An Orange Book Landscape: Drugs, Patents, and Generic Competition

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ABSTRACT

Patents are widely considered to be a critical incentive for drug development because they allow manufacturers to recoup investments in research and development activities. However, patents are also criticized for preventing competition and contributing to higher prices. To better understand the patent landscape for approved drug products and the relationship between patents, other exclusivities, and generic competition, we examined all prescription drug products listed in the Orange Book as of February 2021. Surprisingly, only 31% to 39% of drug products had any remaining patent protection as of this date, meaning the majority of approved drug products are unencumbered by patents. This finding remained true even when regulatory exclusivities were considered. We also found that generic drug approval occurred despite the presence of patent protection in 28% of cases, and that patent expiration was not followed by generic drug approval in 32% of cases. These findings suggest that even valid patents do not necessarily block competition, as is commonly believed, and that dramatic price decreases often cannot be expected when patents expire. As scholars and policymakers craft policies aimed at controlling drug prices, they should seek to better understand how factors other than patents and regulatory exclusivities affect generic competition and patient health.

I. INTRODUCTION

Since the signing of the Constitution, the United States has embraced a philosophy of granting exclusive rights to inventors to promote technological advance, including in the field of medicine.[1] Patents are intended to achieve this goal by giving inventors the ability to temporarily exclude direct competition and last for twenty years from the

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[1] U.S. CONST. Art. I, § 8, cl. 8. For an example of an early medicine patent, see U.S. Pat. No. 4848 (Nov. 12, 1846) (patent on ether as an anesthetic).

date of patent application filing.[2] This, in turn, allows prices to rise so that the inventors may receive a return on up-front investments. The patent system has emerged as a foundational aspect of the pharmaceutical industry, in particular, due to the expensive and high-risk nature of drug development.[3] From 1986 to 2014, only twenty-six drugs came to market with no remaining patent protection at the time of drug approval.[4]

Congress enacted the Hatch–Waxman Act in 1984, which required FDA to publish a list of patents covering brand-name drugs and their expiration dates, helping to promote transparency and facilitating potential patent challenges.[5] The increased transparency, however, has directed excessive attention to the role of patents and their expiration, contributing to overgeneralizations about their effect on price. For example, academic literature and lay media commonly state that competing manufacturers enter the market when patents expire and create competition that substantially reduces prices.[6] Although such reductions in price have sometimes

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[2] 35 U.S.C. § 154(a)(2).

[3] Henry Grabowski, *Patents, Innovation and Access to New Pharmaceuticals*, 5 J INT'L ECON. L. 849, 850 (2002) ("The importance of patents to pharmaceutical innovation has been demonstrated in several studies by economists."); Edwin Mansfield, *Patents and Innovation: An Empirical Study*, 32 MGMT. SCI. 173, 174 (1986) ("Taylor and Silberston (1973), using data from 27 firms, found that about 60 percent of pharmaceutical R and D . . . [was] dependent on patent protection. Mansfield, Schwartz, and Wagner (1981), using data for 48 product innovations, found that about 90 percent of the pharmaceutical innovations . . . would not have been introduced without patents.").

[4] Maxwell R. Morgan, Owen G. Roberts & Aled M. Edwards, *Ideation and Implementation of an Open Science Drug Discovery Business Model*, 3 WELLCOME OPEN RES. 1, 5 (2018) https://doi.org/10.12688/wellcomeopenres.14947.1 ("After the introduction of NCE [new chemical entity] protection in the US through the Hatch–Waxman Act, at least 26 drugs containing novel active ingredients were brought to market in the US reliant entirely on NCE exclusivity without listing any patents against the product in the FDA Orange Book.").

[5] *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. §§ 355(b)(1), (c)(2)); *see also* 21 C.F.R. § 314.53(e) (2021).

[6] *See* Robin Feldman, Evan Frondorf, Andrew K. Cordova & Connie Wang, *Empirical Evidence of Drug Pricing Games—A Citizen's Pathway Gone Astray*, 20 STAN. TECH. L. REV. 39, 46 (2017) ("Over 80% of small-molecule drugs have generic equivalents . . . . After generic competition begins, the price of most drugs eventually falls to 80–85% below the original brand-name cost."); Herbert Hovenkamp, *Antitrust and the Patent System: A Reexamination*, 76 OHIO ST. L.J. 467, 491 (2015) ("[C]ompetition among generics drives prices to the competitive level," which can be "as little as 20% of pre-generic-entry prices."); Elisabeth Rosenthal, *Lawmakers Look for Ways to Provide Relief for Rising Cost of Generic Drugs*, N.Y. TIMES (Nov. 24, 2014), https://www.nytimes.com/2014/11/25/us/lawmakers-look-for-ways-to-provide-relief-for-rising-cost-of-generic-drugs.html [https://perma.cc/W3CY-4KSG] ("Historically, after the patent expires, generic copies have entered the fray, bringing prices down, often sharply."); *Zombie Patents: Free Exchange*, THE ECONOMIST (June 21, 2014), https://www.economist.com/finance-and-economics/2014/06/21/zombie-patents [https://perma.cc/M7R7-TZFZ] ("When the patent reaches its expiry date, the comfortable monopoly evaporates, replaced by cut-throat competition."); C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents*, 8 J. EMPIRICAL LEGAL STUD. 613, 614 (2011) ("Once generic firms enter the market, prices fall, often to less than 10 percent of the price of the brand-name drug."); Eric L. Cramer & Daniel Berger, *The Superiority of Direct Proof of Monopoly Power and Anticompetitive Effects in Antitrust Cases Involving Delayed Entry of Generic Drugs*, 39 U.S.F. L. REV. 81, 124 (2004) (noting "the dramatic price declines that typically accompany generic entry"); *see also* Victor Van de Wiele, Jonathan J. Darrow & Aaron S. Kesselheim, *No Parking Here: A Review of Generic Drug 180-day Exclusivity and Recent Reform Proposals*, 20 YALE J. HEALTH L. POL'Y & ETHICS 131, 135 (2021) ("Following patent expiration, drug prices can drop dramatically."); Ike Brannon & Devorah Goldman, *How Are Generics Affecting Drug Prices*, 42 REGULATION 2, 2 (2019–2020) ("Generally, when a drug goes off patent and generic drugs hit the market, prices steadily fall as more generic makers enter . . . ."); Ravi Gupta, Nilay D. Shah & Joseph S. Ross, *Generic Drugs in the United States: Policies to Address Pricing and Competition*, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 329, 329 (2019) ("[D]rug prices typically decline rapidly once generic drugs . . . enter the market."); Mariana Mazzucato, Heidi Chow, Saoirse

occurred following the end of exclusivity, these outlier events are not representative of most drug product life cycles, making them a poor foundation from which to build policies that will affect the entire pharmaceutical system. Nevertheless, the repetition of such broad statements has led some observers to conclude that patents and other exclusivities are the primary barrier standing in the way of lower prices.[7]

