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Solutions Still Searching for a Problem: A Call for Relevant Data to Support "Evergreening" Allegations

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Kristina M. L. Acri

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Solutions Still Searching for a Problem: A Call for Relevant Data to Support “Evergreening” Allegations

Erika Lietzan and Kristina Acri née Lybecker*

For years pharmaceutical policymaking discussions have been revolving around allegations of supposed “evergreening” by pharmaceutical companies, and policymakers have considered a range of significant policy reforms—including to antitrust law and drug regulatory law—to address this purported problem. This Article evaluates empirical data offered to substantiate “evergreening” and explains that these data—though mostly accurate—do not support proposed policy changes.

The “evergreening” claim is that by securing additional patents and FDA-related exclusivities after approval of their new drugs, brand drug companies enjoy a period of exclusivity in the market that is longer than the initial patent(s) and exclusivity on the drug would have provided, and longer than acceptable as a normative matter. Policymakers have been invited to consider a database, hosted by the University of California Hastings College of Law, that counts patents and exclusivities associated with new drugs, identifies the earliest and latest expiring patent or exclusivity for each, and calculates the number of months between those dates. Our audit of more than 200 entries concludes that the underlying raw dataset can be a useful tool for policymakers, filling a gap that exists because early FDA publications have not been digitized. But our audit

* Erika Lietzan is the William H. Pittman Professor of Law & Timothy J. Heinsz Professor of Law at the University of Missouri School of Law. Kristina M.L. Acri née Lybecker is the John L. Knight Chair of Economics and Professor of Economics, Department of Economics & Business, at Colorado College. The authors are grateful to Emily Weber (University of Missouri School of Law Class of 2022) for research assistance.

also raises questions about inferences drawn in and from the secondary database that interprets the dataset.

If the goal of policymakers is to ensure that current patent and exclusivity policies do not prevent brand products from facing generic competition for “too long”—whatever “too long” might mean—the key questions are (1) when do brand products actually face this competition, and (2) what exactly drives the timing of this competition? For every new chemical entity we examined, a generic drug was commercially available before the date represented in the database as the “latest” expiry date, i.e., the date that—the database claims—reflects the “additional time for which a company may have limited generic competition and monopolized a drug product.” Indeed, within our dataset, generic competition launched on average eighty-four months (seven years) before the Hastings Database implied it would. On average, the seventy-nine new chemical entities in our dataset experienced generic competition sixty-eight months (or more than five years) before the Hastings Database date.

Our claim, therefore, is that the latest expiration date of the various protections applicable to a specific new drug application is not the most relevant data point for policymaking that means to focus on ensuring timely generic competition with new drugs. Patients, healthcare providers, insurers, and the innovating and generic industries share an interest in evidence-based policymaking. But it is not enough for advocates of reform to offer data; the data must be not only accurate but also relevant. A study designed to produce relevant data would consider the market entry date of the first generic drug based on any brand product containing a particular new active ingredient and would actually determine the factors driving that market entry date. And if a more relevant dataset would more precisely document (or rule out or add nuance to) a supposed problem that is said to justify reform, it is incumbent on supporters of reform to generate those data. It would be premature to enact legislative reforms before they do so.

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INTRODUCTION

For several years, pharmaceutical policy discussions have revolved around allegations that brand drug companies engage in “evergreening” and protect their products with “patent thickets.” Some argue that as a result healthcare expenditures are higher than they ought to be.

When new drugs are first launched by innovators (“brand companies”), they tend to be sold under brand names and protected by patents in addition to statutory rights in the data that supported FDA approval (“exclusivity”).¹ The pricing of these products reflects the fact that patent rights and statutory exclusivity preclude, for a while, the launch of less expensive versions of the same products. But the

¹ See *infra* Part I.B.

law eventually permits the company's competitors to file applications seeking approval of their own products based on the brand company's research.² These marketing applications are abbreviated, because they omit some or all of the research that would ordinarily be required to prove safety and effectiveness, relying instead on the data generated by the brand company. Abbreviated applications are less expensive and time-consuming to assemble, and the resulting drugs are less expensive than the "brand drugs" they copy. When a competitor seeks to market a copy through an abbreviated application, we call its drug a "generic" drug. Pharmacists usually dispense generic copies even when doctors prescribe the corresponding brand products by name.

Some legal and health policy scholars, as well as some policy reform advocates, staff of the Federal Trade Commission (FTC), and others argue that brand drug companies obtain too many patents and too much exclusivity — too many and too much because they allow exclusive or nearly exclusive sales with supra-competitive pricing for a period of time that these people think is excessive.³ Some scholars point to situations in which a brand company markets multiple products with the same active ingredient but different patents and exclusivity with differing expiration dates.⁴ Others point to situations in which a brand company holds more than one patent that protects its product, especially patents that are issued after the product was launched and that expire later than patents in place at the time of launch; the brand company, they say, has constructed a "patent thicket."⁵ Others focus on brand companies that introduce

² *Id.*

³ For an overview of this literature, see Erika Lietzan, *The "Evergreening" Metaphor in Intellectual Property Scholarship*, 53 AKRON L. REV. 805, 848–51 (2019) [hereinafter Lietzan, *Evergreening Metaphor*]; see also Erika Lietzan, *The Evergreening Myth*, 43 REGUL. 24, 25 (2020) [hereinafter Lietzan, *Evergreening Myth*].

⁴ E.g., Tahir Amin & Aaron Kesselheim, *Secondary Patenting of Branded Pharmaceuticals: A Case Study of How Patents on Two HIV Drugs Could Be Extended for Decades*, 31 HEALTH AFFS. 2286, 2289–90 (2012).

