depending on the dosage form or other reason for the actual or potential bioequivalence problem. B-ratings may sometimes be converted to AB-ratings if adequate bioequivalence data is provided and products otherwise satisfy therapeutic equivalence standards. Figures 7 and 8 summarize the therapeutic equivalence codes associated with the products in the present study.

Figure 7: FDA’s Therapeutic Equivalence Evaluations of 505(b)(2) Products

Therapeutic Equivalence Code	Description	Number of Products with Code	
		Orange Book, year following approval (n=553)	2017 Orange Book (n=551)
AB	bioequivalence has been demonstrated	3	67

²⁴ See 21 C.F.R. § 314.3 (2017) (“*Pharmaceutical equivalents* are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms . . . , that deliver identical amounts of the active drug ingredient over the identical dosing period; [and] do not necessarily contain the same inactive ingredients . . .”).

²⁵ See FOOD & DRUG ADMIN., THERAPEUTIC EQUIVALENCE EVALUATIONS (37th ed.), *supra* note 4, at vii.

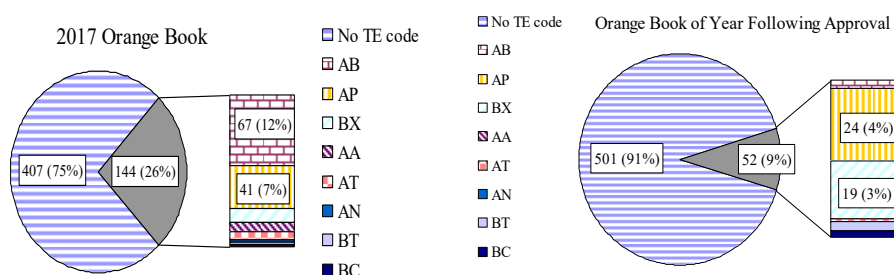
²⁶ NDA 204399 bore both A and B codes based on two different doses/dosage forms and was counted only once, as A.

²⁷ See FOOD & DRUG ADMIN., THERAPEUTIC EQUIVALENCE EVALUATIONS (37th ed.), *supra* note 4, at xiv.

²⁸ See *id.* at xiii.

AN	solutions and powders intended for aerosolization that are marketed for use in general-use delivery systems	0	3
AP	injectable aqueous solutions and some intravenous non-aqueous solutions	24	41
AT	topical products	1	7
BC	extended release dosage forms	2	2
BT	topical products	3	2
BX	drug products for which the data are insufficient to determine therapeutic equivalence	19	13

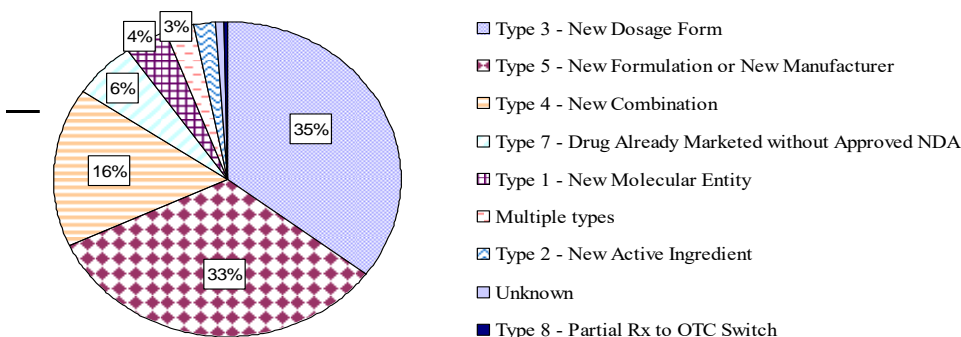
Figure 8: Therapeutic Equivalence Codes



E. Types of Modifications Approved

Three classification codes accounted for eighty-four percent of drugs approved under section 505(b)(2). These included new dosage forms (Type 3: 222 (thirty-five percent) of 628), new formulations or other differences (Type 5: 205 (thirty-three percent)), and new combinations (Type 4: 103 (sixteen percent)) (Figure 9). The remaining drugs were classified as those previously marketed without an approved NDA (thirty-seven (six percent)), new molecular entities (twenty-five (four percent)), new active ingredients (thirteen (two percent)), and prescription to over-the-counter (OTC) switches (two (0.3 percent)). Twenty-one additional drugs bore multiple classification codes (sixteen (three percent)) or did not have a code (five (one percent)). New indications may also be approved under the 505(b)(2) pathway, but no classification code captures only new indications. Type 5 (new formulation or other differences) includes not only new formulations, but also other differences such as new indications.²⁹ Types 2 (new active ingredient) and 3 (new dosage forms) may or may not also be associated with new indications.³⁰

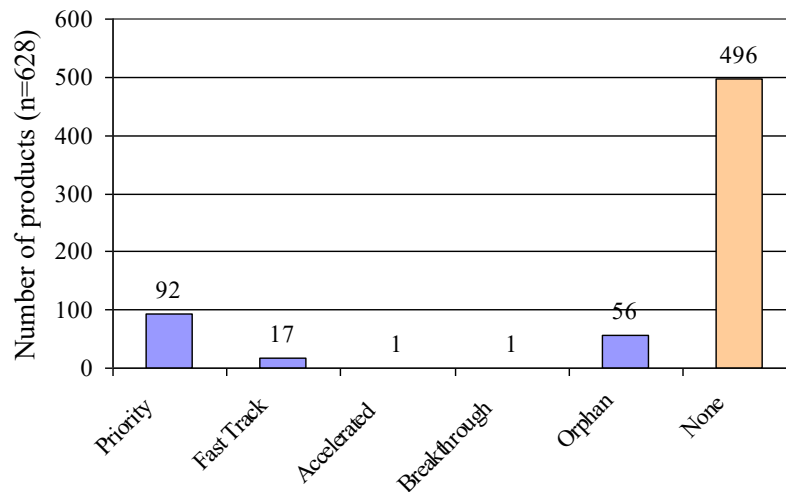
Figure 9: FDA Classification Codes for 505(b)(2) Drugs (1993 to 2016)



F. Expedited Review

A drug approved under 505(b)(2) may be eligible for expedited review or approval, or for designation as an orphan drug product. Of 628 drugs, ninety-two (fifteen percent) received priority review, seventeen (three percent) received a fast-track designation, one (0.2 percent) received accelerated approval, one (0.2 percent) received a breakthrough designation, and fifty-six (nine percent) received an orphan drug designation (Figure 10).

Figure 10: Number of 505(b)(2) Products Benefiting from Expedited Programs



IV. DISCUSSION

A. Why Have 505(b)(2) Applications Increased?

Although the 505(b)(2) pathway has been available since 1984 and its predecessor, the “paper NDA,”³¹ since the 1970s, the pathway was infrequently used until 2004. Before 1984, there was sufficient literature to support 505(b)(2) applications for only approximately fifteen percent of post-1962 drugs,³² and applicants under then-current law were not able to rely on the private data associated with the previously approved

³¹ See *infra* note 153 *et seq.*

³² See H.R. REP. NO. 98-857 (Part 1) (1984).

drugs of another manufacturer.³³ In the years immediately following the passage of the 1984 Hatch-Waxman Act, there was intense interest in the familiar but newly-expanded ANDA pathway as post-1962 drugs for the first time became eligible, potentially diverting attention away from the more costly and cumbersome 505(b)(2) process.

Even before the Hatch-Waxman Act became effective, however, a series of legislative enactments had begun that would indirectly promote the use of the 505(b)(2) pathway. These enactments, which grew in number after 1984, related to the establishment of new non-patent exclusivities, new manufacturer user fees and associated FDA review timelines, new pediatric study requirements, and new expedited development and approval programs. In addition, increasing competition in the generic (i.e., ANDA) drug market over time created pressure on generic drug manufacturers to extend their competitive ambitions beyond mere copying of originator drug products. Each of these factors is explored in turn.

1. 505(b)(2) Applications Became Eligible for Non-Patent Exclusivities

Beginning in 1983, a series of legislative enactments created incentives for the submission of new drug applications, including those submitted under 505(b)(2), that did not apply to the submission of ANDA applications. These incentives have accumulated over time, gradually increasing the relative value of the 505(b)(2) pathway. Under the 1983 Orphan Drug Act, new rare disease products (not including ANDAs) were made eligible for seven years of market exclusivity. The 1984 Hatch-Waxman Act added three-year exclusivity if reports from new clinical investigations (other than bioavailability studies) were essential to a new drug's approval, and five-year exclusivity for most NMEs.³⁴ In 1997, the FDA Modernization Act offered manufacturers the ability to obtain six-month extensions to patent or non-patent exclusivity by conducting studies of the drug in children, when requested by FDA.³⁵

³³ Notice of Publication of "Paper NDA" Memorandum, 46 Fed. Reg. 27,396, 27,396 (May 19, 1981) ("Present interpretation of the law is that no data in an NDA can be utilized to support another NDA without express permission of the original NDA holder.").

³⁴ Five-year exclusivity is available for "new chemical entities" (NCEs), where NCE is defined as "a drug that contains no active moiety that has been approved by FDA in any other NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act." 21 C.F.R. § 314.108 (2017). The term "new molecular entity" is not defined in either FDA's governing statute or regulations, but is defined in FDA's internal procedures manual as "an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under [21 U.S.C. § 355] or has been previously marketed as a drug in the United States." CDER, NDA CLASSIFICATION CODES, *supra* note 14, at 2 n.2. In our study, several NMEs did not receive five-year NCE exclusivity (mostly combination products approved prior to FDA's 2014 exclusivity guidance), while several non-NMEs (including both Type 4 combinations for which only partial five-year exclusivity was available based on a parent product's NCE exclusivity, and Type 7 products previously marketed without an approved application) received five-year NCE exclusivity. See CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: NEW CHEMICAL ENTITY EXCLUSIVITY DETERMINATIONS FOR CERTAIN FIXED-COMBINATION DRUG PRODUCTS 2 (Oct. 2014) (noting that FDA altered its interpretation of applicable law to allow broader availability of NCE exclusivity for combination products). See generally Sarah K. Branch & Israel Agranat, "New Drug" Designations for New Therapeutic Entities: New Active Substance, New Chemical Entity, New Biological Entity, *New Molecular Entity*, 57 J. MED. CHEM. 8729 (2014) (discussing the difference between NMEs and NCEs). FDA has established an Exclusivity Board to oversee exclusivity determinations.

³⁵ Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 111, 111 Stat. 2296, 2305 (1997) (codified as amended at 21 U.S.C. § 355a). See generally CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FOOD & DRUG ADMIN., FDA GUIDANCE FOR INDUSTRY: QUALIFYING FOR

In 2012, Congress created five-year extensions of exclusivity for qualified infectious disease products.³⁶ Of the 553 drugs listed in the Orange Book of the year following approval, 231 (forty-two percent) benefited from at least one of these programs (not including pediatric exclusivity extensions).