In fact, while marketed products may embody patented inventions, they are not required to (and often do not) precisely correspond to them, and competition therefore does not necessarily depend on the existence of a patent or its expiration date. For example, when a patent covers only a particular formulation of a drug or one of its uses rather than its active ingredient, competing firms can often market generic versions without waiting for the patent period to end.[8] Conversely, the expiration of patents does not necessarily herald the end of a monopolistic market, since markets may not be sufficiently attractive to competitors even when no exclusive rights bar generic entry.[9]

Over-broad assertions of the impact of patent expiration have also distracted well-intentioned academics and policymakers from more important underlying issues, such

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Fitzpatrick, Andrea Laplane, Tiziana Masini, Diarmaid McDonald, Victor Roy & Ellen 't Hoen, *The People's Prescription: Reimagining Health Innovation to Deliver Public Value*, UNIV. COLL. LONDON INST. FOR INNOVATION & PUB. PURPOSE (Oct. 15, 2018), https://www.ucl.ac.uk/bartlett/public-purpose/wp2018-10 [https://perma.cc/9W4G-4GGT] ("[G]eneric competition can . . . drive the price of a product down, closer to the marginal costs of production.").

At times, even FDA has contributed to the general narrative that patent expiration is followed by dramatically lower prices. *See Facts About Generic Drugs*, U.S. FOOD & DRUG ADMIN. (June 28, 2016), http://perma.cc/GQ92-QEN4 (stating, without citation: "FACT: . . . On average, the cost of a generic drug is 80 to 85 percent lower than the brand name product."). FDA appears to have since revised this statement to make it more accurate. *See Facts About Generic Drugs*, U.S. FOOD & DRUG ADMIN. (Nov. 1, 2021), http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm [https://perma.cc/A7WB-66JH] ("For example, a single generic competitor can lead to price reductions of 30%, while five generics competing are associated with prices drops of nearly 85%.").

[7] Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 858 (2016) (abstract) ("The most important factor that allows manufacturers to set high drug prices is market exclusivity, protected by monopoly rights awarded upon Food and Drug Administration approval and by patents.").

[8] *See, e.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ANDA SUBMISSIONS—AMENDMENTS AND REQUESTS FOR FINAL APPROVAL TO TENTATIVELY APPROVED ANDAS at 3 n.11 (Sept. 2020) ("[W]hen a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use from the generic drug's labeling can submit a 'section viii statement' that acknowledges that patent information has been submitted to FDA for a patent claiming a given method of use, but states that the patent at issue does not claim a use for which the applicant seeks approval.").

[9] *See generally* Jonathan D. Alpern, Arman A. Shahriar, Min Xi, Sunita Thapa, Amy J. Kodet, William M. Stauffer, Gabriela Vazquez Benitez, Pamala A. Pawloski & Steven P. Dehmer, *Characteristics and Price Increases Among Sole-source, Off-patent Drugs in the United States, 2008 to 2018*, JAMA NETWORK OPEN, Aug. 17, 2020, at 1 (examining 300 off-patent drugs for which only a single manufacturer exists).

as low drug value[10] and the role of insurance in allowing drug prices to rise.[11] Because access to low-value drugs will not provide patients with good health, efforts to enact laws mandating coverage of such drugs exacerbate high healthcare expenditures while largely failing to address patient needs.

Regulatory exclusivities, added by Congress between 1983 to 2010 to incentivize particular types of products,[12] have also received criticism for their role in limiting pharmaceutical competition. Layered over the 200-year-old patent system, the 1983 Orphan Drug Act, as amended, provided seven years of protection for new drugs treating rare diseases affecting fewer than 200,000 people.[13] The following year, the Hatch–Waxman Act provided a waiting period before modifications to existing drugs (three years)[14] or new small-molecule drugs (five years)[15] could expect generic competition. Then, in 1997, Congress authorized a six-month extension to FDA-listed patents or regulatory exclusivities if manufacturers conducted trials in pediatric populations at the request of FDA.[16] The Biologics Price Competition and Innovation Act of 2009 provided twelve years of exclusivity for new biologic drugs.[17]

All of these periods, except six-month pediatric exclusivity, run concurrently with any patent protection[18] and tend to end before patent expiration,[19] creating uncertainty as to the additional effect, if any, of regulatory exclusivities on competition. Unlike patent exclusivities, however, which depend on administrative determinations of

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[10] *See, e.g.*, Jonathan J. Darrow, *Few New Drugs Deserve Expedited Regulatory Treatment*, 27 J. MANAGED CARE & SPECIALTY PHARMACY 685, 686 tbl.1 (2021); Jonathan J. Darrow & Aaron S. Kesselheim, *Nearly One-Third of New Drugs Are No Better than Older Drugs, and Some Are Worse*, HEALTH AFFS. FOREFRONT (Oct. 6, 2017), https://www.healthaffairs.org/do/10.1377/hblog20171021.268271/full/ [https://perma.cc/PYB7-HTDA]; Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073, 2076–78 (2013) (examining the low effectiveness bar for drug approval).

[11] Jonathan J. Darrow & Donald W. Light, *Beyond the High Prices of Prescription Drugs: A Framework to Assess Costs, Resource Allocation, and Public Funding*, 40 HEALTH AFFS. 281, 285 (2021) ("The layering of a prescription drug insurance system over an existing patent regime has led to dramatic price increases in the US.").

[12] *See* Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *FDA Regulation and Approval of Pharmaceuticals, 1983–2018*, 323 JAMA 164, 168–69 & Box 2 (2020) (describing the evolution of expedited FDA development and approval programs).

[13] Orphan Drug Act of 1983, Pub. L. No. 97–414, 96 Stat. 2049 (codified as amended at 21 U.S.C. § 360bb(a)(2)).

[14] *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, 1590 (codified as amended at 21 U.S.C. § 355(j)(5)(F)(iv)); 21 C.F.R. § 314.108(b)(4)–(5) (2021).

[15] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. at 1590 (codified as amended at 21 U.S.C. § 355(j)(5)(F)(ii)); *see also* 21 C.F.R. § 314.108(b)(2) (2021).

[16] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, § 111 (codified as amended at 21 U.S.C. § 355a).

[17] Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, tit. VII, 124 Stat. 119, 804 (codified as amended at 42 U.S.C. § 262(k)(7)(A)).