⁵ See, e.g., Letter from Senator Leahy et al. to the Hon. Kathi Vidal, Dir., U.S. Pat. & Trademark Off. (June 8, 2022), https://www.collins.senate.gov/imo/media/doc/patent_letter.pdf [<https://perma.cc/ED5A-BD3G>] (complaining about "large numbers of patents that cover a single product or minor variations on a single product, commonly known as patent thickets" and quoting the President that, "in the context of prescription drug prices, these patent thickets 'have been misused to inhibit or delay—for years and

newer versions of their previously introduced products. They offer, as examples, new dosage forms,⁶ new active ingredients,⁷ and new fixed-dose combination products,⁸ with many adding the term “product hopping” when prescribers shift to the newer brand product (and especially if the brand company withdraws its original product from the market).⁹ In each case, the essence of the “evergreening” allegation is that, by securing patents and exclusivity *after* new drug approval, and especially by introducing subsequent versions of a new drug, each with its own protections, a brand company enjoys exclusivity in the market and supra-competitive pricing long after the point at which, in the view of these critics, generic substitutes should be dominating the market.¹⁰ Critics have proposed changes to the drug regulatory statute, intellectual property laws, and even competition law to address the supposed “evergreening.”¹¹

Empirical studies offered to support the allegations of “evergreening” tend to count patents and exclusivities associated with drugs (or, sometimes, approved new drug applications)—focusing on the number itself, or on the expiration dates, especially of patents and exclusivities associated with the drugs after initial approval.¹² The most recent and exhaustive piece, Professor Robin Feldman’s

even decades—competition from generic drugs and biosimilars, denying Americans access to lower cost drugs.”).

⁶ See, e.g., Robin Feldman & Evan Frondorf, *Drug Wars: A New Generation of Generic Pharmaceutical Delay*, 53 HARV. J. ON LEGIS. 499, 527–31 (2016); Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1016 (2010).

⁷ E.g., Carrier, *supra* note 6, at 1017; Lars Noah, *Product Hopping 2.0: Getting the FDA to Yank Your Original License Beats Stacking Patents*, 19 MARQ. INTELL. PROP. L. REV. 161, 166 (2015); W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769, 801 (2020); Eugene McCarthy, *The Pharma Barons: Corporate Law’s Dangerous New Race to the Bottom in the Pharmaceutical Industry*, 8 MICH. BUS. & ENTREPRENEURIAL L. REV. 29, 53 (2018).

⁸ E.g., Carrier, *supra* note 6, at 1017; Kevin Outterson, *Death from the Public Domain?*, 87 TEX. L. REV. 45, 50 (2009).

⁹ E.g., Noah, *supra* note 7, at 165; Jordan Paradise, *Regulatory Silence at the FDA*, 102 MINN. L. REV. 2383, 2398 (2018); Dmitry Karshedt, *The More Things Change: Improvement Patents, Drug Modifications and the FDA*, 104 IOWA L. REV. 1129, 1141 n.64 (2019).

¹⁰ See generally *infra* Part I.C.

¹¹ See generally *infra* Part I.C.

¹² See Lietzan, *Evergreening Metaphor*, *supra* note 3, at 848–51 (offering literature review).

May Your Drug Price Be Evergreen, counts both patents and exclusivities associated with new drug applications from January 2005 through December 2015.¹³ The University of California Hastings College of Law, on whose faculty Professor Feldman serves, also launched an electronically searchable database that covers three additional years.¹⁴ The “Hastings Database” does not present raw data; instead it provides metrics tallied from the raw data.¹⁵ The “Hastings Raw Dataset,” however, can also be found on the same website and searched using another online engine.¹⁶ In a significant earlier piece, Professor Amy Kapczynski and colleagues counted and examined more than 1000 patents associated with new molecular entities approved by FDA between 1988 and 2005.¹⁷

In this Article, we offer an audit of the information presented and claims made regarding 224 new drug applications in the Hastings Database and underlying Hastings Raw Dataset, which are all new drug applications in the database for which there is information about a generic launch readily available on FDA’s website.¹⁸ We then explain the conceptual flaw with drawing inferences about

¹³ Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCIENCES 590, 590 (2018) [hereinafter Feldman, *May Your Drug Price Be Evergreen*]. Professor Feldman also released the raw dataset. Robin Feldman, *Identifying Extensions of Protection in Prescription Drugs: Navigating the Data Landscape for Large-Scale Analysis*, OPENICPSR (Dec. 7, 2018), <https://www.openicpsr.org/openicpsr/project/104781/version/V2/view> [https://perma.cc/4SJ5-RY6W].

¹⁴ EVERGREEN DRUG PATENT SEARCH, <https://sites.uchastings.edu/evergreensearch> [https://perma.cc/7R8L-7DGG] [hereinafter HASTINGS DATABASE].

¹⁵ See *About*, EVERGREEN DRUG PATENT SEARCH [hereinafter *About*] , <https://sites.uchastings.edu/evergreensearch/about/#.YkdK8ijMLIk> [https://perma.cc/KZ9L-5A7E] (explaining the scope of the database and explaining how fields in the database are populated with calculations made from the information in the raw dataset); *Evergreen Raw Dataset*, EVERGREEN DRUG PATENT SEARCH [hereinafter *Hastings Raw Dataset*], <https://sites.uchastings.edu/evergreensearch/raw-data-page/#.YpfT83bMLIk> [https://perma.cc/RS65-DA9U] (“The raw dataset is what we used as the basis for the calculations in the Evergreen Patent Database, but it does not include the calculations.”)

¹⁶ See *Hastings Raw Dataset*, *supra* note 15. Both the Hastings Database and the Hastings Raw Dataset can be downloaded; the Hastings Database can be downloaded simply by clicking on “Excel” or “CSV” or “PDF” on its landing page, while the Hastings Raw Dataset can be downloaded by clicking on the “Data Archive” link on its landing page.

¹⁷ Amy Kapczynski et al., *Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of “Secondary” Pharmaceutical Patents*, 7 PLOS ONE 1, 3 (2012).

¹⁸ See *infra* Part III.

competition from these and similar patent and exclusivity counts. We offer three conclusions about the Hastings project.

First, the Hastings Raw Dataset is largely accurate and, where it simply repeats information from the raw dataset, the Hastings Database is also largely accurate. That is, based on our sample of 224 new drug applications, a person who sought to capture every patent and exclusivity entry in annual editions and monthly supplements of the FDA's publication, the Orange Book, for a particular new drug application would capture essentially the information that appears in the Raw Dataset.¹⁹ We found only the occasional minor error. The hosts of the dataset note the possibility of these errors, and in our view the number of these errors is reasonable given the dataset's size and the manual labor involved in its creation. Again, not only is the underlying raw dataset essentially accurate, but generally, the Hastings Database correctly reports information from that dataset—such as, for each new drug application, the patent or exclusivity that was (or will be) the first to expire after 2005.