2. *PDUFA Speeds 505(b)(2) Applications, but Not Suitability Petitions*

Use of the 505(b)(2) pathway was also promoted by the Prescription Drug User Fee Act (PDUFA). Under the 1962 Kefauver-Harris Drug Amendments, once a new drug application was submitted, FDA had to either approve it within 180 days or offer the applicant an opportunity for a hearing.³⁷ In the 1970s and 1980s, however, FDA was regularly unable to meet this deadline due to inadequate staffing. In 1992, Congress addressed this problem by enacting PDUFA,³⁸ under which manufacturers pay fees to FDA upon submission of NDAs, ultimately providing funding to FDA to hire additional personnel to speed the review and approval process.³⁹

Although the current PDUFA application fee is more than ten times higher for 505(b)(2) applications than it is for ANDAs (\$2.42 million⁴⁰ vs. \$0.17 million⁴¹), this cost disadvantage may in some cases be more than outweighed by advantages in time-to-approval. Under PDUFA and analogous legislation for generic drugs enacted in 2012 (GDUFA⁴²), FDA issues “commitment letters” or “goals letters” that set forth the various review timelines, including review of NDAs and ANDAs. These letters set forth performance goals of ten months or less for the initial FDA review of these applications, depending on priority status, NME status, and application type. For example, under PDUFA, FDA aims to review at least ninety percent of non-NME 505(b)(2) applications within ten months of receipt, or six months if the application is granted priority status,⁴³ while the target deadlines under GDUFA for ANDAs are ten months for standard applications and eight months for some priority applications.⁴⁴

PEDIATRIC EXCLUSIVITY UNDER SECTION 505A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (Sept. 1999) (describing FDA’s interpretation of the six-month exclusivity provision).

³⁶ Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, §§ 801–806, 126 Stat. 993, 1077–82 (2012).

³⁷ 21 U.S.C. § 355(c)(1) (2018).

³⁸ Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (1992).

³⁹ See generally Jonathan J. Darrow et al., *Speed, Safety, and Industry Funding: From PDUFA 1 to PDUFA 6*, 377 NEW ENG. J. MED. 2278 (2017) (describing the history of PDUFA, its impact on review times, and the dramatic growth in user fees with each PDUFA reauthorization).

⁴⁰ Prescription Drug User Fee Rates for Fiscal Year 2018, 82 Fed. Reg. 43,244, 43,244 (Sept. 14, 2017).

⁴¹ Generic Drug User Fee Rates for Fiscal Year 2018, 82 Fed. Reg. 41,026, 41,028 (Aug. 29, 2017).

⁴² Generic Drug User Fee Amendments of 2012, Pub. L. No. 112-144, tit. III, §§ 301–308, 126 Stat. 1008, 1008–25 (2012).

⁴³ FOOD & DRUG ADMIN., PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022 4 [hereinafter FOOD & DRUG ADMIN., PDUFA REAUTHORIZATION 2018-2022], <https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf> [<https://perma.cc/7FVF-V8LF>].

⁴⁴ FOOD & DRUG ADMIN., GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018–2022 4–5, <https://www.fda.gov/media/101052/download> [<https://perma.cc/4WDY-8GLG>].

These review deadlines apply only to the first cycle of review. If a drug is not approved during the first cycle of review, additional review cycles can lengthen the total review time. For this reason, although PDUFA review deadlines are similar for 505(b)(1) and 505(b)(2) NDAs (status as an NME extends the review period by sixty days, to eight months for priority applications or twelve months for standard applications⁴⁵), one study found that only about half of 505(b)(2) products are approved during the first review cycle, and that total review times averaged approximately 18 months for 505(b)(2) products approved between 2009 and 2015, compared to ten to sixteen months for 505(b)(1) products.⁴⁶

Critically, the user fee legislation did not result in commitment letter deadlines for the review of suitability petitions. Many modifications can be made to an existing drug product either via the 505(b)(2) pathway or by submitting a petition to FDA that inquires as to whether an ANDA application would be suitable for the change proposed.⁴⁷ Although, by statute, FDA must respond to suitability petitions within ninety days,⁴⁸ FDA has often not been able to meet this deadline, and in some years the actual median review time of these petitions (including pending petitions) has exceeded six years.⁴⁹ The User Fee Acts potentially exacerbated the suitability petition review delay by requiring FDA to commit greater resources to other review activities. Rather than endure an extended petition-based delay, some applicants may prefer the 505(b)(2) application route for which no suitability petition is required.

3. *Under a New Law, Many Drugs No Longer Qualified for the ANDA Pathway*

Although a gradual increase in 505(b)(2) applications had been underway since 1993, 2004 saw a sudden and dramatic rise in the number of 505(b)(2) applications approved (Figure 1). This may be explained in part by a 1998 FDA regulation⁵⁰ that required the submission of safety and effectiveness data from pediatric investigations whenever an applicant sought approval of a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, unless FDA waived the requirement because the product did not represent a meaningful therapeutic benefit

⁴⁵ 21 C.F.R. § 314.101(a) (2017) (“The date of filing will be the date 60 days after the date FDA received the NDA.”). See also FOOD & DRUG ADMIN., PDUFA REAUTHORIZATION 2018-2022, *supra* note 43 (stating that one goal is to “[r]eview and act on 90 percent of standard NME NDA and original BLA [biologics license application] submissions within 10 months of the 60 day filing date”).

⁴⁶ Sharon Sakai et al., *Analysis of Review Times for Recent 505(b)(2) Applications*, 51 THERAPEUTIC INNOVATION & REG. SCI. 651, 654 tbl.2 (2017). But see Angela Drew et al., *The Approval Time for 505(b)(2) and 505(b)(1) NME Products Is Similar*, CAMARGO, Mar. 15, 2017, <https://camargopharma.com/2017/03/505b2-approval-times-the-real-scoop/> [<https://perma.cc/NSY9-E4TQ>] (stating that if an outlier datum was removed from the Sakai study, then approval times are similar between 505(b)(1) and 505(b)(2) products; also noting that 64.5% of 505(b)(2) applications were approved after the first review cycle).

⁴⁷ CDER, ANDA vs. 505(B)(2) DRAFT GUIDANCE, *supra* note 9, at 3 (“In contrast to an ANDA, a 505(b)(2) application allows greater flexibility as to the characteristics of the proposed product.”); *id.* at 4 (“[A]n ANDA may contain certain types of differences from an RLD (e.g., a change approved in a suitability petition or other permissible differences . . .”).

⁴⁸ 21 U.S.C. § 355(j)(2)(C) (2018).

⁴⁹ Kurt Karst, *Letting the Devil Ride: Thirty Years of ANDA Suitability Petitions Under the Hatch-Waxman Act*, 40 WILLIAM MITCHELL L. REV. 1260, 1301 tbl.11 (2014).

⁵⁰ Note that product development and approval can take several years.

over existing treatments or was not likely to be used in a substantial number of pediatric patients.⁵¹

A new product encompassing these types of changes to an existing drug could potentially be approved either by the submission of an ANDA following a favorable FDA review of a suitability petition or by the submission of a 505(b)(2) application. However, because suitability petitions would be denied if safety and efficacy investigations were required—and the 1998 FDA pediatric rule required such investigations as a matter of course—applicants seeking approval of many modified versions of older products could no longer use the suitability petition pathway unless FDA requirements were waived, potentially causing applicants to forego the submission of a suitability petition in favor of the 505(b)(2) pathway. In 2003, similar pediatric study requirements were codified into statute by the Pediatric Research Equity Act (PREA).⁵² Following PREA, FDA reportedly rescinded the approval of more than 100 suitability petitions.⁵³

4. Expedited Programs Benefit 505(b)(2)s, but Not ANDAs

Beginning in the late 1980s, manufacturers submitting 505(b)(2) applications could increasingly benefit from FDA's expedited development and approval programs which, like exclusivity incentive provisions, accumulated over time. These included the fast-track (1988), accelerated approval (1992), priority review (1992), and breakthrough therapy (2012) programs, which were designed to increase regulatory flexibility and the overall speed of development and approval.⁵⁴ ANDAs are not eligible for these expedited programs, although first challengers of patents covering Orange Book-listed drugs can obtain 180-day exclusivity vis-à-vis other ANDA products, and statutory amendments after the end of our study period created new programs to expedite and incentivize certain competitive generic therapies.⁵⁵

B. Have 505(b)(2) Applications Increased or Reduced Competition?

By definition, the introduction of new products into an existing market increases competition if all else is held equal, for example, assuming that no products are

⁵¹ Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632, 66,635 (Dec. 2, 1998) (codified as amended at 21 C.F.R. §§ 314.55, 601.27).

⁵² Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003). *See generally* CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., FDA DRAFT GUIDANCE: HOW TO COMPLY WITH THE PEDIATRIC RESEARCH EQUITY ACT (Sept. 2005) (describing FDA's interpretation of PREA).

⁵³ Nirav Chokshi & Bhaumik Modi, *How Suitable Are the Suitability Petition and 505(b)(2)?*, 8 J. GENERIC MEDS. 23, 25 (2011).

⁵⁴ *See generally* Jonathan J. Darrow et al., *New FDA Breakthrough-Drug Category: Implications for Patients*, 370 NEW ENG. J. MED. 1252 (2014) (describing the history and characteristics of the expedited development and approval programs); Jonathan J. Darrow et al., *The FDA Breakthrough Drug Designation: Four Years of Experience*, 378 NEW ENG. J. MED. 1444 (2018) (describing the characteristics of all drugs approved so far under FDA's most coveted expedited program); Darrow & Kesselheim, *supra* note 12 (indicating, in graphical form, which drugs benefited from which expedited programs).

⁵⁵ Food and Drug Administration Reauthorization Act, Pub. L. No. 115-52, §§ 801–809, 131 Stat. 1005, 1068–76 (2017).

discontinued when new products are introduced. In the pharmaceutical marketplace, however, the introduction of slightly modified products can be part of a “product hopping” strategy that manufacturers use in an attempt to prolong their market dominance,⁵⁶ a practice the Federal Trade Commission has viewed as potentially violating the antitrust laws.⁵⁷ Although the older product, possibly along with generic versions of it, may be available at far lower cost, the existence of insurance partially insulates buyers from increased prices, and manufacturers use various strategies to persuade patients and physicians to switch to newer, more expensive versions of their products, often shortly before the older products lose exclusivity.⁵⁸ These efforts are aided by the disconnect between the prescriber, who chooses the medicine but does not pay for it, and the insurer or patient, who bears some or all of the price burden but may have little if any input into which product is prescribed.

Future research is needed to directly measure the effect of introducing 505(b)(2) products on competition, but some indirect evidence is already available that, taken as a whole, suggests that these products are frequently, but not always, increasing competition and potentially exerting downward price pressure. This evidence includes: (1) information about which manufacturers are filing 505(b)(2) applications; (2) the types of products that are being approved; (3) the regulatory framework surrounding 505(b)(2) applications; (4) the exclusivity awarded for these products and related therapeutic equivalence ratings; and (5) trends in ANDA approvals. Each will be explored in turn.

1. Which Manufacturers are Successfully Filing 505(b)(2) Applications?

Use of the 505(b)(2) pathway is distributed over a large number of firms, suggesting an overall market that is not concentrated. After consolidating firm names that appeared to be identical or affiliated with one another, 318 unique manufacturers were associated with the 628 products. More than half of these manufacturers (sixty-two percent) had only a single 505(b)(2) product, and an additional thirty percent of manufacturers had four approved 505(b)(2) products or fewer (Figure 4). No manufacturer was responsible for more than 2.6 percent of all 505(b)(2) applications. Even though 505(b)(2) products are associated with a range of therapeutic areas and do not all compete in a single market, the large number of manufacturers and small numbers of 505(b)(2) applications per manufacturer are suggestive of a competitive marketplace overall.

Manufacturers holding the largest number of approved 505(b)(2) applications were primarily those meeting our definition of a generic manufacturer. Mylan, Cipla, Teva, and Fresenius are among the world’s largest generic drug manufacturers⁵⁹ and held the top four positions in the list of manufacturers with the most 505(b)(2) applications

⁵⁶ Jonathan J. Darrow et al., *Product Hopping and Substitution of Pharmaceutical Alternatives 2–3* (June 13, 2019) (working paper) (on file with the *Food and Drug Law Journal*).