[18] *See, e.g.*, 21 U.S.C. § 355(c)(3)(E)(ii) (measuring the four- and five-year periods from the date of approval of a new drug application); *id.* § 355a(b)(1) (noting pediatric exclusivity is added to the end of other exclusivities).

[19] *See* Reed F. Beall, Jonathan J. Darrow & Aaron S. Kesselheim, *Patent Term Restoration for Top-Selling Drugs in the United States*, 24 DRUG DISCOVERY TODAY 20, 23 fig.2 (2018) (illustrating median time segments since FDA approval for a cohort of eighty-three drugs with patent term restoration, which yield a median total exclusivity period of 13.75 years, or substantially more than the regulatory exclusivity periods that typically span three to seven years).

nonobviousness or other patentability criteria that courts may later overturn, regulatory exclusivities are virtually immune from judicial invalidation because the legal bases for their grant tend to be less vulnerable to alternate interpretations.[20]

Concern over this accumulation of patents and overlapping regulatory exclusivities has fueled efforts to measure the increase over time in the average number of exclusivities per brand-name drug, particularly patents. For example, Hemphill and Sampat[21] examined drugs approved from 1985–2002, finding that the number of patents at any time during a drug's lifespan (through 2009) increased from an average of 1.9 patents per drug in the 1985–1987 cohort, to 3.9 patents per drug for the final 2000–2002 cohort. However, they excluded all injectable drugs and 449 (30%) of the remaining 1,481 drugs because those 449 drugs had no Orange Book patents, leaving just 1,032 drugs in their data set.[22] By focusing on only patent-protected drugs, such studies do not address the full pharmacopeia of potentially available brand-name products. These studies also generally include Orange Book patents that have expired and are no longer relevant to generic competition.[23]

The focus on expiration dates and rates of patenting has left important questions about drugs and exclusivities largely unaddressed, including the extent to which approved drugs are currently encumbered by patents and exclusivities. To more comprehensively evaluate the landscape of brand-name drugs and their exclusivities in a way that is most relevant to today's patients, who are not adversely affected by patents that have expired (or that have not yet issued), we examined all brand-name prescription drugs currently approved by FDA. We also sought to evaluate the association between exclusivity and the availability of generic drug products. Specifically, we sought to determine how many drugs lacked exclusivity yet nevertheless had no approved generic counterparts, and how many already faced generic competition despite still having unexpired patent or regulatory exclusivities.

II. METHODS

We obtained a list of all brand and generic drugs currently approved by FDA and not discontinued from marketing by downloading the data files of FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("Orange Book") on February 19, 2021.[24] We excluded biologic drugs, which are listed in a separate

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[20] Litigation challenging the award *vel non* of non-patent exclusivity does occur but is uncommon. *See, e.g.*, AstraZeneca Pharm. LP v. Food & Drug Admin., 872 F. Supp. 2d 60, 64 n.3 (D.D.C. 2012) (challenging FDA's approval of generic versions of quetiapine despite asserted three-year exclusivity).

[21] Hemphill & Sampat, *supra* note 6, at 619.

[22] *See id.* ("Removing those drugs that have no Orange Book patents . . . yields a set of 1,032 drugs."). The previous year Ouellette, relying in part on Sampat's data, examined 938 drugs approved from 1988–2005 and found a mean of 2.97 (median: 2) patents per drug. Lisa Larrimore Ouellette, Note, *How Many Patents Does It Take to Make a Drug: Follow-On Pharmaceutical Patents and University Licensing*, 17 MICH. TELECOMM. & TECH. L. REV. 299, 314 (2010).

[23] *Id.* ("Our measure is the number of unique patents that are listed in (*any edition of*) the Orange Book") (emphasis added).

[24] *Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. (July 18, 2019), https://www.fda.gov/drugs/drug-approvals-and-databases/orange-book-data-files [https://perma.cc/2KNV-7V4M].

"Purple Book" that does not disclose most patents.[25] From these files, we extracted new drug application (NDA) numbers, abbreviated new drug application (ANDA) numbers, approval years, therapeutic equivalence codes, dosage forms, manufacturers, patents, patent type codes, and regulatory exclusivities. Over-the-counter and discontinued products, and different doses listed under the same NDA, were excluded from NDA counts. Author judgment was used to categorize manufacturers with similar names (e.g., "Allergan" and "Allergan Inc." were considered together as a single manufacturer).

NDAs are used both for new molecular entities (NME) and for modifications of existing drugs, such as a chewable version of a drug previously approved in tablet form.[26] ANDAs are used for the approval of generic drugs that generally have the same strength, dosage form, and route of administration as their brand name counterpart, although a petition process is available that allows products to be approved via the ANDA pathway with different active ingredients (e.g., different salt forms of the same active moiety), dosage forms, or strengths.[27] Patent type codes include drug substance (DS), drug product (DP), and method of use (U). Patents of these types generally claim, respectively, active ingredients (DS), features of the product such as its formulation (DP), and uses of the drug, for example, to treat a particular patient group or a particular disease (U).[28] Patents with more than one patent type code were assigned a single code in the following order of precedence: drug substance, drug product, and method of use. Dosage forms were grouped into broad categories of oral (including, e.g., sublingual), injectable (including, e.g., intravenous), and "other" (e.g., topical, nasal, suppository). FDA generally assigns therapeutic equivalence codes to products having the same strength, dosage form, and route of administration as one another, with the codes identifying the products as either bioequivalent and therefore substitutable (A-codes or A-rated) or not established as bioequivalent and therefore not substitutable (B-codes or B-rated).[29]

III. RESULTS

A review of the Orange Book revealed a total of 2,410 NDAs and 8,516 ANDAs, which were associated with 4,535 patents and 501 manufacturers. Of all NDAs, 1,479 (61.4%) were associated with no patents, 101 (4.2%) with one patent, 232 (9.6%) with two patents, 113 (4.7%) with three patents, 94 (3.9%) with four patents, 263 (10.9%) with five to ten patents, 110 (4.6%) with eleven to twenty patents, and eighteen (0.7%)

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[25] The Biological Product Patent Transparency section of the Consolidated Appropriations Act of 2021 required FDA to include patents in the Purple Book once the reference product sponsor provides a list of such patents as part of the biosimilar litigation process. Consolidated Appropriations Act of 2021, Pub. L. No. 116–260, Div. BB, Sec. 325, 134 Stat. 1182, 2936 (codified at 42 U.S.C. § 262(k)(9)(A)(iii)).