Second, the Hastings Database also includes metrics that reflect selection, interpretation, and characterization of the data in the raw dataset. Policymakers should not confuse these metrics with the underlying raw data. The Hastings team has been transparent about the methodology it used to create the raw dataset, but it has noted that it did not show the calculations used to generate the metrics in the database.²⁰ We see value in describing the choices that appear to have been made when preparing the database, and in this Article, we offer observations based on our own audit. To give an example, we determined that when reporting on the number of unique patents associated with a new drug application, the Hastings Database consistently counts a patent that has been reissued by the Patent and Trademark Office as *two* patents—even though the reissued patent replaces the original patent (which has been surrendered) and expires on the same date. This approach biases their results towards higher patent

¹⁹ See *infra* notes 35 & 150 for more discussion of this publication. For the current edition, see FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (43d ed. 2022) [hereinafter 43D ORANGE BOOK].

²⁰ *Hastings Raw Dataset*, *supra* note 15 (“The raw dataset is what we used as the basis for the calculations in the Evergreen Patent Database, but it does not include the calculations.”).

counts, which supports their claims. Again, the database reflects selection, interpretation, and characterization of the data, and policymakers should understand the difference between the raw data and these interpretive metrics.

Third, although useful, the Hastings Database does not provide the most important piece of information for policymakers considering the “evergreening” allegation: when new drugs actually face generic competition in the market. Our dataset comprises every new drug application for which there is a readily available generic launch date on FDA’s website.²¹ For the 224 new drug applications in our dataset, the corresponding generic drug was commercially available on average seven years *before* the date represented in the Hastings Database as the “latest protection end date.”²² The Hastings website places this label on the latest expiration date of any patents and statutory exclusivities associated with a brand company’s new drug application, and it uses this date to calculate its key metric (“months added to the protection time”).²³ But, again, we consistently found generic competition well before that date. Although capturing actual generic entry dates was not meant to be part of the Hastings project, our finding that these dates may significantly precede the “latest” date touted in the database calls into question the inference proposed by the Hastings website—that until this date, the brand company may have “limited generic competition and monopolized a drug product.”²⁴

Readers should not, however, generalize from our finding that every new drug in the Hastings Database faced generic competition before the latest protection end date recorded. To take advantage of publicly available generic launch dates on the FDA’s website, our

²¹ An Excel spreadsheet of our dataset is available on request.

²² See *About*, *supra* note 15 (explaining how the Hastings Database calculates the “latest protection end date”).

²³ See *About*, *supra* note 15 (explaining how the Hastings Database calculates the “months added to the protection time”).

²⁴ See *About*, *supra* note 14; Jonathan J. Darrow & Daniel T.C. Mai, *An Orange Book Landscape: Drugs, Patents, and Generic Competition*, 77 FOOD & DRUG L.J. 51, 51 (2022) (examining all prescription drug products listed in the Orange Book as of February 2021 and finding that generic drug approval had occurred despite the presence of listed patents in 28% of cases, while patent expiration was not followed by generic drug approval in 32%).

audit focused only on the subset of new drugs for which there was already generic competition. That said, we would expect to see broadly similar results with a larger and better designed audit, because the “months added” metric is nothing more than the number of months between two dates that themselves have no fixed or standardized significance. One is the earliest expiration after 2005 of any patent or exclusivity associated with the new drug application, and one is the latest expiration associated with the application as of 2018. These dates lack fixed significance because of a basic conceptual flaw with patent and exclusivity counting exercises, as we explain below.

The term “drug” is ambiguous at the FDA. The agency approves brand *products* (not active ingredients), and generic companies copy discrete brand *products*. But—as a result of FDA policies and the idiosyncratic regulatory framework—the brand company’s new active ingredient may be spread over multiple separately approved brand company applications, and each application may cover multiple discrete products. Further, patents and exclusivities are not aligned perfectly with any of these—products, new drug applications, *or* (with narrow exceptions) active ingredients. Patents protect inventions, and statutory exclusivities generally reward research; patent and exclusivity protection may vary from application to application and even within an application from product to product. Even at the product level, they may protect only one aspect—perhaps even an aspect that need not be copied. As a result, a count of patents and exclusivities—for instance, all associated with an active ingredient, or all associated with a new drug application—tells policymakers nothing meaningful about the prospects for, let alone the likely timing of, the first competing generic product in the market. And the entire exercise overlooks the fact that timing of generic drug approval and launch may turn on business considerations, scientific challenges, and regulatory impediments faced by the generic company. In light of these considerations, we therefore conclude with a detailed description of the dataset that *should* be gathered to assess the “evergreening” allegation as we understand it.

This Article proceeds as follows. Part I provides a brief background on new drug approval and the patents and statutory exclusivities that protect new drugs and affect generic drug approval, and

then it explains the “evergreening” allegation and briefly surveys the empirical literature making that allegation. Part II describes the Hastings Database and underlying Raw Dataset, as well as the inferences drawn on the database website and in Professor Feldman’s paper that relate to the “evergreening” policy discussion. Part III presents our audit of the database and explains why patent and exclusivity counting will not—cannot—provide the right type of evidence to inform this policy discussion. Part IV describes the study that *is* needed and concludes.

I. THE “EVERGREENING” ALLEGATION

The essence of the “evergreening” allegation is that, by securing patents and exclusivity that issue after new drug approval, and especially by introducing subsequent versions of their new drug products, brand companies enjoy exclusivity in the market for longer than is, in some sense, normatively desired. Understanding this allegation requires a brief introduction to the regulatory framework that governs brand drugs and generic drugs, as well as the patents and statutory exclusivities that affect the timing of generic drug applications and approval.

A. *Approval of Brand Drugs and Generic Drugs*

Federal law—the Federal Food, Drug, and Cosmetic Act (FDCA)—requires that every “new drug” be approved by the FDA before its introduction to the market.²⁵ Both “drug” and “new drug” are terms of art, and they can refer to an active ingredient, a finished product, or both.²⁶ An active ingredient is, in essence, the active component or components of a finished product.²⁷ It is the

²⁵ 21 U.S.C. § 355(a).

²⁶ 21 U.S.C. § 321(g)(1)(B)–(D) (defining “drug” to include (1) any article (other than a device) intended for use in diagnosis, cure, mitigation, treatment, or prevention of disease, (2) any article (other than food) intended to affect the structure or function of the body, and (3) any article intended for use as a component of one of the articles just described); 21 U.S.C. § 321(p)(1) (defining a “new drug” is a “drug” that is not “generally recognized . . . as safe and effective” for use under the conditions described in its labeling, subject to exceptions not relevant here).