⁵⁷ Federal Trade Commission’s Brief as Amicus Curiae, *Mylan Pharm., Inc. v. Warner Chilcott Pub. Ltd. Co.*, No. 12-3824, at 1 (E.D. Pa. Nov. 21, 2012).

⁵⁸ Jonathan J. Darrow, *Debunking the “Evergreening” Patents Myth*, 131 HARVARD L. RECORD 6 (Dec. 8, 2010).

⁵⁹ Eric Sagonowsky, *Top Drugmakers by 2016 Generics Revenue in USD Billions*, FIERCE PHARMA (May 16, 2017), <https://www.fiercepharma.com/special-report/top-15-generic-drugmakers-2016> [<https://perma.cc/B3PU-4KJ9>].

(Figure 3). Although some primarily brand-name firms also appeared on the list of successful top 505(b)(2) applicants, these firms can and do introduce products to compete with the branded products of other firms. For example, in 2004 Novartis obtained approval via the 505(b)(2) pathway of delayed-release mycophenolic acid (Myfortic), indicated for the prophylaxis of organ rejection.⁶⁰ Myfortic competed in the market⁶¹ with several of Roche's non-delayed release mycophenolate mofetil products (including capsule, tablet, injection, and oral suspension forms), approved between 1995 and 1998,⁶² which had neither patent nor non-patent exclusivity, nor any pharmaceutical equivalents through 2003.⁶³

Brand-name manufacturer participation in the 505(b)(2) market may represent part of a larger trend toward a blurring of the distinction between generic and brand-name manufacturers. Our study results suggest that traditionally brand-name manufacturers sometimes compete in the generic market, while traditionally generic manufacturers sometimes compete in the brand-name market. For example, Baxter met our definition of a brand-name manufacturer, but forty-nine (thirty-one percent) of its 157 products (not including its 505(b)(2) products) listed in the 2016 Orange Book were ANDA products. Similarly, while Fresenius met our definition of a generic manufacturer, thirty-two (fourteen percent) of its 230 products were NDA products.

Although sponsors of 505(b)(2) products may sometimes use the pathway to obtain approval of a modified version of their own products (such as a combination product that relies in part on the data of a third party for the other component in the combination), this is infrequent. Only fifty-six (nine percent) products were associated with a 505(b)(2) applicant that was the same as the sponsor of one or more of the RLDs relied on in the 505(b)(2) application. By contrast, 432 (sixty-nine percent) applications relied only on the existing data of unrelated third parties. For the remaining 140 (twenty-two percent) 505(b)(2) products, we were unable to identify RLD information, which could indicate that the applicant relied on the published literature or that the RLD was not identified with sufficient specificity in the available documentation. These data suggest that most 505(b)(2) applications are not serving as part of a manufacturer's product hopping strategy to extend the market dominance of one of its existing products.

2. *What Types of Products are Being Approved under 505(b)(2)?*

FDA's classification codes offer a sense of the types of changes that are being approved under 505(b)(2). Approximately two-thirds of products were classified as either new dosage forms (Type 3) or new formulation or other differences (Type 5), with the remaining third split between new combinations (Type 4) and a number of

⁶⁰ Approval Letter (mycophenolic acid (Myfortic), NDA 050791) from Renata Albrecht, Director, Special Pathogen and Immunologic Drug Products (FDA), to M. Daniel Gordin, Director, Drug Regulatory Affairs, Novartis Pharmaceuticals Corp. (Feb. 27, 2004), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/50-791_Myfortic_approv.PDF.

⁶¹ Hans W. Sollinger et al., *Mycophenolate Mofetil Versus Enteric-Coated Mycophenolate Sodium: A Large, Single-Center Comparison of Dose Adjustments and Outcomes in Kidney Transplant Recipients*, 89 *TRANSPLANTATION* 446, 446 (2010).

⁶² *FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS* 3-253 (25th ed. 2005).

⁶³ See *FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS* (23th ed. 2003) (not listing any patents for these products); *FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS* (18th ed. 1998) (same).

less common types. This suggests that most products approved under 505(b)(2) represent relatively small changes to existing pharmaceutical products.

FDA's coarse classifications, however, do not adequately capture the variety of changes that are permissible under 505(b)(2), the importance of these changes, or the complex ways these changes may affect the competitive environment. For example, the "other differences" of Type 5 can include changes as diverse as new indications, new applicants, or changes to inactive ingredients.⁶⁴ Some new dosage forms, such as a transdermal patch that discretely releases a drug substance over an extended period of time, may contribute more to the therapeutic arsenal than others, such as a change from a tablet to a capsule. Subtle changes with no obvious therapeutic rationale may be more likely to reflect an attempt to obtain or extend market exclusivity rather than to introduce products offering valuable new benefits that compete with older ones. On the other hand, the greater the therapeutic contribution of a new 505(b)(2) product, the less likely it is to compete with the reference product primarily on the basis of price, and the more likely its own exclusivity will define the competitive environment of the newly created market niche.

Several other factors further complicate the analysis. Multiple changes may be encompassed by a single 505(b)(2) application, or an application may rely on data from one RLD, more than one RLD, or no RLD at all. When multiple 505(b)(2) products have been approved for the same or similar active ingredients, FDA classifications cannot convey the implications for competition without considerations of timing, applicant identity, and a more detailed description of the changes made. To provide a richer sense of the impact of 505(b)(2) products on the competitive landscape, we briefly examine several examples of products or groups of products approved under this pathway, organized either by FDA classification type or by active ingredient.

i. Previously Unapproved Active Moieties

Although the 505(b)(2) pathway is most often used for the approval of modified versions of previously approved drugs, it can also be used to approve products containing active moieties that have not previously been approved. Twenty-five (four percent) of 628 products were designated as Type 1 NMEs, and four (one percent) as both Types 1 and 4 (new combination). Eleven (thirty-eight percent) of the twenty-nine Type 1 or Type 1,4 NMEs received five-year exclusivity, ten (thirty-four percent) received seven-year exclusivity, two (seven percent) received three-year exclusivity,⁶⁵ one (three percent) received ten-year exclusivity, and five (seventeen percent) had not received any non-patent exclusivity by the time of our study.

Among the Type 1 products receiving five-year exclusivity were: a high-concentration capsaicin patch (Qutenza) for the treatment of postherpetic neuralgia (low-dose topical capsaicin products were available over-the-counter);⁶⁶ trypan blue (Vision Blue), a staining agent for the anterior lens capsule, which may be used during

⁶⁴ CDER, NDA CLASSIFICATION CODES, *supra* note 14, at 4.

⁶⁵ NDA 021502 (Type 1,4) and NDA 202535 (Type 1).

⁶⁶ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (CAPSAICIN PATCH (QUTENZA), NDA 022395) 7 (Oct. 1, 2009).

cataract surgery, and which was previously approved in Europe;⁶⁷ three hyaluronidase products, a biologic used for several indications including to increase the absorption of other drugs, which are generally classified as NMEs despite similarity with previous hyaluronidase products due to the difficulty in fully characterizing the active ingredient;⁶⁸ and gabapentin enacarbil (Horizant, Arbor/Glaxo), an extended-release prodrug of gabapentin (Neurontin, Pfizer) that could be more readily and completely absorbed and that was indicated for restless leg syndrome.⁶⁹ Among Type 1 NMEs receiving seven-year exclusivity was tinidazole (Tindamax, Presutti/Mission) for the treatment of trichomoniasis (NDA 021618), giardiasis (NDA 021681), and amebiasis (NDA 021682), all approved the same day.⁷⁰ Tinidazole had not previously been marketed in the United States, and approval was therefore based on studies reported in the literature and foreign use.⁷¹

For products designated as both Types 1 and 4, the applicant generally relies on third-party data for the older of the drug's components. For example, in 1985 Glaxo obtained approval of the NME ceftazidime (Fortaz), an antibiotic.⁷² In 2015, Cerexa, Inc. obtained approval under 505(b)(2) for the combination product ceftazidime/avibactam (Avycaz), relying in part on Glaxo's data.⁷³ Avibactam, an NME, had no independent antibacterial activity, but helped protect ceftazidime from degradation by an enzyme produced by treatment-resistant bacteria.⁷⁴

In addition to Types 1 and 1,4 products, thirty-seven (six percent of 628) Type 7 products were approved, defined as those products already marketed without an approved NDA, a status that can occur, for example, when a product was first marketed before the 1962 Kefauver-Harris Drug Amendments. Six (sixteen percent) of the thirty-seven Type 7 products received five-year exclusivity, all of which were pancreatic enzyme products used to treat exocrine pancreatic insufficiency.⁷⁵ Only one

⁶⁷ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (TRYPAN BLUE (VISION BLUE), NDA 021670) 5 (Apr. 5, 2004).

⁶⁸ *See, e.g.*, CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (HYALURONIDASE INJECTION (HYDASE), NDA 021716) 15 (July 19, 2005).

⁶⁹ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (GABAPENTIN ENACARBIL (HORIZANT), NDA 022399) 11 (Apr. 5, 2011). Approval under 505(b)(2) for an extended release gabapentin product was received in 2011 by Depomed, Inc., which relied in part on Pfizer's data. *See* CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (GABAPENTIN (GRALISE), NDA 022544) 8 (Dec. 13, 2010).

⁷⁰ Approval Letter (tinidazole (Tindamax), NDA Nos. 021618, 021681, 021682) from Mark J. Goldberger, Director, Office of Drug Evaluation IV (FDA), to John Presutti, President, Presutti Labs., Inc., May 17, 2004, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-618_Tindamax_Approv.pdf.

⁷¹ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (TINIDAZOLE (TINDAMAX), NDA Nos. 021618, 021681, 021682) 31 (May 17, 2004).

⁷² Alan D. Lourie, *Patent Term Restoration—The First Two Years*, 68 J. PAT. & TRADEMARK OFF. SOC'Y 538, 551 (1986).

⁷³ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (CEFTAZIDIME/AVIBACTAM (AVYCAZ), NDA 206494) 17 (Feb. 18, 2015).

⁷⁴ Thomas J. Hwang & Aaron S. Kesselheim, *Leveraging Novel and Existing Pathways to Approve New Therapeutics to Treat Serious Drug-Resistant Infections*, 42 AM. J. L. & MED. 429, 439 (2016).

⁷⁵ *See generally* FOOD & DRUG ADMIN., FDA GUIDANCE FOR INDUSTRY: EXOCRINE PANCREATIC INSUFFICIENCY DRUG PRODUCTS—SUBMITTING NDAs (Apr. 2006) (explaining the historical status of exocrine pancreatic insufficiency drug products, including that most have historically been marketed without NDAs).

(three percent) Type 7 product, colchicine (Colcrys), for the treatment of Familial Mediterranean Fever, received seven-year exclusivity, and one (three percent) Type 7 product, sodium phosphate (Visicol), for the cleansing of the bowel prior to colonoscopy, received three-year exclusivity. The remaining twenty-nine (seventy-eight percent) received no non-patent exclusivity.