[26] *See* OFF. OF PHARM. QUALITY, CTR. FOR DRUG EVALUATION & RSCH., MAPP 5018.2 NDA CLASSIFICATION CODES 2–3 (2015) (explaining, for example, that NDAs can be assigned "Type 1" codes, which correspond to new molecular entities and "Type 3" codes, which correspond to new dosage forms); Jonathan J. Darrow, Mengdong He & Kristina Stefanini, *The 505(b)(2) Drug Approval Pathway*, 74 FOOD & DRUG L. J. 403, 425 (2019) (describing chewable and otherwise modified versions of drugs).

[27] 21 U.S.C. § 355(j)(2)(C); *see also* 21 C.F.R. § 314.92(a)(3) (2021).

[28] *See generally* U.S. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS iv, vi, xxi, xxv (41st ed. 2021) [hereinafter FDA, APPROVED DRUG PRODUCTS].

[29] *Id.* at xii–xiii.

with twenty-one or more (Figure). Of the 2,410 NDAs, 208 (8.6%) had at least one drug substance patent, 485 (20.1%) had at least one drug product patent but no drug substance patent, and 238 (9.9%) had at least one method of use patent but neither drug product nor drug substance patents. An additional ninety-two (3.8%) NDAs had only regulatory exclusivity (such as Orphan Drug Act exclusivity), including eleven (<0.5%) that had only pediatric exclusivity. The product with the greatest number of patents was icosapent ethyl (Vascepa) with sixty-two, followed by ibrutinib (Imbruvica) with thirty-five, aripiprazole (Abilify Mycite Kit) with thirty-one, and epinephrine (Auvi-Q) with twenty-nine.

Of all NDAs, 1,147 (48%) were oral dosage forms, 730 (30%) were injectable dosage forms, and 533 (22%) had other dosage forms. Two NDAs included both injectable and oral formulations, but were counted only once, as injectable. Most drugs, regardless of dosage form, had no patents, including 525 (72% of 730) injectable drugs, 613 (53% of 1,147) oral drugs, and 331 (62% of 533) "other" drugs. Manufacturers with the most NDAs included Novartis (91, 4%), Baxter (77, 3%), and Pfizer (70, 3%).

A. Generic Competition

Of all NDAs, 1,185 (49.2%) were associated with no A-rated ANDAs, 187 (7.8%) with one A-rated ANDA, 184 (7.6%) with two A-rated ANDAs, 126 (5.2%) with three A-rated ANDAs, 109 (4.5%) with four A-rated ANDAs, 388 (16.1%) with five to ten A-rated ANDAs, and 231 (9.6%) with eleven or more A-rated ANDAs. (To facilitate comparison with an earlier study, we also found that 259 [10.7%] NDAs had ten or more approved ANDAs.) Of all NDAs, 1,208 (50.1%) had A-rated ANDAs only, sixteen (0.7%) had A- and B-rated ANDAs, and five (0.2%) had B-rated ANDAs only. Of the 1,387 NDAs with no remaining patent or regulatory exclusivity, 448 (32.3%) nevertheless had no A-rated ANDAs, 447 (32.2%) had no A- or B-rated ANDAs (only one NDA had a B-rated ANDA but no A-rated ANDA), 124 (8.9%) had one A-rated ANDA, 143 (10.3%) had two A-rated ANDAs, 101 (7.3%) had three A-rated ANDAs, 84 (6.1%) had four A-rated ANDAs, 302 (21.8%) had five to ten A-rated ANDAs, and 185 (13.3%) had eleven or more A-rated ANDAs. Of the 1,023 NDAs with remaining patent or regulatory exclusivity, 286 (28.0%) nevertheless had at least one A-rated ANDA, an additional three (0.3%) had B-rated ANDAs (B-rated ANDAs can sometimes be converted to A-rated ANDAs upon the submission of equivalence data), and 737 (72.0%) had no A-rated ANDAs. Specifically, sixty-three (6.2%) had one A-rated ANDA, forty-one (4.0%) had two A-rated ANDAs, twenty-five (2.4%) had three A-rated ANDAs, twenty-five (2.4%) had four A-rated ANDAs, eighty-six (8.4%) had five to ten A-rated ANDAs, and forty-six (4.5%) had eleven or more A-rated ANDAs.

B. "Orphaned" Generic Products

Of the 8,516 ANDAs, 2,899 (34.0%) were not associated with an NDA. This could occur if, for example, the NDA was withdrawn for reasons other than safety or efficacy. When ANDAs were grouped such that all ANDAs with the same active ingredient (or same multiple ingredients for fixed-dose combination products), dosage form, and route of administration were considered as a single product, 39.6% (629 of 1,587) of ANDA products had no corresponding NDA.

If the 2,410 NDAs and the 629 orphaned ANDA product-groups are considered together, 2,108 (69.4%) of 3,039 products were associated with no patents, 101 (3.3%) with one patent, 232 (7.6%) with two patents, 113 (3.7%) with three patents, 94 (3.1%)

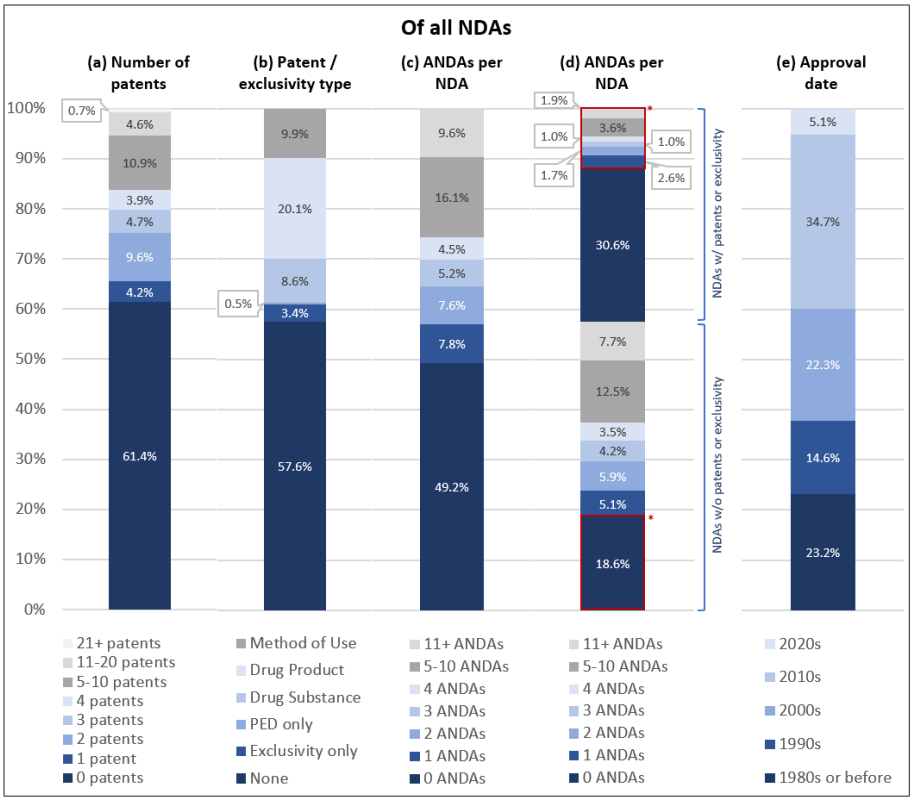
with four patents, 263 (8.7%) with five to ten patents, 110 (3.6%) with eleven to twenty patents, and 18 (0.6%) with twenty-one or more patents.