²⁷ 21 C.F.R. § 314.3(b) (defining “active ingredient” as “any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of

fluoxetine in Prozac, for instance, and the sildenafil in Viagra.²⁸ In contrast, a “product” is a medicine in its finished form, meaning the form sold in the market and administered to patients.²⁹ In addition to its active ingredient, a product has a particular dosage form (such as tablets or lotion), strength (the amount of its active ingredient), and route of administration (such as oral or topical), and it contains specific inactive ingredients.³⁰

Although a “new drug” requires preapproval, and “drug” and “new drug” can refer to active ingredients, the FDA does not approve active ingredients. It approves products. If a product is new, it requires approval, even if the active ingredient has been approved before.³¹

The first company to develop a new active ingredient files a new drug application (NDA) showing that its proposed product will be safe and effective when used as described in its proposed labeling, including for the proposed medical uses (“indications”).³² Generating proof of safety and effectiveness for a product containing a new

man or other animals.” The active ingredient includes the ester, salt, or other noncovalent derivative of the molecule responsible for the physiological or pharmacological action of the drug substance. That molecule, in turn, is the “active moiety”).

²⁸ “Fluoxetine” and “sildenafil” are nonproprietary names for the active ingredients and are used by any company marketing a product containing those ingredients. “Prozac” and “Viagra” are brand names—trademarks used by Eli Lilly and Pfizer (and now its spinoff Viartis), respectively, in association with their finished products containing fluoxetine and sildenafil, respectively. *E.g.*, 43D ORANGE BOOK, *supra* note 19, at 2-3 (explaining how to identify the “active ingredient” and the “trade” name for drugs in the entries that follow); *id.* at 3-205 to 206 (listing all drugs marketed with fluoxetine active ingredient and showing brand name of “Prozac” for Lilly’s product); *id.* at 3-411 to -412 (listing all drugs marketed with the active ingredient sildenafil and showing brand name of “Viagra” for Viartis product); Pfizer, *Pfizer Completes Transaction to Combine Its Upjohn Business with Mylan* (Nov. 16, 2020), <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-completes-transaction-combine-its-upjohn-business> [https://perma.cc/PB5W-JNRJ] (announcing spinoff of Viartis).

²⁹ 21 C.F.R. § 314.3(b) (defining “drug product” as a “finished dosage form”).

³⁰ 21 C.F.R. § 314.3(b) (defining “inactive ingredient” as any component of a drug product other than its active ingredient).

³¹ *See* *United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983) (holding that a generic drug product is a “drug” and a “new drug” even if the active ingredient has been marketed previously).

³² *See* 21 U.S.C. §§ 355(b)(1)(A)(i), 355(b)(1)(A)(iv). Other showings are also required for approval, including a showing that the company’s manufacturing process complies with current good manufacturing practices. *See id.*

(not previously marketed) active ingredient generally entails performing laboratory tests, followed by animal testing, in turn followed by a series of clinical (human) trials that usually progress from small safety tests in healthy volunteers to larger randomized, controlled, blinded trials in hundreds or thousands of patients with the disease targeted.³³ The process is time-consuming, expensive, and risky.³⁴ Once the FDA approves the new drug (product), it lists the drug (product)—as having been approved on the basis of safety and effectiveness—in an agency publication and database known informally as the “Orange Book.”³⁵ The company that holds the approved application usually sells the product under a brand name; this company—the innovator—is often called a “brand company” and the product a “brand drug.” We adopt this convention for simplicity.

In addition to a full NDA proving a product’s safety and effectiveness, federal law permits the submission and approval of “abbreviated” applications that do not themselves present the results of extensive safety and effectiveness testing.³⁶ An abbreviated application instead contains data and information to create a scientific bridge to a new drug that *was* approved on the basis of safety and effectiveness—meaning to a (brand) drug listed in the Orange Book.³⁷ This second application then relies on the safety and

³³ See Jonathan J. Darrow et al., *FDA Approval and Regulation of Pharmaceuticals, 1938-2018*, 323 JAMA 164, 166–68 (2020); Amy M. Avila et al., *An FDA/CDER Perspective on Nonclinical Testing Strategies: Classical Toxicology Approaches and New Approach Methodologies (NAMs)*, 114 REG. TOX. & PHARM., July 2020, at 1; Louis D. Fiore & Philip W. Lavori, *Integrating Randomized Comparative Effectiveness Research with Patient Care*, 374 NEW ENG. J. MED 2152, 2152 (2016).

³⁴ See Erika Lietzan & Kristina M.L. Aciri née Lybecker, *Distorted Drug Patents*, 95 WASH. L. REV. 1317, 1326–29 (2020).

³⁵ The publication’s full name is APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, and FDA published its 43rd edition at the beginning of 2023. See *infra* note 150 for more discussion of this publication.

³⁶ 21 U.S.C. § 355(j)(1).

³⁷ E.g., FDA, GUIDANCE, DETERMINING WHETHER TO SUBMIT AN ANDA OR A 505(b)(2) APPLICATION 4 (May 2019), <https://www.fda.gov/media/124848/download> [<https://perma.cc/BD5S-GUQU>] [hereinafter 505(b)(2) GUIDANCE] (“The [505(b)(2)] applicant is expected to establish a bridge (e.g., by using comparative bioavailability data) between the proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate that reliance on the listed drug is scientifically justified.”); Howard Chazin, *Generic Drug Development and Safety Evaluation* 3 (Sept. 20, 2018), <https://www.fda.gov/media/116452/download> [<https://perma.cc/7HPX-5JFY>].

effectiveness data in the application for the listed drug. The listed drug is called the new product's "reference listed drug" or "reference drug."

The most common form of abbreviated application is the "abbreviated new drug application" (ANDA).³⁸ An ANDA, also called a "generic drug application," proposes a product that essentially duplicates the reference drug.³⁹ For simplicity, we refer to the ANDA applicant as a "generic" applicant. This applicant shows that its "generic" drug (product) has the same active ingredient, route of administration, dosage form, strength, and labeling as the reference drug (product).⁴⁰ In addition, the applicant shows that the two products are bioequivalent, meaning that their active ingredients reach the site of action in the body to the same extent and at the same rate.⁴¹ These showings establish the scientific bridge that justifies the generic company's reliance on the brand company's safety and effectiveness data.

B. The Effect of Patents and Exclusivities on Generic Approval Timing

In some cases, the date on which a generic application may be submitted, and in other cases the date on which it may be approved, depends in part on patents owned by the brand company as well as on statutory exclusivities applicable to the reference product.⁴²

1. Patents Covering the Brand Product

The U.S. Patent and Trademark Office (PTO) will issue a patent on a new and useful process, machine, manufacture, or composition

³⁸ See 21 U.S.C. § 355(j) (describing the "abbreviated new drug application").