The variety of products approved as NMEs under 505(b)(2) underscores the difficulty in making generalizations about the motivations and effects of submitting a 505(b)(2) application. The approval of the pancreatic enzymes, for example, followed a 2004 FDA announcement in the Federal Register that regulatory action would be taken if the makers of these unapproved drug products, which had been sold both over the counter and by prescription for many years, did not submit their drugs to the NDA approval process.⁷⁶ When the manufacturer of trypan blue first approached FDA, it believed its staining agent would be regulated as a Class 1 device, but FDA ruled that it would be treated as a new drug, leading to the 505(b)(2) application.⁷⁷ The approval of Glaxo's gabapentin enacarbil in 2011, by contrast, may have been intended in part to compete with Pfizer's gabapentin market,⁷⁸ which continued to earn Pfizer \$289 million in 2011,⁷⁹ despite facing generic competition the mid-2000s.⁸⁰

ii. *New Active Ingredients*

Although sometimes used interchangeably, the terms “new active ingredient” and “new molecular entity” are distinct in FDA's classification scheme.⁸¹ A new salt form or other non-covalent derivative of a previously approved product would generally meet the definition of a new active ingredient, but would not be an NME.⁸² Thirteen (two percent) 505(b)(2) products were classified by FDA as Type 2 (new active ingredients). These included: an injectible emulsion of amino acids, electrolytes, dextrose, and lipids (Kabiven and Perikabiven, Fresenius 2014), used for parenteral nutrition when oral nutrition is not possible (multiple RLDs, including Novamine, Hospira, 1978);⁸³ esomeprazole strontium (unbranded, Hanmi Pharm Co., 2013), an

⁷⁶ Exocrine Pancreatic Insufficiency Drug Products, 69 Fed. Reg. 23,410, 23,410 (Apr. 28, 2004).

⁷⁷ Gillian McDermott, *Bringing Trypan Blue to Market: How this Capsular Dye Made it to the US at Last*, CATARACT & REFRACTIVE SURGERY TODAY (Mar. 2005), https://crstoday.com/articles/2005-mar/0305_0305dorc.html [<https://perma.cc/R63R-ANYA>].

⁷⁸ Jim Edwards, *Can Glaxo Make \$1.2B Treating a Disease that Doesn't Exist?*, CBS NEWS (Apr. 12, 2011), <https://www.cbsnews.com/news/can-glaxo-make-12b-treating-a-disease-that-doesnt-exist/> [<https://perma.cc/2TGV-KMAA>].

⁷⁹ PFIZER, 2011 FINANCIAL REPORT, App. A at 112 (2012), <https://www.pfizer.com/files/annualreport/financial/financial2011.pdf> [<https://perma.cc/AUC5-URQZ>].

⁸⁰ FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS 3-178 to 3-179 (27th ed. 2007) (listing various gabapentin products produced by competing manufacturers). See also William J. Storck, *Pfizer Launches Generic Gabapentin*, CHEMICAL & ENG'N NEWS (Oct. 12, 2004), <http://pubs.acs.org/cen/news/8241/8241gabapentin.html> [<https://perma.cc/BZ3R-QJZT>] (describing several companies selling or seeking to sell generic products that would compete with Pfizer's Neurontin).

⁸¹ CDER, NDA CLASSIFICATION CODES, *supra* note 14, at 3.

⁸² *Id.*

⁸³ FOOD & DRUG ADMIN., Approval Letter from Joyce Korvick, Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products to Lakshmi Rebbapragada, Senior Regulatory Specialist, Fresenius Kabi USA on Injectible Emulsion ((Kabiven and Perikabiven), NDA 200656) (Aug. 25, 2014), available at https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2014/200656Orig1s000ltr.pdf;

alternate salt form of esomeprazole magnesium (Nexium, AstraZeneca, 2001), used to treat gastric acid disorders;⁸⁴ glycerol phenylbutyrate (Ravicti, Horizon Therapeutics, 2013), used to treat rare urea cycle disorders and an alternative to sodium phenylbutyrate (Buphenyl, Ucyclid/Horizon, 1996) in which phenylbutyric acid is joined to glycerol in an ester linkage and that lacks the bad taste and odor associated with Buphenyl;⁸⁵ fenofibric acid (Trilipix, Abbott, 2008), a choline salt of fenofibrate (Tricor, Fournier/Abbott 1993), which also included a new indication of co-administration with statins for the treatment of dyslipidemia;⁸⁶ and bupropion hydrobromide (Aplenzin, Valeant, 2008), an alternate salt form of bupropion hydrochloride (Wellbutrin XL, Glaxo, 2002), used to treat depression.⁸⁷

These examples suggest the small “new active ingredient” category is being used both to introduce competing products by new manufacturers, but in a few cases also as part of a product hopping strategy by incumbents. Indeed, Abbot’s actions with respect to fenofibrate (TriCor) resulted in widely-covered antitrust litigation,⁸⁸ and the case has been frequently cited as an example of the abusive tactics of the drug industry.⁸⁹ However, Abbott’s introduction of fenofibric acid (Trilipix) is not representative of the overall use of the 505(b)(2) pathway, not only because the same manufacturer was associated with both the 505(b)(2) product and the RLD, or because it was in a category that made up only two percent of 505(b)(2) approvals, but because it was allegedly accompanied by substantial additional actions that were potentially anticompetitive, such as discontinuing sales of the older product and changing its code in the Nation Drug Data File to “obsolete” to discourage generic substitution.⁹⁰ Other commonly cited product hops, including those involving esomeprazole (Nexium), a single enantiomer version of the heartburn medicine omeprazole (Prilosec),⁹¹ doxycycline (Doryx MPC), a capsule-to-tablet switch of the antibiotic doxycycline

CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW ((KABIVEN AND PERIKABIVEN), NDA 200656) 7 (Aug. 25, 2014).

⁸⁴ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (ESOMEPRAZOLE STRONTIUM (UNBRANDED), NDA 202342) 1 (July 31, 2013).

⁸⁵ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (GLYCEROL PHENYLBUTERATE (RAVICTI), NDA 203284) 7, 8, 10 (Nov. 27, 2012).

⁸⁶ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (FENOFIBRIC ACID (TRILIPIX), NDA 022224) 7, 8 (Dec. 15, 2008).

⁸⁷ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (BUPROPION HYDROBROMIDE (APLENZIN), NDA 022108) 1 (July 19, 2007).

⁸⁸ Abbott Labs. v. Teva Pharm. USA, Inc., 432 F. Supp. 2d 408 (D. Del. 2006). For news coverage, see, e.g., Shirley S. Wang, *TriCor Case May Illuminate Patent Limits*, WALL ST. J. (June 2, 2008), <https://www.wsj.com/articles/SB121236509655436509> [<https://perma.cc/G2PN-FN6R>].

⁸⁹ See, e.g., Aaron S. Kesselheim & Jonathan J. Darrow, *Hatch-Waxman Turns Thirty: Do We Need a Redesigned Approach for the Modern Era?*, 15 YALE J. HEALTH POL’Y L. & ETHICS 293, 337 (2015); Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1019–20 (2010); Steve D. Shadowen, Keith B. Leffler & Joseph T. Lukens, *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 RUTGERS L. J. 1, 62–65 (2009); and Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 COLUM. L. REV. 1471, 1491–97 (2008).

⁹⁰ The 505(b)(2) pathway was also used by Lupin, a competitor of Abbott, to approve a new dosage form of fenofibrate (Antara) in 2004, four years before the approval of Trilipix.

⁹¹ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., CORRESPONDENCE (ESOMEPRAZOLE (NEXIUM), NDA 021154) 6 (Mar. 10, 2000).

(Doryx),⁹² and memantine (Namenda XR), an extended-release version of the Alzheimer's medication memantine (Namenda),⁹³ each involved a new product that was approved under 505(b)(1).

iii. *Methylphenidate*

Methylphenidate has been used for decades as a treatment for attention deficit disorders, though it was first used for a number of other conditions, including depression.⁹⁴ FDA's drugs@FDA database indicates a new dosage form was FDA-approved in 1955 and is currently owned by Novartis.⁹⁵ Seven methylphenidate products have been approved under the 505(b)(2) pathway since 1993. Although these products have various dosage forms addressing markets that may not entirely overlap, the number of approvals and multiplicity of manufacturers suggests the pathway has been used to compete with the existing products of other manufacturers.

The first was obtained by Celltech Pharmaceuticals in 2001, for methylphenidate 20mg extended-release capsules (Metadate CD),⁹⁶ which competed with Novartis's extended-release version, Ritalin SR, approved in 1982.⁹⁷ In 2002 and 2003, Mallinckrodt obtained approval of an oral methylphenidate solution (Methylin, NDA 021419) and a chewable tablet (Methylin CT, NDA 021475) under the 505(b)(2) pathway. Mallinckrodt conducted only pharmacokinetic and bioequivalence studies, relying on Ritalin data and the published literature and was not awarded exclusivity. No patents were listed in either the 2004 or 2007 Orange Books for either product. In 2006, Noven Pharmaceuticals obtained approval of a transdermal methylphenidate patch (Daytrana, NDA 021514), based in part on Novartis's Ritalin data. Six years later, Nextwave obtained approval of an extended-release oral suspension (Quillivant XR), relying on Mallinckrodt's Methylin data.⁹⁸ Pfizer acquired Nextwave the following year, and in 2015 obtained approval of its own methylphenidate product, a chewable extended-release version (Quillichew ER), based in part on Mallinckrodt's Methylin CT. Pfizer did not obtain non-patent exclusivity, but an Orange Book-listed patent is scheduled to expire in 2033. Also in 2015, Rhodes Pharmaceuticals obtained approval of an extended-release capsule methylphenidate product (Aptensio XR), relying in part on Novartis's Ritalin and Ritalin SR data.

⁹² CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS (DOXYCYCLINE HYCLATE (DORYX), NDA 050795) 8 (June 4, 2004).

⁹³ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS (MEMANTINE HYDROCHLORIDE (NAMENDA XR), NDA 022525) 2 (June 21, 2010).

⁹⁴ Avrohm Jacobson, *Ritalin—A New Agent for Mild Depressions*, 25 MED. ANN. D.C. 491, 491 (1956).

⁹⁵ *New Drug Application: NDA 010187*, US FOOD & DRUG ADMIN: DRUGS@FDA, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=010187> [<https://perma.cc/5G4G-9CLP>].

⁹⁶ FOOD & DRUG ADMIN., DRUGS@FDA: FDA APPROVED DRUG PRODUCTS (METHYLPHENIDATE HYDROCHLORIDE (METADATE CD), NDA 021259), <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021259> [<https://perma.cc/TZ9W-TNPG>].

⁹⁷ FOOD & DRUG ADMIN., DRUGS@FDA: FDA APPROVED DRUG PRODUCTS (METHYLPHENIDATE HYDROCHLORIDE (RITALIN SR), NDA 018029), <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> (last visited Nov. 12, 2018) [<https://perma.cc/Q3FZ-DW8W>].

⁹⁸ CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (METHYLPHENIDATE ER POWDER (QUILLIVANT ER), NDA 202100) 6 (Sept. 30, 2012).

iv. Insulin Products

Like human growth hormones, hyaluronidase, and a few other protein products, insulins have the unusual status of biologic drugs that for historical reasons have been approved under the NDA process rather than under the biologics license application process of the Public Health Service Act.⁹⁹ The 505(b)(2) program has been used to introduce new products in an insulin market characterized by few competitors and insufficient price competition.