C. Time Elapsed Since Approval

The median approval year was 2005 for NDAs and 2013 for ANDAs. Of the 2,410 drugs, 559 (23%) were approved in the 1980s or before, 352 (15%) from 1990–1999, 538 (22%) from 2000–2009, 837 (35%) from 2010–2019, and 124 (5%) in 2020. Of the 2,899 orphaned ANDAs, 1,092 (37.7%) were approved in 2010 or later.

Figure

Patent, exclusivity, and ANDA information associated with 2,410 NDAs listed in the Orange Book as of February 19, 2021.



Legend. (a) Of 2,410 unique NDAs, eighteen (0.7%) had twenty-one or more patents at the time of our study; (b) Eighty-two NDAs (3.4%) had only regulatory exclusivity ("Exclusivity only") at the time of our study, of which ten (0.4%) had only pediatric exclusivity ("PED only"), and 8.6% had drug substance patents, which are generally regarded as the strongest patent type; (c) Approximately half of NDAs (49.2%) had no ANDAs, and fewer than one in ten (9.6%) had eleven or more ANDAs; (d) Of the 1,023 NDAs with remaining patent or regulatory exclusivity (top portion of bar), 286 (28.0%) nevertheless had at least one A-rated ANDA (top box with asterisk); of the 1,387 NDAs with no remaining patent or regulatory exclusivity (bottom portion of bar), 448 (32.3%) nevertheless had no A-rated ANDAs (bottom box with asterisk);

(e) nearly 40% of drugs listed in the 2021 Orange Book were approved in 2010 or later. The percent figures in all columns are presented as a share of the 2,410 NDAs.

IV. DISCUSSION

In this landscape analysis of FDA-approved prescription brand-name and generic drugs as of February 2021, we found that the presence of exclusive rights frequently did not preclude generic competition: more than a quarter (28%) of NDAs with remaining exclusivity nevertheless had at least one approved ANDA. This finding cannot be accounted for by "tentative approvals," which FDA grants when generic drug application requirements have been satisfied but certain types of patent or non-patent exclusivity remain, because tentative approvals are not approvals, are not included in the Orange Book, and therefore were intentionally not captured in our data.[30] It is also possible that approved generic drugs remain off the market due to pending patent litigation, but this appears to occur infrequently. A previous study found that of fifty-one first generics approved from 2013–2015 that sought to enter the market before patent expiry, a third (seventeen, or 37%) did not result in Hatch–Waxman litigation at all.[31] Of the twenty-nine actually launched by 2020, approval occurred an average of about 4.6 years after litigation began,[32] leaving ample time for most litigation to resolve.[33]

Conversely, the expiration or other absence of exclusive rights frequently did not lead to the entry of generic products. Of NDAs with no remaining patent or regulatory exclusivity, nearly one-third nevertheless had no corresponding therapeutically equivalent ANDAs. This finding contrasts with that of Gupta et al., who found that only 17.1% of drugs with no exclusivity had no approved ANDAs.[34] Gupta et al. examined only tablet or capsule dosage forms approved between 1984–2016 and excluded certain combination tablets or capsules, yielding just 210 exclusivity-free drugs (thirty-six of which had no generic counterparts).[35] The present study was seven times larger (n=1,387), comprehensively considering the full population of exclusivity-free brand-name drugs.

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[30] *See* FDA, APPROVED DRUG PRODUCTS, *supra* note 28 at vi ("The Agency will not include drug products with tentative approvals in the Orange Book because a drug product that is granted tentative approval is not an approved drug product.").

[31] Sunand Kannappan, Jonathan J. Darrow, Aaron S. Kesselheim & Reed F. Beall, *The Timing of 30-Month Stay Expirations and Generic Entry: A Cohort Study of First Generics, 2013–2020*, 14 CLINICAL & TRANSLATIONAL SCI. 1917, 1920 fig.2 (2021).

[32] *Id.* at 1921 tbl.1 (stays expire thirty months after the patent challenge begins, and stay expiration was found to occur a median of 2.1 years before generic drug approval). The remaining five generic drugs had not launched by 2020.

[33] *See* 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, 300 n.29 (2015) ("[T]he average time to a district court decision [in Hatch–Waxman cases] was 2.3 years, with an additional 1.2 years to reach an appellate court decision.").

[34] Ravi Gupta, Aaron S. Kesselheim, Nicholas Downing, Jeremy Greene & Joseph S. Ross, *Generic Drug Approvals Since the 1984 Hatch–Waxman Act*, 176 JAMA INTERNAL MED. 1391, 1392 tbl. (2016).

[35] *Id.*

These findings have important implications for drug pricing policy. Published articles frequently state that prices decline dramatically after patent expiration,[36] suggesting that policy solutions aimed at shortening or eliminating patent protection will lead to substantially lower prices. However, such descriptions are premised on the faulty assumption that patents preclude generic entry and that their expiration leads to entry. Reports suggesting that 80% reductions in price can be expected following generic entry are typically accurate only in those cases when ten or more generic competitors enter the market,[37] but we found that only about one in ten (10.7%) NDAs had this many approved ANDAs. Even considering only those drugs with no remaining patent or regulatory exclusivity, just 14.9% (206 of 1,387) had ten or more competitors. If orphaned ANDA products are included, then 13.0% (263 of 2,016) of products with no remaining patent or regulatory exclusivity had ten or more competitors.

Even in the minority of cases in which multiple generics enter the market, the impact of patent expiration on expenditures may be overstated. Financial savings depend not only on the price of a drug, but also on the number of patients who use the drug and the number of years over which that drug is used. To the extent that loss of exclusivity leads to declining use (for example, due to discontinuation of product promotion),[38] efforts to challenge drug patents or shorten exclusivity periods may simply be accelerating the time at which that product fades from relevance rather than expanding access and improving patient health. In our study, fewer than one in four (23.2%) listed NDAs were approved before 1990, and nearly 40% were approved in 2010 or later even though many more NMEs were approved from 1963–2009

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[36] *See id.* at 1391 ("[The] availability of at least 4 generic drugs has been associated with brand-name price reductions of approximately 60% when compared with fewer or no generics."); *see also* sources cited *supra*, note 6.