³⁹ See 21 U.S.C. § 355(j)(2)(A) (describing the contents of an ANDA); FDA, DRAFT GUIDANCE, APPLICATIONS COVERED BY SECTION 505(b)(2) 1 (Oct. 1999), <https://www.fda.gov/media/72419/download> [<https://perma.cc/TZ7S-XT56>] (referring to "approval under 505(j) of *duplicates* of approved drugs" (emphasis added)).

⁴⁰ See 21 U.S.C. § 355(j)(2).

⁴¹ See 21 U.S.C. §§ 355(j)(2)(A)(vi), 355(j)(8)(B)(i). Like the innovator, the generic applicant must show that its manufacturing process complies with current good manufacturing practices. *Id.*

⁴² In some situations, the patent owner is a different company, and the brand company holds a license to use the patent. For simplicity, though, we refer only to the "brand company."

of matter (or new and useful improvement thereof) invented or discovered by the applicant for the patent.⁴³ A single drug product may embody numerous discrete inventions.⁴⁴ Commonly the active ingredient is protected by a patent.⁴⁵ The product's formulation (combination of specific amounts of specific active ingredients and inactive ingredients) may also be protected by a patent.⁴⁶ So, too, the dosage form (e.g., capsule versus tablet) and dosage (i.e., strength—twenty milligrams versus forty milligrams), the method of making the product, and the method of using or administering the product.⁴⁷

The various patents associated with a single product may expire on the same date or on differing dates. Typically, a brand company files for the active ingredient patent before starting its clinical trials, but other inventions (such as the formulation) may emerge later in the premarket research and development process, which means the patent applications are filed, and the patents generally issue, later.⁴⁸ A patent today lasts for twenty years from its application date, but in some cases, this is measured from the date of an earlier filed application.⁴⁹ As a result, whether these additional patents expire on the same day as the active ingredient patent or later depends mostly on whether the corresponding patent applications refer to the active ingredient patent.⁵⁰

Certain patents owned by the brand company affect the timing of generic drug applications and approval. The provisions linking these patents to generic drug approval appear in both the drug statute and the Patent Act, and they impose obligations on both the brand

⁴³ See 35 U.S.C. § 101. This standard requires the applicant to establish both the novelty and the utility of the invention. *E.g.*, 35 U.S.C. § 102(a)(1)–(2) (elaborating on the novelty standard); see also 35 U.S.C. § 103 (requiring various other conditions to also be satisfied for the patent to issue, such as, the invention must not have been obvious).

⁴⁴ See generally JOHN R. THOMAS, PHARMACEUTICAL PATENT LAW 46–64 (3d ed. 2015) (listing various types of pharmaceutical patent claims).

⁴⁵ See 21 C.F.R. § 314.53.

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ Lietzan, *Evergreening Metaphor*, *supra* note 3, at 817–18.

⁴⁹ See 35 U.S.C. § 154(a)(2). If the patent relates to an earlier-filed patent, it lasts for twenty years from the earlier patent's application date. *Id.* Previously, a patent lasted for seventeen years from its issuance. See *infra* note 223.

⁵⁰ See 35 U.S.C. § 154(a)(2).

company and generic company.⁵¹ To begin with, the brand company must identify these patents in its new drug application. Specifically it must identify (1) any patent that “claims the drug” and is either a “drug substance (active ingredient) patent or a drug product (formulation or composition) patent” and (2) any patent that “claims a method of using” the drug for which the brand company seeks approval.⁵² Any such patent must be identified, and its expiration date noted, if the patent owner could “reasonably assert” a claim of patent infringement against a person who made, used, or sold the drug without the patent owner’s permission.⁵³ After approval of its drug (product), the brand company finalizes the list, which the FDA then publishes in the Orange Book.⁵⁴

A generic applicant must in turn address in its own application any patents that satisfy this same standard.⁵⁵ Specifically, if a patent claims the drug or an approved method of using a drug, and it has not expired, the generic company has three choices in its application. The choice that it makes will dictate when, and on what terms its application may be approved:

⁵¹ In the drug statute, these provisions appear in 21 U.S.C. § 355(b)(1)(A)(viii), (b)(2), (b)(3), (j)(2)(A)(vii)-(viii), (j)(2)(B), and (j)(5), and in the Patent Act they appear in 35 U.S.C. § 271(e)(2), (e)(4), and (e)(5).

⁵² 21 U.S.C. § 355(b)(1)(A)(viii). The governing language has changed. From 1984 to 2021, the statute required disclosure of any patent “which claims the drug for which the applicant submitted the application or which claims a method of using such drug.” *E.g., id.* § 355(b)(1) (2000). Congress revised the language in the Orange Book Transparency Act of 2020, Pub. L. No. 116–290, 134 Stat. 4889.

⁵³ 21 U.S.C. § 355(b)(1)(A)(viii). A person “infringes” a patent by making, using, offering to sell, or selling the patented invention during the patent term without the patent owner’s permission. 35 U.S.C. § 271(a). It is also an act of infringement to import the patented invention without permission. *Id.* After NDA approval, the company has a continuing obligation to list new patents that satisfy the listing standard. 21 U.S.C. § 355(c)(2).

⁵⁴ 21 U.S.C. § 355(c)(2).

⁵⁵ 21 U.S.C. § 355(j)(2)(A)(vii). The obligation attaches to patents that satisfy the listing standard, not patents identified in the Orange Book. Thus, if the generic company identifies a patent that satisfies the standard but is omitted from the Orange Book, it submits a “paragraph I” certification, which is named after the provision of law in which it appears. 21 U.S.C. § 355(j)(2)(A)(vii)(I). If a patent satisfied the standard but has expired, the applicant includes a “paragraph II” certification. 21 U.S.C. § 355(j)(2)(A)(vii)(II). If, instead, the generic company concludes that no patents—none in the Orange Book and none omitted from it—satisfy the standard, it submits a “no relevant patents” certification. 21 C.F.R. § 314.94(a)(12)(B)(ii).