The 2013 Orange Book lists only a single insulin glargine product (Lantus), made by Sanofi Aventis, and several insulin lispro products (Humalog), all made by Eli Lilly. In 2014, Eli Lilly obtained tentative approval under the 505(b)(2) pathway for an insulin glargine product (Basaglar), which could not be made effective before the resolution of a patent infringement suit brought by Sanofi or until other statutory conditions were satisfied.¹⁰⁰ Final approval was granted the following year, and Basaglar entered the market at a fifteen percent lower cost than Lantus.¹⁰¹ In 2017, Sanofi obtained tentative approval under 505(b)(2) for its insulin lispro product (Admelog). The approval was made final the same year, and Admelog was introduced at a fifteen percent lower cost than Humalog.¹⁰²

Former FDA commissioner Scott Gottlieb referenced the efforts of FDA in approving lower cost alternative products as part of its press release announcing the approval of Sanofi's insulin lispro product under the 505(b)(2) pathway.¹⁰³ The entry of additional competitors could further increase competition and may occur in the near future. Merck's insulin glargine product (Lusdana) has been tentatively approved under the 505(b)(2) pathway,¹⁰⁴ and insulin glargine (Semglee), co-developed by

⁹⁹ FOOD & DRUG ADMIN., FDA DRAFT GUIDANCE: IMPLEMENTATION OF THE "DEEMED TO BE A LICENSE" PROVISION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 1, 10 (Mar. 2016), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf> [<https://perma.cc/C2YT-W3GB>]. On March 23, 2020, biological products approved under section 505(b)(2) will be "deemed" to be a section 351(a) Biologics License Application, *see id.* at 7–8, and no new biological products may be submitted under section 505 after this date, *id.* at 3. Chemically synthesized polypeptides, defined as those made by chemical synthesis that are greater than forty but fewer than 100 amino acids in length, are not biological products and will generally continue to be regulated under the Food, Drug, and Cosmetic Act. *Id.* at 4. Human insulin contains fifty-one amino acids in two chains, but recombinant synthesis is excluded from the definition of "chemically synthesized." 83 Fed. Reg. 63,817, 63,822 (2018).

¹⁰⁰Food & Drug Admin., Approval Letter (NDA 205692) from Jean-Marc P. Guettier, Director, Division of Metabolism and Endocrinology Products (FDA), to Joerg Pfeifer, Advisor, Global Regulatory Affairs, Eli Lilly and Co., at 1 (Aug. 18, 2014).

¹⁰¹Jack T. Rasmussen & Heather J. Ipema, *Formulary Considerations for Insulins Approved Through the 505(b)(2) "Follow-on" Pathway*, 53 ANNALS PHARMACOTHERAPY 204, 207 (2019).

¹⁰²*In Brief: Another Insulin Lispro (Admelog) for Diabetes*, MED. LETTER (June 18, 2018), <https://secure.medicalletter.org/w1549g> [<https://perma.cc/T5AF-DEAY>].

¹⁰³*FDA Approves Admelog, the First Short-Acting "Follow-on" Insulin Product to Treat Diabetes*, FOOD & DRUG ADMIN. (Dec. 11, 2017), <https://www.fda.gov/newsevents/newsroom/ucm588466.htm> [<https://perma.cc/K6PY-CQTP>].

¹⁰⁴*Merck Wins Tentative FDA Approval for Lusdana*, GENETIC ENGINEERING & BIOTECH. NEWS (July 20, 2017), <https://www.genengnews.com/gen-news-highlights/merck-wins-tentative-fda-approval-for-lusdana/81254690> [<https://perma.cc/AX2L-5QYY>].

Biocon and Mylan, has been approved in Europe and Australia and is currently pending 505(b)(2) review and approval in the United States.¹⁰⁵

v. *Over-the-Counter (OTC) Products*

Guaifenesin¹⁰⁶ is an expectorant that has been marketed for decades and is contained in thousands of OTC products,¹⁰⁷ including some that, for historical reasons, are currently marketed in the United States illegally without a prescription under FDA's enforcement discretion policy.¹⁰⁸ A number of guaifenesin-containing products have been approved under the 505(b)(2) pathway, including timed-release OTC guaifenesin (Mucinex, NDA 021282, 2002), as well as the combination OTC product dextromethorphan hydrobromide/guaifenesin (Mucinex DM; NDA 021620; 2004). Prescription guaifenesin-containing products have also been approved under the 505(b)(2) pathway, including the opioid combination products hydrocodone/guaifenesin (Obredon, NDA 205474, Sovereign Pharmaceuticals, 2014), hydrocodone/pseudoephedrine/guaifenesin (Hycufenix, NDA 022279, Mikart Inc./Mission Pharmacal Co., 2015), and hydrocodone/guaifenesin (Flowtuss, NDA 022424, Mission Pharmacal Co., 2015).¹⁰⁹

3. *Exclusivity Characteristics of 505(b)(2) Applications and Therapeutic Equivalence*

Based on the Orange Book of the year following each drug's approval, 451 (eighty-two percent) of 553 products were designated as RLDs, suggesting that most were eligible for copying by downstream ANDA or 505(b)(2) products, subject to any exclusivity. When a 505(b)(2) product is not designated as an RLD, however, it can be partially shielded from ANDA or further 505(b)(2) competition.¹¹⁰ This could occur, for example, when a 505(b)(2) product is pharmaceutically equivalent but bears a different indication from its upstream RLD, because FDA generally will not designate a drug product approved through the 505(b)(2) pathway as an RLD if a pharmaceutically equivalent drug product (i.e., one with the same active ingredient,

¹⁰⁵ *Mylan and Biocon Receive Approvals from the European Commission and TGA Australia for Semglee™, Biosimilar Insulin Glargine*, MYLAN (Mar. 27, 2018), <http://newsroom.mylan.com/2018-03-27-Mylan-and-Biocon-Receive-Approvals-from-the-European-Commission-and-TGA-Australia-for-Semglee-TM-Biosimilar-Insulin-Glargine> [https://perma.cc/7UY9-EP3V]; *Biocon Update on Insulin Glargine*, BIOCON (June 2, 2018), https://www.biocon.com/180602_Biocon_Statement_SE.asp [https://perma.cc/BA8Y-BTA6].

¹⁰⁶ *Unapproved Prescription Cough, Cold, and Allergy Products*, FOOD & DRUG ADMIN. 2 (Sept. 30, 2015), <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm245106.htm> [https://perma.cc/GZP2-CJYT].

¹⁰⁷ *Timed-Release Drug Products Containing Guaifenesin; Enforcement Action Dates*, 72 Fed. Reg. 29,517, 29,517 (May 29, 2007).

¹⁰⁸ FOOD & DRUG ADMIN., FDA GUIDANCE FOR STAFF AND INDUSTRY: MARKETED UNAPPROVED DRUGS WITHOUT APPROVED NDAS OR ANDAS, FDA COMPLIANCE POLICY GUIDE § 440.100, 2–3 (Sept. 19, 2011) <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf> [https://perma.cc/L9HS-DY2L].

¹⁰⁹ See Lineau Vilson & Joel S. Owen, *Pharmacokinetic Studies in Healthy Subjects for the Development of an Extended-Release Tablet Formulation of Guaifenesin: A 505(b)(2) New Drug Application Approval*, 2 CLINICAL PHARMACOLOGICAL DRUG DEV. 25, 29–30 (2013) (noting that the 505(b)(2) pathway allowed for an efficient development plan that did not involve Phase 3 trials).

¹¹⁰ FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, ix–x (39th ed. 2019).

dose, dosage form, and route of administration) has been approved in a 505(b)(1) application.¹¹¹ In such a case, the 505(b)(1) product would serve as the RLD and allow the manufacture of downstream duplicates, potentially raising above eighty-two percent the share of drugs in our study that were subject to copying in the first year after a 505(b)(2) product's approval, pending any exclusivity. Where an ANDA applicant wishes to duplicate a 505(b)(2) product not designated as an RLD (including, for example, its different indication), the applicant can request that FDA make the designation.¹¹²

Like ANDAs, 505(b)(2) applications can themselves be temporarily blocked from approval by the exclusivity of their upstream reference products (505(b)(1) applications are not similarly subject to these exclusivity periods, except for orphan drug exclusivity).¹¹³ Sixty-six (eleven percent) of the products in our study received tentative approvals that had not been finally approved by September 2018, indicating that approval was delayed due to exclusivity of an upstream product.¹¹⁴ Exclusivity can be waived either as to a particular 505(b)(2) application or as to all 505(b)(2) applications,¹¹⁵ so the tentative approval status of these sixty-six products suggests the absence of waiver by the upstream RLD holder. Because the purpose of exclusivity is to temporarily suppress competition, the delayed approval of these 505(b)(2) products suggests competition would have increased if these approvals could have occurred earlier.

In turn, 505(b)(2) applicants can waive exclusivity as to any downstream 505(b)(2) products or ANDAs. Based on an examination of the Orange Book of the year following each drug's approval, exclusivity was waived for only a single drug product. That product was choline C11 injection, a radioactive substance used in positron emission tomography (PET) scans, approved under an application submitted by the Mayo Clinic (NDA 203155) that relied on scientific literature rather than an RLD.¹¹⁶ The virtual absence of waiver suggests that manufacturers of 505(b)(2) products are not only seeking to take market share from the makers of upstream RLDs (if any), but are effectively excluding competition from downstream copyists, as intended under the Hatch-Waxman Act.¹¹⁷ At the same time, of 490 applicants for which adequate documentation was available, only 201 (forty-one percent) actually requested exclusivity, and fifty applicants did not request exclusivity but nevertheless received it, suggesting that they were either unaware of its availability, did not believe it to be sufficiently important, or incorrectly believed they were not eligible for it.

In rare circumstances, non-patent exclusivity can delay the approval of a 505(b)(2) product, even if that product does not rely on the data of the product protected by

¹¹¹*Id.* at x.

¹¹²*Id.*

¹¹³Both the 505(b)(2) and ANDA pathways require applicants to certify whether their products will infringe any relevant Orange Book-listed patents, and both types of products are subject to thirty-month stays of approval if a patent infringement suit is timely filed. *See* 21 U.S.C. § 355(b)(2)(A), (c)(3)(A) (discussing 505(b)(2) applications); 21 U.S.C. § 355(j)(2)(A)(vii), (j)(5)(B) (discussing ANDAs).

¹¹⁴21 C.F.R. § 314.3(b) (2018) (defining "tentative approval").

¹¹⁵FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, xxiii (39th ed. 2019).

¹¹⁶CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MEDICAL REVIEW (CHOLINE C-11 INJECTION (UNBRANDED), NDA 203155) 16 (Aug. 15, 2012).

¹¹⁷Pub. L. No. 98-417, § 101, 98 Stat. 1585, 1590 (1984) ("five years"); *id.* ("three years").

exclusivity.¹¹⁸ For example, in 2014, Veloxis received tentative approval for tacrolimus (Envarsus XR), an immunosuppressant used in transplantation, the reference drug of which was an immediate-release version of tacrolimus (Prograf, Fujisawa/Astellas, 1994), but the approval did not become effective until 2015 because of the exclusivity of an extended-release capsule version of tacrolimus (Astagraf XL, Astellas, 2013), the data of which Veloxis did not reference in its application.¹¹⁹ When Veloxis challenged FDA's interpretation, a federal district court held that "FDA ha[d] correctly interpreted [the statute] to delay approval of a second-in-time 505(b)(2) NDA where it shares conditions of approval with a first-in-time 505(b) NDA, even if the second-in-time 505(b)(2) NDA *does not rely on* clinical investigations from the first-in-time 505(b) NDA."¹²⁰ Three-year exclusivity is thus triggered by an overlap in the conditions of approval and not by an overlap in the new clinical investigations supporting the two applications.¹²¹

Although 505(b)(2) products, unlike ANDA products, are eligible for three-, five-, and seven-year exclusivity, this non-patent exclusivity is unlikely to be the primary factor motivating submission for the majority of 505(b)(2) applicants. Of the 553 products listed in the Orange Book of the year following approval, 322 (fifty-eight percent) were not awarded any non-patent exclusivity (Figure 6). Of the 231 (forty-two percent) products that were awarded non-patent exclusivity, 124 (fifty-four percent) had patents that extended beyond the last expiring exclusivity date, diminishing the value of that exclusivity. Patents may be vulnerable to challenge,¹²² however, and exclusivity can, therefore, provide more reliable protection. Figure 11 compares several key characteristics of ANDAs and 505(b)(2) products.