[37] *See* Chintan V. Dave, Abraham Hartzema & Aaron S. Kesselheim, *Prices of Generic Drugs Associated with Numbers of Manufacturers*, 377 NEW ENG. J. MED. 2597, 2598 fig.1 (2017) (finding that prices decline by an average of 79% following patent expiration when ten or more generic competitors enter the market.).

[38] Studies finding increases in product volume after generic entry are few in number, tend to examine only a limited number of products, and usually measure only a short time horizon after generic entry, when the effects of brand-name promotion may continue to linger. *See* Xiaodong Guan, *Interrupted Time-Series Analysis of the Impact of Generic Market Entry of Antineoplastic Products in China*, 8 BMJ OPEN e022328, at 4 fig.1 (2018) (finding increased volume following generic entry for four oncology treatments over a 2.5 to 3.5 year time horizon in Chinese hospitals). Other studies have found that total volume decreases or does not change after generic entry, despite lower prices. *See* Micael Castanheira, Carmine Ornaghi & Georges Siotis, *The Unexpected Consequences of Generic Entry*, 68 J. HEALTH ECON. 102243, at 4 (2019) ("[Despite lower prices,] sales in volume drop, on average, by more than 25% within three years of patent expiry . . . . Put differently, few new patients are directed to the cheap genericized molecule, and a number of existing patients switch to competing molecules just when their treatment becomes cheaper."); Ernst R. Berndt, Margaret K. Kyle & Davina C. Ling, *The Long Shadow of Patent Expiration: Generic Entry and Rx-to-OTC Switches*, *in* SCANNER DATA AND PRICE INDICES 229, 251 (Robert C. Feenstra & Matthew D. Shapiro eds., 2003) ("Total quantity of brand plus generic Rx cimetidine sales . . . shrunk by about one-third since Tagamet lost patent protection, even though the average price . . . declined precipitously."); Gautier Duflos & Frank R. Lichtenberg, *Does Competition Stimulate Drug Utilization? The Impact of Changes in Market Structure on US Drug Prices, Marketing and Utilization*, 32 INT'L REV. L. ECON. 95, 101 (2012) ("[I]ncreased utilization of prescriptions for generics after patent expiration is almost perfectly offset by reduced utilization of branded prescriptions."); Darius Lakdawalla & Tomas Philipson, *Does Intellectual Property Restrict Output? An Analysis of Pharmaceutical Markets*, 55 J. L. ECON. 151, 152 (2012) ("For about 40 percent of drugs, output falls [in the month] after patent expiration and expands only modestly for many others."); *see also id.* at 168 fig.7 (illustrating that, based on data of 101 drugs, average total quantity remained essentially unchanged in the eighteen months after patent expiry).

compared to 2010–2020.[39] Given historical approvals, this chronological distribution of current NDAs raises the possibility that drug product life cycles may be shorter than assumed, even before considering that product volume generally declines for older products prior to discontinuation[40] and that sales may cease before products are moved to the discontinued section of the Orange Book. Greater efforts are therefore needed to understand patterns of clinical use following generic entry, such as the frequency with which drug volume remains high ten or more years after generic entry and whether patent expiration or generic entry itself tends to trigger a sequence of events that lead to the end of a product's life cycle.

The impact of patent expiration on health may also be overstated. Aggregate health value depends not only on the number of patients using a drug and the number of years of use, but also on the incremental benefit that product confers.[41] Multiple independent studies by academics, nonprofit entities, and government-affiliated bodies have concluded that the incremental benefit of most (69% to 98%) new drugs is modest or zero,[42] or occasionally even negative.[43] Although the expiration of patents on highly effective new drugs could produce large health benefits if patent expiration leads to substantially wider use, such drugs and patterns of use are not representative of most drugs.

The dynamics of patent expiration, generic entry, and product decline also raise important questions about the value of post-approval evidence collection. Expedited drug development programs have increasingly deferred some evidence collection to the post-approval period, but these studies are often not completed for five or more years.[44] To the extent that products have short life cycles, information generated years after approval may have little enduring relevance to clinical care. Brand name manufacturers, who recognize the profit loss that coincides with patent expiration, have an incentive to not only reduce promotion, but also to delay the release of disappointing post-approval evidence until the end of exclusivity periods. In doing so,

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[39] Jonathan J. Darrow & Aaron S. Kesselheim, *Drug Development and FDA Approval, 1938–2013*, 370 NEW ENG. J. MED. 2465, 2465 (2014) (one of the authors maintains an updated version of the database underlying this Article).

[40] *See* Hans H. Bauer & Marc Fischer, *Product Life Cycle Patterns for Pharmaceuticals and Their Impact on R&D Profitability of Late Mover Products*, 9 INT'L BUS. REV. 703, 714 & fig.2 (2000) (describing a sales peak followed by decline); Marc Fischer, Peter S. H. Leeflang & Peter C. Verhoef, *Drivers of Peak Sales for Pharmaceutical Brands*, 8 QUANTITATIVE MARKETING & ECON. 429, 434 fig.1 (2010) (illustrating the decline phase for calcium channel blockers); *see generally* Henry Grabowski, Tracy Lewis, Rahul Guha, Zoya Ivanova, Maria Salgado & Sally Woodhouse, *Does Generic Entry Always Increase Consumer Welfare?*, 67 FOOD & DRUG L.J. 373, 381–82 (2012) (summarizing studies showing that quantity can decrease after generic entry due to reduced promotional efforts).

[41] *See generally* WORLD HEALTH ORG., WHO METHODS AND DATA SOURCES FOR GLOBAL BURDEN OF DISEASE ESTIMATES 2000-2019 (Dec. 2020), https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_daly-methods.pdf?sfvrsn=31b25009_7 (describing the burden of disease over a particular time period as "the number of incident cases in that period [] multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease"). Since pharmaceuticals aim to reverse the burden of disease, the calculation for aggregate health value follows essentially the same formula, but with the opposite sign.

[42] Darrow, *supra* note 10, at 686 tbl. (summarizing ten studies collectively concluding that most drugs provide modest incremental value).

[43] Darrow & Kesselheim, *supra* note 10.

[44] Steven Woloshin, Lisa M. Schwartz, Brian While & Thomas J. Moore, *The Fate of FDA Postapproval Studies*, 377 NEW ENG. J. MED. 1114, 1114 tbl.1 (2017).

their goal is to encourage the market to switch to patented, more expensive, and newer products (for which FDA may in turn allow the deferral of higher-quality evidence collection to the post-approval period). Earlier patent expiration could simply accelerate such tactics, with unclear health benefits except in the minority of cases in which the incremental therapeutic value of the newer product is substantial.