First, the generic company may indicate that it does not intend to market its product before patent expiry. To do this, it submits a “paragraph III” certification.⁵⁶ In this case, although the FDA will review the application, the agency may not grant final approval until patent expiry.⁵⁷

Second, the generic company may assert that the patent is invalid or would not be infringed by its product. To do this, it includes a “paragraph IV” certification and notifies the brand company.⁵⁸ If the brand company sues for patent infringement within forty-five days, the drug statute stays final approval of the generic drug for thirty months.⁵⁹ (The brand company may sue after the forty-five days instead, but in that case there is no stay.) The FDA may review the application in the meantime, however, and when the stay expires the agency must approve the application immediately if the drug is otherwise approvable and no statutory exclusivities need to expire.⁶⁰ If the district court decides that the generic product infringes the patent and this ruling is not appealed or is affirmed on appeal, or if it rules for the generic company but upon appeal the appellate court concludes the generic product infringes the patent, the effective date of final approval of the generic drug may be no sooner than patent expiry.⁶¹

Third, if the patent claims a method of using the brand drug, the generic applicant may file a “section viii” statement, indicating that it chooses not to seek approval for that method of use.⁶² For instance, if the brand drug is approved for two indications, the generic

⁵⁶ 21 U.S.C. § 355(j)(2)(A)(vii)(III).

⁵⁷ *Id.* § 355(j)(5)(B)(ii).

⁵⁸ *Id.* § 355(j)(2)(A)(vii)(IV); § 355(j)(2)(B)(i).

⁵⁹ *Id.* § 355(j)(5)(B)(iii). The stay ends earlier if a court finds the patent invalid or not infringed. *Id.* Under the Patent Act, it is an act of patent infringement to submit an abbreviated application for a drug claimed in a patent or the use of which is claimed in a patent, if the purpose is to obtain approval to market the drug before patent expiry. 35 U.S.C. § 271(e)(2). This creates an injury for standing purposes, allowing the brand company to sue the generic company in federal court during the stay even though the FDA has not approved the generic drug and the generic company has not launched its product. Because this suit may begin before product launch, infringement issues can be resolved with no risk to the generic company of a damages award.

⁶⁰ We discuss statutory exclusivities in Part I.B.2., *infra*.

⁶¹ 21 U.S.C. § 355(j)(5)(B)(iii)(II)(bb) (cross-referencing 35 U.S.C. § 271(e)(4)(A)).

⁶² *Id.* § 355(j)(2)(A)(viii).

company might seek approval of its product for only one of the two, omitting the indication that is patent protected.⁶³

The preceding bullets illustrate that some patents listed for a particular brand drug product may preclude approval of a generic drug based on that product until their expiry, while others may not. On the one hand, a listed patent will preclude generic drug approval until its expiry if (1) a generic company submits a “paragraph III” certification indicating that it plans to wait for patent expiry, or (2) a generic company submits a “paragraph IV” certification, but its product is found to infringe a valid patent. On the other hand, though, a patent listed for the product will not preclude generic drug approval until its expiry if (1) the patent claims a method of using the brand drug for which the generic company does not seek approval, or (2) the generic company files a paragraph IV certification, and the brand company does not sue for patent infringement. In addition, a listed patent will preclude generic drug approval for thirty months if the generic company submits a paragraph IV certification and the brand company sues within forty-five days. It will not, however, if the generic company sues *after* forty-five days have lapsed, or if it declines to sue at all.

A generic company must follow this scheme for every patent that satisfies the listing standard for the brand drug.⁶⁴ And approval of its drug depends on how it resolves every applicable patent. For example, if a generic company challenges one patent (with a paragraph IV certification) but includes a paragraph III certification to a second patent, the FDA may not grant final approval of the generic drug until the second patent expires.

⁶³ See 21 C.F.R. § 314.127(a)(7). If, however, the generic drug would be less safe and effective than the innovative drug for the remaining labeled uses, FDA will refuse the carveout. In this case, the agency cannot approve the generic drug until its labeling is the same—either because the generic company obtained a license or when the patent/exclusivity expire. *Id.*

⁶⁴ See 21 U.S.C. 355(j)(2)(A)(vii) (requiring that an ANDA include “a certification . . . with respect to *each patent* which claims the listed drug . . . or which claims a use for such listed drug . . . for which information is required to be filed” under the listing standard (emphasis added)).

2. Statutory Exclusivities

In addition to patents protecting aspects of its approved product(s), a brand company may also briefly enjoy exclusivity provided by the FDCA. The statute provides several types of exclusivity; we focus on four below. In essence, these exclusivities reward drug research and development—performing the preclinical and clinical research needed to bring a medicine to market for patients—rather than invention (discovery) itself, which earns a patent. Exclusivities run side by side with any patents the brand company might hold, and are available even if there is no patent protection.

First, if the brand company's product contains a new active moiety, the statute precludes the submission of abbreviated applications for five years.⁶⁵ The FDA interprets the statute to preclude submission of abbreviated applications citing any brand product containing that active moiety. In other words, a second or third drug product marketed by the same brand company will also be protected until five years after the FDA first approved the active moiety (in the first brand product).⁶⁶ This five-year exclusivity period is known as “new chemical entity” (NCE) exclusivity. Although NCE exclusivity precludes submission of a generic application for five years, if the generic company includes a paragraph IV certification (that a patent is invalid or not infringed), it may instead submit after four years.⁶⁷

Second, if the brand company's product does not contain a new active moiety, but clinical data (other than bioavailability data) were necessary to support its approval, the FDA cannot approve a generic application for the same active moiety for the same condition(s) of

⁶⁵ See 21 U.S.C. § 355(c)(3)(E)(ii). From 1984 to 2021, the statutory language governing this exclusivity referred to a brand product “no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application.” *Id.* The FDA decided that this language required inquiring whether the brand product's “active moiety” had previously been approved. 21 U.S.C. § 355(c)(3)(E)(i) (2018). Congress codified the FDA's approach in Act of Apr. 23, 2021, Pub. L. No. 117-9, 135 Stat. 256, which revised the statutory language to read “no active moiety . . . of which has been approved in any other application.” *Id.* The active moiety is the molecule or ion responsible for the physiological or pharmacological action of the active ingredient. 21 C.F.R. § 314.3(b).

⁶⁶ See 54 Fed. Reg. 28,872, 28,896 (July 10, 1989).