Figure 11: Comparison of the 505(b)(2) and ANDA Pathways

	505(b)(2) Pathway	ANDA Pathway
Must be identical to reference product?	No	No (via suitability petition)
Patent certification required?	Yes	Yes
Reference product exclusivity, if any, can temporarily bar approval?	Yes	Yes
Potential exclusivity for follow-on product?	6-month extension	180-day

¹¹⁸21 C.F.R. § 314.108(b) (2018).

¹¹⁹CTR. FOR DRUG EVALUATION & RES., FOOD & DRUG ADMIN., MEDICAL REVIEW (TACROLIMUS (ENVARUSUS XR), NDA 206406) 2 (Jul. 8, 2015); *see also id.* at 2 (describing litigation by Veloxis against FDA over the exclusivity period).

¹²⁰*Veloxis Pharm., Inc. v. FDA*, 109 F. Supp. 3d 104, 119–20 (D.D.C. 2015) (emphasis added).

¹²¹*Id.* at 117.

¹²²*See generally* Jonathan J. Darrow, Reed F. Beall & Aaron S. Kesselheim, *The Generic Drug Industry Embraces a Faster, Cheaper Pathway for Challenging Patents*, 17 APPLIED HEALTH ECON. & HEALTH POL'Y 47, 48(2018) (forthcoming) (offering a quantitative analysis of the use of the *inter partes* review procedure to challenge Orange Book-listed patents); Jonathan J. Darrow, Reed F. Beall & Aaron S. Kesselheim, *Will Inter Partes Review Speed US Generic Drug Entry?*, 35 NATURE BIOTECH. 1139, 1139–40 (2017) (describing the advantages of *inter partes* review over litigation from the perspective of the patent challenger).

	3-year (most common) 5-year 5-year extension (QIDP*) 7-year	
Petition required to modify product?	No	Yes
Pathway provides applicant with possible 30-month stay in applicant's favor	Sometimes	No
Clinical studies can be submitted (other than bioavailability studies)	Yes	No
New use permitted?	Yes	No (carve-outs possible)
User fees	PDUFA (\$2.42 million)	GDUFA (\$0.17 million)

*QIDP = qualified infectious disease product

Three-year exclusivity, in particular, may play a smaller role than commonly believed in stifling downstream competition for 505(b)(2) products. In the present study, three-year exclusivity was the last expiring non-patent exclusivity for only 168 (thirty percent of 553) 505(b)(2) products, in part because other exclusivities extended beyond the three-year exclusivity, and in part because the 505(b)(2) applications may not have received three-year exclusivity at all if the applicants did not conduct clinical studies (other than bioavailability studies) essential to approval.¹²³ Research examining 106 NDAs approved under 505(b)(2) between 2010 and 2012 found that twenty-five percent included only clinical pharmacology information and no applicant-conducted safety/efficacy study, suggesting they would not have received three-year exclusivity.¹²⁴ Safety and efficacy studies may not be needed, for example, for the approval of extended-release versions of previously approved products, which may in some cases be approved on the basis of bioavailability studies alone.¹²⁵ In one such case, Upsher-Smith Laboratories obtained approval of its extended-release topiramate product (Qudexy XR), an anti-epilepsy drug, based in part on Johnson &

¹²³Kurt R. Karst, *Deliverance: FDA Is Sued Over the Applicability of 3-Year Exclusivity in the Context of Dueling Tacrolimus NDAs; Agency Gets a Short Reprieve to Make a Final Decision*, FDA LAW BLOG (Dec. 18, 2014), <http://www.fdalawblog.net/2014/12/deliverance-fda-is-sued-over-the-applicability-of-3-year-exclusivity-in-the-context-of-dueling-tacro> [<https://perma.cc/VYY3-NPLD>].

¹²⁴Agarwal et al., *supra* note 17, at 1334.

¹²⁵CTR. FOR DRUG EVALUATION & RES., FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES SUBMITTED IN NDAs OR INDs—GENERAL CONSIDERATIONS 14 (2014) (“[A]dditional safety or efficacy studies or PK/PD assessments may be recommended.”) (emphasis added); *see also id.* at 16 (“[I]f in vivo [bioavailability] or [bioequivalence] data are required for a product, a sponsor may seek a waiver of that requirement under certain circumstances.”); Jennifer King, *505(b)(2) Patent & Marketing Exclusivity*, CAMARGO (Apr. 23, 2008), <https://camargopharma.com/2008/04/505b2-patent-marketing-exclusivity/> [<https://perma.cc/VV5T-63NF>] (explaining that 505(b)(2) extended-release products approved without additional safety or efficacy studies will not receive non-patent exclusivity).

Johnson's topiramate (Topamax) data,¹²⁶ and did not receive any non-patent exclusivity.

Three-year exclusivity may also be irrelevant if competitors would not have entered the market before the end of three years even absent such exclusivity. One study found that, of drugs without three-year exclusivity, only twenty percent faced competition from ANDA products or from subsequently approved 505(b)(2) products with the same dosage form within three years, and only eleven percent more had competition after this time period.¹²⁷ Another study not limited to 505(b)(2) applications found that of 425 drug product reformulations or other changes, only eighty-one (nineteen percent) occurred within the "generic window," which the authors defined as the period extending three years before and one year after the first tentative or final generic drug approval of the reference product, which the authors considered to be suggestive of a strategy to impair generic competition.¹²⁸

Orphan designations also appear to play a less important role for 505(b)(2) products than might be expected. Fifty-six (nine percent of 628) products were granted orphan designations, but only thirty-nine (six percent) received the seven-year exclusivity generally associated with the designation. This discrepancy may be explained by a statutory provision that denies exclusivity to orphan-designated products that are "the same" as an already approved drug and indicated for the treatment of the same rare disease.¹²⁹ An applicant submitting a 505(b)(2) application for such a product can obtain orphan exclusivity only if it can demonstrate that the 505(b)(2) product is "clinically superior" to the already approved drug, which is defined by statute to mean that the drug offers greater efficacy or safety or "provid[es] a major contribution to patient care."¹³⁰ The fact that some orphan-designated 505(b)(2) applicants received seven-year exclusivity while others did not suggests that, for orphan-designated products, the pathway is being used to compete both through brand/brand-style competition, where differentiation is important, and through generic/generic-style competition, where clinical features of the products are similar.

The various types of legal exclusivity associated with 505(b)(2) products are likely to be narrower, shorter, or weaker than the exclusivity associated with NMEs. Three-year exclusivity—by far the most common type of non-patent exclusivity for 505(b)(2) products—is not only shorter than the five-year exclusivity available to NMEs, but the exclusivity extends only to the innovation embodied in the new product and generally not to the underlying active ingredients.¹³¹ For example, if a 505(b)(2) application is approved based on a new use, it will not prevent an ANDA product from gaining approval for the previously approved use and competing in the market with the

¹²⁶See CTR. FOR DRUG EVALUATION & RES., FOOD & DRUG ADMIN., MEDICAL REVIEW (TOPIRAMATE (QUDEXY), NDA 205122) 17 (Mar. 6, 2014), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205122Orig1s000MedR.pdf [<https://perma.cc/T4B6-5H3D>].

¹²⁷Jennifer King, *3-year Exclusivity May Not Be Worth as Much as You Think*, CAMARGO (Jan. 27, 2016), <https://camargopharma.com/2016/01/3-year-exclusivity-may-not-be-worth-as-much-as-you-think/> [<https://perma.cc/T8LE-D3DG>].

¹²⁸Shadowen et al., *supra* note 89, at 25–27.

¹²⁹21 U.S.C. § 360cc(c)(1) (2018).

¹³⁰*Id.*

¹³¹See Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,873, 28,899 (July 10, 1989) ("FDA expects that only those changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use would be granted exclusivity.").

505(b)(2) product, such as through off-label prescription. Five-year exclusivity may prevent FDA approval of downstream copies containing the identical chemical substance, but many 505(b)(2) NMEs are similar to upstream products already on the market,¹³² the sale of which is not prevented by the 505(b)(2) product's NME exclusivity. For example, when the prodrugs uridine triacetate (Xuriden, Wellstat), gabapentin enacarbil (Horizont, Glaxo), and aripiprazole lauroxil (Aristada, Alkermes) were approved under the 505(b)(2) pathway as NMEs, uridine (an inexpensive and widely-available dietary supplement), gabapentin (Neurontin, Pfizer), and aripiprazole (Abilify, Otsuka) continued to be available on the market as very close clinical substitutes. Orphan drugs approved under 505(b)(2) may be eligible for seven-year exclusivity, but such exclusivity can be more difficult to obtain for follow-on products, as previously noted.¹³³ Patents can be obtained for 505(b)(2) products, but these are more likely to cover secondary aspects of the drug product, such as its formulation or use rather than the active ingredient itself, and these secondary patents are generally more likely to be invalidated.¹³⁴ For all exclusivity types, the 505(b)(2) product will usually compete to some extent with any RLD on which it relies, if any, making such exclusivity less expansive.

In some cases, patents may temporarily limit competition for new 505(b)(2) products that offer important advantages not available from the reference product. For example, in 1971, Endo Pharmaceuticals received FDA approval for naloxone hydrochloride (Narcan, NDA 016636), an injectable opioid antagonist. Between 2013 and 2016, five manufacturers received approval for six products containing naloxone under the 505(b)(2) pathway, including three abuse-deterrent formulations of opioids (Figure 12). Although the 505(b)(2) pathway has therefore helped to promote competition for injectable formulations of naloxone and abuse-deterrent opioid products, only one company, Adapt Pharma, has obtained approval of a metered nasal spray version (Narcan, 2015). No non-patent exclusivity is listed in the 2016 Orange Book for naloxone nasal spray (Narcan), but the 2018 Orange Book lists seven drug product and/or use patents that will not expire until 2035. In 2018, Teva obtained tentative ANDA approval for a generic version of the metered spray, which awaits resolution of outstanding patent issues.¹³⁵

Figure 12: Naloxone-Containing Products Approved Under the 505(b)(2) Pathway

Generic (Brand) (NDA No.)	Manufacturer	Orange Book Description	Year
buprenorphine/naloxone (Zubsolv) (204242)	Orexo US Inc.	tablet; sublingual	2013

¹³²See *supra* notes 66–71 and accompanying text.

¹³³21 U.S.C. § 360cc(b) (2018).

¹³⁴See Darrow et al., *supra* note 122, at 51.

¹³⁵ANDA Tentative Approval to Teva Pharm. USA, Inc., U.S. FOOD & DRUG ADMIN., 1 (June 8, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/209522Orig1s000TAltr.pdf [<https://perma.cc/M6CV-4RSB>].