Another surprising finding was that most (61%) drugs are not protected by patents, regardless of dosage form. If orphaned ANDA products are included, this figure rises to 69.4% (2,108 of 3,039). Although many of these drugs were likely protected by patents at the time of approval, the expiration or invalidation of those patents means the majority of approved drugs are now in the public domain and can be used freely without payment to the holder of the now-expired patents—the intended outcome of the patent system. Even if regulatory exclusivity is included, most drugs (57.6%) still had no exclusivity at the time of our study. Policymakers considering legislative changes that would shorten exclusivity periods must consider not only the immediate impact of such changes on costs and access to the latest popular medicine, but also the long-term impact on the flow of medicines of lasting value into the pharmacopeia.

Despite concern that the number of patents per drug has increased, drugs with a large number of patents were rare. Of all 2,410 NDAs listed in the Orange Book as of 2021, less than 1% (eighteen, or 0.7%) had twenty-one or more patents. The Orange Book-listed drug with the greatest number of patents was icosapent ethyl (Vascepa), with sixty-two patents. Including icosapent ethyl, only three (0.1%) of the 2,410 listed NDAs had more than thirty patents, and only about one in ten (9.6%) had more than ten patents. Regulatory exclusivity in the absence of patent exclusivity was rare, affecting only 3.8% of NDAs (including those with only pediatric exclusivity remaining). Pediatric exclusivity stood alone as the only remaining exclusivity for just 0.5% of NDAs, reflecting its short six-month duration.

These data contrast with claims suggesting that drugs often have "dozens" or "hundreds" of patents protecting them.[45] Frequent commentaries expressing concern over the large number of patents covering drugs such as adalimumab (Humira) or certain HIV medications[46] describe circumstances that are not representative of traditional small-molecule products. Adalimumab is atypical because it is a biologic,

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[45] *See* Tahir Amin, *We Need to Take On Drug Companies' Abuse of the Patent System*, JACOBIN MAG. (Dec. 18, 2020), https://www.jacobinmag.com/2020/12/pharmeceutical-industry-patent-system-antitrust-law [https://perma.cc/XE5F-6SED] ("Pharmaceutical companies regularly file dozens, and increasingly hundreds, of patents on a single drug."); Aaron S. Kesselheim, *Improving Competition to Lower U.S. Prescription Drug Costs*, WASH. CTR. FOR EQUITABLE GROWTH (Feb. 18, 2020), https://equitable growth.org/improving-competition-to-lower-u-s-prescription-drug-costs/ [https://perma.cc/2ZKD-NNV6] ("[P]harmaceutical manufacturers usually build a broad thicket of dozens, or hundreds, of patents around the product prior to approval."); Mark E. Miller, *The Four Arguments You're Likely to Hear from Drug Executives*, ARNOLD VENTURES (Feb. 26, 2019), https://www.arnoldventures.org/stories/the-four-argument s-youre-likely-to-hear-from-drug-executives-at-tuesdays-hearing/ [https://perma.cc/NWC2-D3Z5] ("Drug manufacturers apply for hundreds of patents on drugs—after they have gone to market."). Such claims possibly originate from the patent estate of a single biologic drug, adalimumab (Humira), and perhaps from a small number of other biologic or non-biologics for which patent data are available (biologics are not listed in the Orange Book), but their outlier nature is not always apparent when these sweeping claims are made.

[46] *See, e.g.*, Diane Bartz, *Lawmakers Say AbbVie Exploits U.S. Patents to Protect Humira Profits, Price Hikes*, REUTERS (May 18, 2021), https://www.reuters.com/business/legal/abbvie-exploits-us-patents-protect-profits-congress-report-2021-05-18/; Tahir Amin & Aaron S. Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study on How Patents on Two HIV Drugs Could Be Extended for Years*, 31 HEALTH AFFS. 2286, 2289 exh.1 (2012).

an emerging class of complex therapeutic molecules, often directed to limited patient populations, for which challenges in manufacturing, dosing, treatment regimens, and storage has created a need for solutions that can then be patented.[47] It is not yet clear whether, as biologics technology ages, biologics manufacturers will be able to obtain as many patents on future biologic products. Similarly, HIV was a new infectious disease in the 1980s that presented numerous new scientific problems in formulation, methods of manufacturing, stability, etc. that were required to be solved.[48] These are not typical circumstances for most new drugs, which are often additions to existing classes, variations of existing products, or new drugs that address long-known diseases.

Among the minority of drugs in our study that had unexpired patents, those patents had an incomplete exclusionary effect. Fewer than one in ten (8.6%) NDAs had drug substance patents, which cover the active ingredient and are generally considered to be the most difficult to design around or invalidate. The remaining patents were characterized by FDA as drug product or method of use patents, which may cover aspects of a drug such as new formulations or uses in treating particular diseases or patient populations. Generic manufacturers can often design around such patents by using a different excipient or omitting the patented indication from the labeling ("skinny labeling"[49]) to avoid infringement and facilitate on-label or off-label generic use. More than one quarter (28%) of drugs with unexpired patents nevertheless had approved generic counterparts.

Even when drugs are associated with large patent thickets, generic competition may emerge sooner than expected. For instance, when competitors sought to market generic versions of icosapent ethyl (the most patented product in the Orange Book), the NDA holder asserted only six of its patents and all asserted claims were held invalid as obvious.[50] Three generic versions of icosapent ethyl were approved in 2020, including one by Hikma Pharmaceuticals PLC that was launched in November of that year.[51] The first generic version thus became available less than eight years after the originator

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[47] Ameet Sarpatwari, Rachel Barenie, Gregory Curfman, Jonathan J. Darrow & Aaron S. Kesselheim, *The US Biosimilar Market: Stunted Growth and Possible Reforms*, 105 CLINICAL PHARMACOLOGY & THERAPEUTICS 92, 95 (2019) ("Manufacturing biosimilars is more challenging and costly than generics."); Jonathan J. Darrow, *Biosimilar Approvals and the BPCIA: Too Soon to Give Up*, HEALTH AFFS. BLOG (July 19, 2019), https://www.healthaffairs.org/do/10.1377/hblog20190718.722161/full/ [https://perma.cc/R72T-XD4J] ("The complexity of biologics is associated with technical challenges in their discovery, manufacturing, storage, packaging, administration, and use. As these challenges are overcome, manufacturers have been able to obtain larger numbers of patents than is typical of small-molecule drugs."). Adalimumab is likely not representative even of biologics, given its approval years before the Biologics Price Competition and Innovation Act of 2009, its status as the best-selling drug in the world, and its unusually large patent estate.