⁶⁷ See 21 U.S.C. § 355(j)(5)(F)(ii). In that case, if the generic company submits its application before the five-year mark, timely suit by the brand company will produce a stay of FDA approval that expires 7.5 years after approval of the brand drug. See *id.*

approval for three years.⁶⁸ Three-year exclusivity can arise in different ways. For instance, additional innovation with a new chemical entity can lead to three-year exclusivity; the brand company might develop a new dosage form or route of administration, for example, and the supporting research might earn it three years of exclusivity. Or a brand company might develop a new treatment using a previously approved active moiety—even an older moiety first introduced by a different company—in which case its product might receive three-year exclusivity. Three-year clinical investigation exclusivity differs from new chemical entity exclusivity because (a) it prevents *approval* (rather than submission) of generic applications, and (b) it prevents approval of applications only if they propose the same condition(s) of approval.⁶⁹ A generic company could copy the brand company's original dosage form and route of administration in the first example, or another company's product containing the active moiety in the second.

Third, if a brand drug has been designated as an “orphan” drug, intending to treat a rare disease or condition, then when approved, it will enjoy seven years of “orphan drug exclusivity.”⁷⁰ This exclusivity differs from the five-year NCE exclusivity period, because it does not preclude abbreviated applications, alone. Instead, during the orphan exclusivity term, FDA may not approve *any* application for the same drug for the same orphan disease for seven years.⁷¹ In other words, this exclusivity blocks approval of both abbreviated applications and full applications supported by their own safety and effectiveness data.

Fourth, the drug statute allows a brand company to earn six months of “pediatric” exclusivity by performing pediatric studies (including at least one clinical investigation) of its active moiety in

⁶⁸ See *id.* §§ 355(j)(5)(F)(iii)–(iv).

⁶⁹ *Id.*

⁷⁰ See *id.* § 360cc(a)(2). A drug qualifies for orphan drug designation if it is intended for “any disease or condition which affects less than 200,000 persons in the United States, or [] affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.” *Id.* § 360bb(a)(2).

⁷¹ See *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 23 (D.D.C. 1996) (noting Orphan Drug Act preclusion); 21 U.S.C. § 360cc(a).

response to a written request from the FDA.⁷² Unlike patents and the statutory exclusivities just described, pediatric exclusivity does not stand on its own and run in parallel with other protections that a brand company may enjoy. Instead, it *extends* other exclusivities. The six months are added to the end of any existing exclusivity based in the drug statute.⁷³ Thus, orphan exclusivity becomes seven years and six months, NCE exclusivity becomes five years and six months (or four years and six months with a patent challenge), and a generic company's paragraph III certification to a brand patent with pediatric exclusivity will preclude generic drug approval until the patent's expiration plus six months.

C. Continuing Innovation and the “Evergreening” Allegation

Some of the patents and exclusivities just described will pertain to the very first brand product approved with a particular new active moiety. The active ingredient patent (if one exists) and new chemical entity exclusivity are classic examples, as is orphan drug exclusivity if the initial approved indication is a rare disease. Patents and exclusivities pertaining to this first product will appear immediately in the Orange Book with the product's listing.⁷⁴ Other patents and exclusivities may come later in time.⁷⁵ Some patents pertaining to the first approved product may issue after FDA approval simply because the patent applications were filed at the PTO later in the

⁷² See 21 U.S.C. §§ 355a(d)(4), (h), and (j). The company's pediatric testing need not find the drug safe and effective in children; indeed, it does not even need to produce information important enough to be added to the drug's labeling. See *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)*, FDA, <https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently> [https://perma.cc/WBE6-GQUE]. Exclusivity is awarded for doing a specific type of research—long understood to be more difficult than research in normal adult populations—requested by the FDA. Pediatric exclusivity is awarded after the research is complete, when the brand company submits a report to the agency that “fairly” responds to the written request. See 21 U.S.C. § 355a(d)(4).

⁷³ Another exclusivity provision works the same way. Under section 505E of the FDCA, certain anti-infective drugs are eligible for a five-year extension to existing exclusivities based in the drug statute. See 21 U.S.C. § 355f. None of the drugs in our dataset earned this exclusivity period.

⁷⁴ See 21 U.S.C. § 355(c)(2).

⁷⁵ See *id.*

premarket research program than the active ingredient patent.⁷⁶ But other patents and exclusivities stem from the brand company's continuing innovation with the active moiety and do not pertain to the brand product as it appears initially in the market.⁷⁷ These patents and exclusivities are the focus of "evergreening" allegations.⁷⁸

1. Continuing Innovation

Continuing research and development with a new active moiety, and introducing new products that reflect this continuing research, is not only very common in the drug industry but a natural consequence of the modern drug approval paradigm. The process of developing a new molecular entity for approval (of meeting FDA's modern standards of safety and effectiveness) is notoriously time consuming and expensive.⁷⁹ The final clinical stages are the most expensive, and much of the active ingredient patent term runs while the company is prohibited from commercial launch.⁸⁰ As a result, in our experience, once a company completes enough research to secure approval of its first formulation for its first studied indication, that company will generally seek approval and launch, in order to convert to a revenue generation model, even while it continues to pursue its broader research plan with that molecule. This leaves the remaining research for the post-approval period. Innovation after

⁷⁶ See *supra* note 49 and accompanying text.

⁷⁷ See *infra* notes 82–120 and accompanying text (discussing continuing innovation that may be associated with new patent listings).

⁷⁸ See, e.g., Lietzan, *Evergreening Metaphor*, *supra* note 3, at 831–32 (citing various articles that allege "evergreening" when drug companies introduce innovations after initial approval).

⁷⁹ See Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 20 (2016) (estimating average out-of-pocket cost per approved compound of \$1.4 billion and total preapproval cost of \$2.56 billion).

⁸⁰ See, e.g., AYLIN SERTKAYA ET AL., EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT FINAL, 4-1 (2014), https://www.aspe.hhs.gov/sites/default/files/migrated_legacy_files/44516/rpt_erg.pdf?_ga=2.159143994.1098889773.1657562704-1568990339.1657562704 [<https://perma.cc/8F8Q-8DJ4>] ("Although experts debate the accuracy of various cost estimates, there is widespread agreement that clinical trial costs are substantial and rising. . . . Costs also tend to increase as a drug progresses through each phase of the pipeline, and, as the Institute of Medicine (IOM) notes, Phase 3 clinical trials have become "extraordinarily expensive."); Lietzan & Aciri, *Distorted Drug Patents*, *supra* note 34, at 1346 (finding effective patent life at time of FDA approval to average 8.71 years).

approval may be associated with new patents, and some of these will be listed in the Orange Book. It could also be associated with new statutory exclusivity, which will always be listed.⁸¹