Naloxone (Evzio) (205787)	Kaleo Inc.	solution; intramuscular, subcutaneous	2014
buprenorphine/naloxone (Bunavail) (205637)	Biodelivery Sci. Int'l, Inc.	film; buccal	2014
naloxone/oxycodone (Targiniq ER) (205777)	Purdue Pharma, LP	tablet, extended release; oral	2014
Naloxone (Narcan) (208411)	Adapt Pharma Ops. Ltd.	spray, metered; nasal	2015
Naloxone (Evzio) (209862)	Kaleo Inc.	solution; intramuscular, subcutaneous	2016

Naloxone's (Narcan) patent protection is illustrative of a larger trend toward "tertiary patents" covering the delivery devices associated with some pharmaceutical products.¹³⁶ However, of the 1,135 products listed in the 2016 Orange Book, only 127 (eleven percent) were drug-device combination products,¹³⁷ indicating that both the product and exclusivity characteristics of products such as naloxone (Narcan) are not representative of either 505(b)(2) products or of drugs generally. Naloxone is also unusual in that it is a fast opioid reversal medication that can be easily administered in the field and potentially impacts survival, whereas the large majority of dosage form changes are a matter of convenience or patient preference rather than clinical benefit, such as a change from a bitter-tasting liquid to a flavorless coated pill, or at most offer small, incremental changes in safety or efficacy. Although only forty-two percent of products received non-patent exclusivity, when patent exclusivity is also considered, the percent of 505(b)(2) drugs receiving any type of exclusivity rises to fifty-eight percent based on the Orange Book of the year following approval. This figure could rise further if new patents are added to the Orange Book after NDA approval, as was the case for naloxone (Narcan).¹³⁸

Even if a product receives no patent or non-patent exclusivity, 505(b)(2) applications can provide manufacturers with de facto exclusivity due to the time it takes to approve an ANDA whose reference product is the 505(b)(2) product. This de facto exclusivity distinguishes 505(b)(2) applications from ANDAs.¹³⁹ Neither upstream nor downstream equivalence was frequent within a short time following approval of the 505(b)(2) product (Figure 8). Based on the Orange Book of the year following approval, only fifty-two (eight percent) of the 628 505(b)(2) products bore either an A-type or B-type therapeutic equivalence code. By the 2017 Orange Book, 144 (twenty-six percent) of 551 products bore therapeutic equivalence ratings, including 127 (twenty-three percent) that were A-rated (seventy-seven products were not listed in the 2017 Orange Book).

¹³⁶Reed Beall & Aaron Kesselheim, *Tertiary Patenting on Drug-Device Combination Products in the United States*, 36 NATURE BIOTECHNOLOGY 142, 142 (2018).

¹³⁷*Id.*

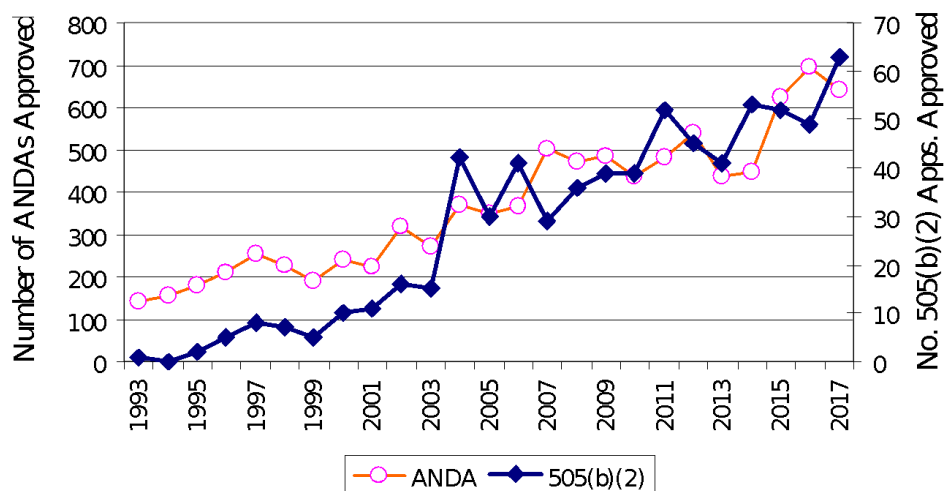
¹³⁸21 C.F.R. § 314.53(d)(3) (2018).

¹³⁹Products approved under section 505(b)(1) would generally benefit from similar de facto exclusivity.

4. 505(b)(2) Applications May Reflect Increased Competition in the ANDA Market

Competition in the generic drug market has increased over time. The average duration between brand-name drug approval and first generic challenge has declined to approximately six years from more than ten years during the 1990s, the share of new drugs experiencing patent challenges has increased to more than seventy-five percent from less than thirty-three percent in the 1990s, and the pace of erosion of the brand-name product's market share following generic entry has accelerated.¹⁴⁰ Although price decreases associated with the entry of a given number of generic manufacturers appear to have lessened between 2005 and 2017,¹⁴¹ a larger volume of ANDA approvals suggests that, on average, there are more ANDAs for any given product, potentially resulting in greater overall price competition and narrowing profit margins for generic manufacturers (Figure 13). The increase in 505(b)(2) application approvals—though still only about a tenth the number of ANDA approvals—may therefore reflect efforts by generic manufacturers to compete not only in the traditional generic space, but to expand their competitive ambitions by encroaching into the traditional domain of brand-name companies: the creation of new products and their variations.¹⁴²

Figure 13: ANDA Approvals vs. 505(b)(2) Approvals, 1993-2017



¹⁴⁰Henry Grabowski, *Updated Trends in US Brand-name and Generic Drug Competition*, 19 J. MED. ECON. 836, 841 fig.3, 843 fig.5 (2016).

¹⁴¹Chintan Dave, Abraham Hartzema & Aaron S. Kesselheim, *Prices of Generic Drugs Associated with Number of Manufacturers*, 377 NEW ENG. J. MED. 2597, 2597 (2017) (“[W]e found that the second manufacturer of a generic drug resulted in a smaller decrease in the relative price . . .”).

¹⁴²Ken Phelps, *Using 505(b)(2) to Solve Shortfall from Generic Cliff*, 24(6/7) APPLIED CLINICAL TRIALS 22, 22 (2015) (“As the slate of top-selling pharmaceuticals going off-patent declines, competition is heating up in generics to find new ways to remain profitable . . .”); see also *Understanding the 505(b)(2) Approval Pathway*, CAMARGO, at 2, https://camargopharma.com/assets/general/whitepapers/cmrgo_cwhitepaper_approvalpthwy_vfb.pdf [<https://perma.cc/29YX-RRDT>] (“This path [i.e., 505(b)(2)] allows a sponsor to get out of the competitive environment of generics . . .”).

As discussed above, applicants submitting 505(b)(2) applications, particularly those based on reference products rather than scientific literature, can sometimes increase competition in the marketplace. For example, eight manufacturers received approval via the 505(b)(2) pathway for various products containing single-agent docetaxel, a cancer treatment, between 2011 and 2015, following loss of patent protection on Sanofi's docetaxel (Taxotere) in November 2010.¹⁴³ Six manufacturers received tentative approval under the 505(b)(2) pathway for eight lamivudine/nevirapine/zidovudine products, an HIV treatment, between 2005 and 2012, while seven manufacturers received approval for levothyroxine, a medicine used to treat hormone deficiency, between 2000 and 2016.

In some cases, the 505(b)(2) applicant can be the same as the RLD holder. When a brand-name manufacturer relies on both its own prior data as well as investigations that it did not conduct, it may qualify for approval under the 505(b)(2) pathway. For example, Merck obtained 505(b)(1) approval for the NME sitagliptin (Januvia) on October 16, 2006.¹⁴⁴ On March 30, 2007, Merck obtained approval under 505(b)(2) for sitagliptin/metformin (Janumet), relying in part on data obtained from other drugs in the same class as sitagliptin that were being investigated under other investigational new drug applications.¹⁴⁵ As a reward for submitting clinical investigations supporting the new combination, Merck received three years of exclusivity, expiring on March 30, 2010. In addition, Merck's 505(b)(2) product benefited from the five-year NME exclusivity of its parent sitagliptin product (Januvia),¹⁴⁶ expiring (for both products) on October 16, 2011, i.e., five years after the approval date of the parent product. Although non-patent exclusivity of the 505(b)(2) product, therefore, did not extend beyond the non-patent exclusivity of the parent product, the 2008 Orange Book lists five patents for the 505(b)(2) product, the last of which was set to expire in 2022.¹⁴⁷

5. Regulatory Framework of 505(b)(2) Applications

Observations regarding the identity of 505(b)(2) applicants and the probable overall impact on competition are consistent with the regulatory framework, which originally envisioned the 505(b)(2) pathway as a means of increasing competition and lowering prices. Since 1970, FDA's ANDA policy (not yet codified by the Hatch-Waxman Act into the Food, Drug, and Cosmetic Act) had provided an abbreviated

¹⁴³*Generic Taxotere Gets FDA Marketing Okay*, MEDPAGE TODAY (Mar. 11, 2011), <https://www.medpagetoday.com/productalert/prescriptions/25296> [<https://perma.cc/Z7JD-VSST>].

¹⁴⁴CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *Administrative and Correspondence Documents* (sitagliptin phosphate (Januvia), NDA 021995), at 12.

¹⁴⁵ CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *Medical Review* (sitagliptin/metformin (Janumet), NDA 022044) (Mar. 5, 2007), at 22. Similarly, in 2015, Boehringer Ingelheim obtained approval under 505(b)(2) for empagliflozin/metformin (Synjardy), based in part on the data it previously submitted to support empagliflozin (Jardiance, NDA 204629), for which Boehringer Ingelheim obtained approval in 2014, and in part on the data supporting the approval of metformin (Glucophage, NDA 020357), a third-party product for which Boehringer Ingelheim did not have a right of reference. See CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *Medical Review* (empagliflozin and metformin hydrochloride (Synjardy), NDA 206111).

¹⁴⁶The listed drug on which Janumet relied was metformin hydrochloride (NDA 020357). See CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *Administrative and Correspondence Documents* (sitagliptin/metformin (Janumet), NDA 022044) (Mar. 5, 2007), at 69.

¹⁴⁷FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at ADA-93 (28th ed. 2008).

pathway for duplicates of pre-1962 drugs,¹⁴⁸ and antibiotics were eligible for similar treatment.¹⁴⁹ As the patents on drugs approved after 1962 began to expire, FDA experienced increasing pressure to extend the ANDA policy to post-1962 drugs,¹⁵⁰ and legislation was introduced in Congress that would have done so.¹⁵¹ Although this legislation was never enacted, similar abbreviated approval provisions were eventually incorporated into the Hatch-Waxman Act of 1984.

It was in this context that FDA formalized its “paper NDA” policy in 1978, which was intended to serve as an interim means of approving generic copies of some post-1962 drugs until either FDA or Congress expanded the availability of the ANDA pathway to include post-1962 drugs.¹⁵² The paper NDA policy allowed generic manufacturers to obtain approval based on published reports in the scientific literature of adequate and well-controlled investigations, or possibly on unpublished reports, rather than on individual case reports from new clinical investigations.¹⁵³ The main focus of the paper NDA policy, like that of the 1970 ANDA process, was to encourage the introduction of competing generic products that were essentially identical¹⁵⁴ to already-marketed products and thereby lower consumer drug costs.¹⁵⁵

Even before 1978, informal FDA practice had allowed the approval of drugs, including pioneer drugs, largely on the basis of scientific literature, and applications submitted for such products were therefore sometimes referred to as “scientific literature” NDAs.¹⁵⁶ Pre-1978 drugs approved via FDA’s flexible approach included sodium nitroprusside (Nipride, Hoffman-La Roche, 1974), an antihypertensive medication, and somatropin (Ascellacrin, Calbio Pharmaceuticals; Crescormon, Kabi Group, 1976), a human growth hormone.¹⁵⁷ Other drugs approved primarily on the basis of literature reports prior to the Hatch-Waxman Act included methyltyrosine (Demser, Merck, 1979), used to treat pheochromocytoma, a rare type of adrenal gland tumor, and sodium valproate (Abbott Laboratories), an anti-epileptic medicine. In

¹⁴⁸Abbreviated Applications, 35 Fed. Reg. 6,574 (Apr. 24, 1970).