[48] *See* Amin & Kesselheim, *supra* note 47, at 2289 exh.1 (classifying 210 patents on ritonavir and lopinavir/ritonavir into categories such as formulations, manufacturing methods, and new uses).

[49] *See generally* Bryan S. Walsh, Ameet Sarpatwari, Benjamin N. Rome & Aaron S. Kesselheim, *Frequency of First Generic Drug Approvals With "Skinny Labels" in the United States*, 181 JAMA INTERNAL MED. 995, 995 (2021) (finding that 43% of those drugs for which skinny labels were possible in fact had generic competition that used skinny labels).

[50] Amarin Pharma, Inc. v. Hikma Pharm. USA Inc., 449 F. Supp. 3d 967, 1015 (D. Nev. 2020), *aff'd* 819 F. App'x 932 (Fed. Cir. 2020), *cert. denied*, 141 S. Ct. 2794 (2021).

[51] Press Release, Hikma Pharm. PLC, Hikma Launches Icosapent Ethyl Capsules (Nov. 5, 2020), https://www.hikma.com/newsroom/article-i4928-hikma-launches-icosapent-ethyl-capsules/ [https://perma.cc/9E9Y-CKFB].

product was first introduced,[52] substantially less than the empirically measured 13.6-year average exclusivity period for new drugs.[53]

Although patents and other exclusivities are potentially important for the 42% of drugs with remaining exclusivity,[54] the large number of approved products no longer covered by any type of exclusivity suggests greater scholarly attention is needed to study the end, as well as the beginning, of drug life cycles. More specifically, greater research is needed to determine why generic entry does not always occur after patent expiration, whether older generic products that exist might be more frequently substituted for therapeutically similar but more costly new products, and why such substitution has not already occurred.[55] Although the generic prescription fill rate has risen to approximately 90% from just 19% in 1984[56]—a testament to the tremendous success of the Hatch–Waxman Act in promoting generic competition—the amounts spent on the remaining 10% of prescriptions impose a disproportionate financial burden on patients and payers, and their therapeutic value deserves closer scrutiny.

Finally, our research raises questions about whether the common narrative surrounding high-cost patented drugs may be drawing excess attention to those products because of their patent status and increasing their use beyond what is justified by their therapeutic value. Commentators should consider whether this traditional scholarly criticism of patents and high drug prices is inadvertently contributing unintended publicity[57] that helps to drive the market toward those drugs that are the most expensive[58] and away from effective, older products with longer safety records and lower costs.

A. Limitations

Categorization of patents into substance, product, or use categories was based on Orange Book listings; we did not independently review or categorize patents. FDA moves drugs to its discontinued product list when notified that these products are no

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[52] *See* Press Release, Amarin Corp. PLC, Amarin Announces Market Introduction of Vascepa(R) (icosapent ethyl) Capsules for the Treatment of Very High Triglycerides (VHTG) (Jan. 24, 2013), https://www.globenewswire.com/news-release/2013/01/24/518253/10019128/en/Amarin-Announces-Market-Introduction-of-Vascepa-R-icosapent-ethyl-Capsules-for-the-Treatment-of-Very-High-Triglycerides-VHTG.html [https://perma.cc/Q5PQ-5NWZ].

[53] Henry Grabowski, Genia Long, Richard Mortimer & Ani Boyo, *Updated Trends in US Brand-Name and Generic Drug Competition*, 19 J. MED. ECON. 836, 839 (2016).

[54] *See supra* Figure, column (b).

[55] *See, e.g.*, Jonathan J. Darrow, Jessica E. Chong & Aaron S. Kesselheim, *Reconsidering the Scope of State Laws Allowing Pharmacist Substitution of Generic Drugs*, 369 BRIT. MED. J. m2236 (2020) (suggesting that state legislatures provide pharmacists with greater authority to substitute therapeutically equivalent but lower cost products to serve as a backup when physicians fail to prescribe those drugs in the first instance); Mark L. Metersky, *Is There Any Reliable Clinical Evidence to Suggest that Acthar Is More Effective than Other forms of Corticosteroids in Treating Sarcoidosis and Other Diseases it Is Being Marketed to Treat?*, 149 CHEST 866, 866 (2016) (describing pennies-per-pill corticosteroids and the extent to which they are therapeutically equivalent to corticotrophin injection, which costs nearly $29,000).

[56] Kesselheim & Darrow, *supra* note 33, at 324.

[57] *See* Jonah Berger, Alan T. Sorensen & Scott J. Rasmussen, *Positive Effects of Negative Publicity: When Negative Reviews Increase Sales*, 29 MKTG. SCI. 815, 816 (2021) (noting that even "negative publicity may have positive effects . . . by increasing product awareness or accessibility").

[58] *See* Jonathan J. Darrow, *Pharmaceutical Gatekeepers*, 47 IND. L. REV. 363, 392 (2014) (describing the "premium price halo," by which the high price of drugs or other credence goods may serve to increase their perceived value).

longer being marketed, but manufacturers may not always timely notify FDA. Approved products are not necessarily marketed. This study is intended to present a cross-sectional view of the current exclusivity landscape associated with approved drugs. Historical patents and exclusivities that no longer appear in the Orange Book due to expiration or other reasons, and pending or not-yet-filed patents that may be granted in the future, were intentionally excluded from the data because they were not relevant to our research question. Measures of the frequency of regulatory exclusivities may understate their importance because concurrently running patents are frequently invalidated in court or administrative proceedings,[59] while regulatory exclusivities are relatively immune from invalidation. Pediatric exclusivity, although serving as the only remaining exclusivity for approximately one in two hundred drugs at the time of our study, is likely to be pursued for those drugs with the largest markets, magnifying its importance. Even weak patents can deter generic entry by increasing uncertainty and litigation costs.

V. CONCLUSION

Considered together, patent and regulatory exclusivities may have a smaller impact on drug expenditures and public health than previously believed because patents do not affect most currently approved drugs, the presence or absence of patents does not necessarily determine the availability or use of approved generics, and the availability of high-cost medicines does not necessarily mean that they should be purchased or consumed. Policymakers wishing to reduce unnecessary spending on prescription drugs must consider not only the legal exclusivities affecting the prices of a minority of approved drugs, but also the various business, regulatory, and other factors that deter potential competitors from entering the market. Moreover, policymakers should seek to understand why prescribers use high-cost medicines when therapeutically similar lower-cost medicines are available.

[59] Jonathan J. Darrow, Reed F. Beall & Aaron S. Kesselheim, *Will* Inter Partes *Review Speed US Generic Drug Entry?*, 35 NATURE BIOTECHNOLOGY 1139, 1139 (2017).