¹⁴⁹Drug Regulation Reform Act: Section by Section Analysis, H.R. 11611 and S. 2755, 95th Congress (2d Sess. 1978), at 99 of 220.

¹⁵⁰See Abbreviated New Drug Applications, 43 Fed. Reg. 39,126, 39,128 (Sept. 1, 1978) (“[T]he Commissioner intends to extend the ANDA concept at a later time to post-1962 drug products.”).

¹⁵¹See Drug Regulation Reform Act, H.R. 12980, 95th Cong. (1978); Drug Regulation Reform Act, H.R. 11611, 95th Cong. (1978).

¹⁵²Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, House of Representatives, 97th Cong. 2 (1981).

¹⁵³Publication of “Paper NDA” Memorandum, 46 Fed. Reg. 27,396 (May 19, 1981).

¹⁵⁴*Id.*

¹⁵⁵Response to Petition Seeking Withdrawal of the Policy Described in the Agency’s “Paper” NDA Memorandum of July 31, 1978, 45 Fed. Reg. 82,052 (Dec. 12, 1980) (“The agency believes that the paper NDA policy will help to reduce prescription drug costs through increased competition . . .”).

¹⁵⁶Hearing Before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, House of Representatives, 97th Cong. (1st Sess. Apr. 7, 1981), at 34; Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, House of Representatives, 97th Cong. (1st Sess. Mar. 10, 1981), at 2.

¹⁵⁷Response to Petition Seeking Withdrawal of the Policy Described in the Agency’s “Paper” NDA Memorandum of July 31, 1978, *supra* note 155.

total, approximately fifty-seven paper NDAs associated with thirteen chemical entities were approved under the paper NDA process by 1984.¹⁵⁸

Commentators around the time of the 1984 Hatch-Waxman Act considered ANDAs and paper NDAs or 505(b)(2) applications to serve a similar function and to be subject to similar rules under the new law.¹⁵⁹ In 1985, FDA issued a letter to industry observing that pending paper NDAs could be “converted” to ANDAs.¹⁶⁰ More recent commentary and FDA documents continue to view the 505(b)(2) pathway as primarily used to approve generic-type drugs,¹⁶¹ with advantages over ANDAs such as not being subject to 180-day exclusivity, not requiring suitability petitions, and allowing companies to design around patents.¹⁶² Under the current framework, the kinds of changes from existing products that are permitted via either the ANDA suitability petition pathway or the 505(b)(2) pathway are similar.¹⁶³ FDA describes both the 505(b)(2) and ANDA procedures as “abbreviated approval pathways,” and in 2017, promulgated a guidance document entitled “Determining Whether to Submit an ANDA or a 505(b)(2) Application”¹⁶⁴ reflecting the agency’s awareness that manufacturers must frequently decide between these two pathways.

Regardless of its intent and general framework, however, manufacturers have occasionally sought to use the 505(b)(2) pathway for commercial advantage by leveraging its exclusivity provisions based on changes that have little, if any, therapeutic rationale, as demonstrated by the fenofibrate (TriCor) case. This rent-seeking behavior was made possible by one of the broadening changes that Congress made when it incorporated the paper NDA policy into the Hatch Waxman Act, namely, allowing the approval of follow-on products that were modifications of previously approved products, rather than identical copies of them. Exclusivity for such modifications was justified as an incentive for creating improved versions of existing drugs, but it was predictable that manufactures would sometimes seek to meet technical requirements to obtain the statutorily defined reward while offering little

¹⁵⁸Vodra, *supra* note 11, at 357.

¹⁵⁹Michael P. Peskoe, *Paper NDAs and the Drug Price Competition Act: A Last Hurrah*, 40 FOOD DRUG COSMETIC L. J. 323, 325 (1985) (“[T]he unambiguous direction of the statute is to treat paper NDAs and ANDAs essentially the same.”); Peter Barton Hutt, *Landmark Pharmaceutical Law Enacted*, 1(3) HEALTH SCAN 11 (1984), *reprinted in* Hutt et al., *supra* note 11, at 1001, 1002 (“The new statute keeps abbreviated NDAs and paper NDAs [i.e., section 505(b)(2) NDAs] separate, but applies the . . . same rules to both.”).

¹⁶⁰Letter from Harry M. Meyer, Director, Center for Drugs and Biologics, to Gerald J. Mossinghoff, President, Pharmaceutical Manufacturer’s Association (May 1, 1985) (on file with Jonathan J. Darrow).

¹⁶¹Shana K. Cyr, Li Feng & Thomas L. Irving, *FDA Amends Regulations for 505(b)(2) Applications and ANDAs—Part I*, 29(9) INTELL. PROP. & TECH. L. J. 11 (2017).

¹⁶²Vure Prasad, Moumita Biswas & Sagar Vishal, *Is 505(b)(2) Filing a Safer Strategy: Avoiding a Known Risk?*, 7(1/2) INT’L J. INTELL. PROP. MGMT. 2, 4, 8 (2014).

¹⁶³CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *FDA Draft Guidance: Applications Covered by Section 505(b)(2)* (Oct. 1999), at 4–5 (dosage form, strength, route of administration, substitution of active ingredient in a combination product, formulation, dosing regimen, active ingredient, NME, combination product, indication, Rx/OTC switch, change from OTC monograph, naturally derived ingredient, or bioequivalence); 21 U.S.C. § 355(j)(2)(C) (2018) (dosage form, strength, route of administration, or active ingredient); 21 C.F.R. § 314.93 (2018) (same); CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *ANDA Suitability Petitions*, MAPP 5240.5 (Aug. 10, 2018), at 1.

¹⁶⁴*Draft Guidance: Determining Whether to Submit an ANDA or a 505(b)(2) Application*, *supra* note 9.

patient-relevant benefits, as has occurred with other well-intentioned pharmaceutical incentive programs.¹⁶⁵

Under the 505(b)(2) pathway, it is relatively uncommon for drugs to be essentially identical to previously approved products, although it can occur, for example, when the primary difference is a new indication or new inactive ingredient.¹⁶⁶ Indeed, applications filed by manufacturers seeking approval via the 505(b)(2) pathway will be denied if the proposed drug is a duplicate of an Orange Book-listed drug and eligible for approval via the ANDA pathway.¹⁶⁷ Conversely, manufacturers whose ANDA suitability petitions are denied may respond by pursuing approval via the 505(b)(2) pathway.¹⁶⁸

The 505(b)(2) pathway is also broader than the paper NDA policy in that it allows reliance not only on the scientific literature,¹⁶⁹ but also on any investigations “not conducted by or for the applicant and for which the applicant has not obtained a right of reference,”¹⁷⁰ such as studies submitted by unrelated manufacturers in support of previously approved brand-name drug products.¹⁷¹ The revisions to the paper NDA process codified into the 505(b)(2) provision of the Hatch-Waxman Act thus had a complex effect on competition. By allowing 505(b)(2) applicants to rely on data associated with previously approved products, the law greatly expanded the number of approved drugs that could be subject to 505(b)(2) competition. At the same time, the Hatch-Waxman shift that allowed 505(b)(2) products to encompass modifications of previously approved products represents a critical difference from the paper NDA policy, because it means that most 505(b)(2) products will often not receive A-type therapeutic equivalence ratings (or any therapeutic equivalence rating) until downstream ANDAs are approved that reference the 505(b)(2) product as the RLD. Until such ANDAs are approved, these 505(b)(2) products will not be substitutable at the pharmacy for their upstream RLDs, and any resulting increased competition will tend to more closely resemble brand/brand competition rather than brand/generic competition, meaning that downward price pressure will tend to be weaker.¹⁷²

CONCLUSION

More than thirty years after it was enacted, the broader scope and flexibility of the 505(b)(2) pathway has finally emerged as an important part of the drug development landscape. Its rise to prominence has been driven by a number of factors, including a

¹⁶⁵Jonathan J. Darrow, Michael S. Sinha & Aaron S. Kesselheim, *When Markets Fail: Patents and Infectious Disease Products*, 73 FOOD & DRUG LAW J. 361, 377 (2018) (discussing priority review vouchers).

¹⁶⁶CTR. FOR DRUG EVALUATION & RES, FOOD & DRUG ADMIN., *Manual of Policies and Procedures 5018.2* (“NDA Classification Codes”) (Nov. 4, 2015), at 4.

¹⁶⁷21 C.F.R. § 314.101(d)(9) (2018).

¹⁶⁸*Id.* § 314.93.

¹⁶⁹See Publication of “Paper NDA” Memorandum, 46 Fed. Reg. 27,396, 27,396 (May 19, 1981) (“published reports from scientific journals”).

¹⁷⁰Pub. L. No. 98-417, § 103, 98 Stat. 1585, 1593 (1984).

¹⁷¹Karst, *supra* note 49, at 1266 n.27.

¹⁷²Jonathan J. Darrow & Aaron S. Kesselheim, *Promoting Competition to Address Pharmaceutical Prices*, HEALTH AFF. (Mar. 15, 2018), https://www.healthaffairs.org/doi/10.1377/hpb20180116.967310/full/HPP_2018_CMWF_02_W.pdf [https://perma.cc/2H6M-GXUZ].

complex series of legislative measures that created exclusivity incentives for new drug applications, including 505(b)(2) applications, that generally did not apply to ANDAs. Heightened pediatric study requirements beginning in 1998 sharply accelerated the shift toward increasing numbers of 505(b)(2) applications. User fees were not available to speed the review of ANDAs until 2012—twenty years after they were made available to speed the review of NDAs—and user fee legislation even today does not offer accelerated deadlines for the review of ANDA suitability petitions.

Applications submitted under 505(b)(2) now result in the majority of new drug approvals, yet relatively little research has been devoted to studying the impact of this change on the competitive pharmaceutical environment. Our study suggests that the 505(b)(2) pathway has generally been used to introduce new products that potentially compete with older ones in the marketplace. Increased competition is suggested not only by the large number of 505(b)(2) applications being approved, but also by the dispersed nature of the applicants and the association of most 505(b)(2) products with companies that manufacture primarily ANDA products. Only a minority of 505(b)(2) products received non-patent exclusivity—many did not even request it—and the exclusivity that such products received tended to be narrower and shorter than the exclusivity available to 505(b)(1) NME products. A few exceptions to the general trend of increasing competition stand out, such as the frequently cited fenofibrate (Tricor) and naloxone (Narcan) examples, but these outliers appear not to be representative of most use of the 505(b)(2) pathway.

Nevertheless, more work is needed to examine the impact of the 505(b)(2) pathway. For example, greater understanding of the impact of 505(b)(2) product introductions on price, expenditures, and patient outcomes would help legislators evaluate whether revisions to the statutory framework are needed. The extent of applicability of PREA requirements to 505(b)(2) applications is also worthy of reconsideration. Additional study may be needed, for example, to determine whether waivers are being granted with sufficient frequency in cases where the drug “does not represent a meaningful therapeutic benefit over existing therapies,” as contemplated by the statute.¹⁷³ To minimize unnecessary burdens on manufacturers who may prefer to avoid the more costly and challenging 505(b)(2) development pathway, specific deadlines for FDA review of suitability petitions should be included in future GDUFA commitment letters.

As use of the 505(b)(2) new drug approval pathway continues to increase, the ways in which it is used may evolve. Continued vigilance by scholars and policymakers is needed to ensure that the new drug approval statute is promoting the development of patient-relevant therapeutic advances, while simultaneously ensuring that price competition helps keep the cost of these new products aligned with their clinical benefit.

¹⁷³21 U.S.C. § 355c(5)(A)(iii)(I) (2018).