Some innovation after initial approval involves changing the marketed product—adding information to its labeling, for instance, or changing how it is made. These changes are proposed through a supplement to the approved new drug application (also called a “supplemental NDA”).⁸² Other innovations after initial approval inherently generate discrete new products.⁸³ A classic example would be development of a new dosage form (a tablet now, after a capsule earlier).⁸⁴ FDA policy states that some new products should be proposed through supplements to the approved NDA, while others must be proposed in entirely separate new drug applications.⁸⁵

⁸¹ Some innovations will not lead to statutory exclusivity or patents listed in the Orange Book. These include manufacturing innovations. If a company changes any aspect of its manufacturing process (including a change in the source of raw materials and a change of manufacturing site), it must assess the effect of the change on the drug’s safety and effectiveness. Most changes require a supplemental NDA, and significant changes require prior FDA approval. *See* 21 C.F.R. § 314.70(b)(3), (c)(4)–(7), (d)(3); 21 C.F.R. § 314.53; FDA, GUIDANCE FOR INDUSTRY CHANGES TO AN APPROVED NDA OR ANDA (Apr. 2004) [hereinafter CHANGES GUIDANCE], <https://www.fda.gov/files/drugs/published/Changes-to-an-Approved-NDA-or-ANDA.pdf> [<https://perma.cc/JG9W-JBDE>]. The company might have a patent covering the new manufacturing process, but it does not submit this information with the supplement, and the FDA does not list manufacturing patents. Nor is there any prospect for three-year clinical investigation exclusivity, because a manufacturing change is not a change in the “conditions of use” of the product.

⁸² *See* 21 C.F.R. § 314.70.

⁸³ Again, the product is the finished dosage form (tablet, capsule, or the like) that contains a particular active ingredient and, typically, inactive ingredients. *See* 21 C.F.R. § 314.3. We are distinguishing here between a change merely to the labeling that accompanies the product, *see* 21 U.S.C. § 321(m) (defining “labeling”), and the introduction of a different *product* itself—such as the introduction of a capsule containing the active ingredient, after having marketed a tablet. *See, e.g., infra* note 84.

⁸⁴ Lilly first marketed Prozac in capsules, for instance, under NDA No. 018936, approved in December 1987, and it obtained approval of tablets under NDA No. 020974 in March 1999. Search Results for “Prozac,” Drugs@FDA: FDA-Approved Drugs, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> [<https://perma.cc/E3KY-C8FZ>].

⁸⁵ *See generally* FDA, GUIDANCE FOR INDUSTRY SUBMITTING SEPARATE MARKETING APPLICATIONS AND CLINICAL DATA FOR PURPOSES OF ASSESSING USER FEES (Dec. 2004) [hereinafter BUNDLING GUIDANCE], <https://www.fda.gov/media/72397/download> [<https://perma.cc/436B-VU95>].

New dosage forms and new routes of administration may be introduced for a variety of reasons, ranging from enhancing effectiveness (e.g., providing a controlled release and a steady level of the active ingredient in the blood) to optimizing patient convenience and improving compliance.⁸⁶ No matter the reason, new dosage forms and routes of administration require separate—freestanding—new drug applications.⁸⁷ Whether a dosage form is distinct (thus new) is a matter of FDA policy.⁸⁸ The FDA considers the “extended release” capsule to be distinct from an ordinary capsule, for instance, and similarly distinguishes between “delayed release” and “extended release” tablets⁸⁹; because these are distinct dosage forms, they require separate new drug applications.⁹⁰

A quick note about terminology is important here. Scholars, policy writers, and policymakers sometimes refer to new dosage forms

⁸⁶ E.g., Reed F. Beall, et al., *New Drug Formulations and Their Respective Generic Entry Dates*, 25 J. MANAGED CARE & SPEC. PHARM. 218 (2019) (noting that new strengths, dosage forms, and routes of delivery can “meaningfully expand patient treatment options” and that new routes of administration in particular “may be more convenient for certain patients”); FDA, GUIDANCE, PATIENT-FOCUSED DRUG DEVELOPMENT: COLLECTING COMPREHENSIVE AND REPRESENTATIVE INPUT 34 (2020) (suggesting that “a more convenient dosing regimen or route of administration” . . . “may lead to improved patient compliance”); James W. Wheless & Stephanie J. Phelps, *A Clinician’s Guide to Oral Extended-Release Drug Delivery Systems in Epilepsy*, 23 J. PED. PHARMACOL. THER. 277, 277 (2018) (“Extended-release formulations have many advantages compared with IR formulations, including simplification of dosing regimens, reduction in pill burden, and reduction in the peak-to-trough fluctuations in serum drug concentration that may be associated with a decreased risk of adverse effects and of seizures. These advantages have the potential to increase adherence to antiepileptic therapy, improve the quality of life of patients, and reduce health care costs.”).

⁸⁷ See FDA, *supra* note 85, at 3–4 (Dec. 2004). A narrow exception applies if the products are quantitatively and qualitatively identical in composition.

⁸⁸ See 21 C.F.R. § 314.3 (defining dosage form as “physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product” and noting that dosage form takes into account factors such as (1) the physical appearance of the drug product, (2) the physical form of the drug product before dispensing to the patient, (3) the way the product is administered, and (4) the design features that affect frequency of dosing.); 80 Fed. Reg. 6802, 6813 (Feb. 6, 2015) (quoting *Abbott Laboratories v. Young*, 691 F. Supp. 462, 464 n.1 (D.D.C. 1988)) (“The final dosage form of a drug is the form in which it appears prior to administration to the patient.”).

⁸⁹ The agency maintains a list of dosage forms in the Orange Book. See 43D ORANGE BOOK, *supra* note 19, at C-1.

⁹⁰ See FDA, *supra* note 85.

as new “formulations.”⁹¹ A different dosage form will, indeed, have a different formulation, meaning different inactive ingredients in combination with the active ingredient. But drug companies make a variety of formulation changes that are *not* associated with new dosage forms.⁹² This prevalent but imprecise use of the phrase “new formulation” confuses matters. In this Article, we refer to new dosage forms as just that: new dosage forms. So, too, with new routes of administration, which inherently entail new dosage forms as well as new formulations; we call them new routes of administration.

Although new dosage forms and new routes of administration require separate new drug applications, a new strength does *not*. If a brand company develops a new strength of its product, it seeks permission to market that strength in a supplement to its NDA.⁹³ The FDA first approved Prozac (fluoxetine), for instance, in 20mg capsules.⁹⁴ Five years later, Eli Lilly secured approval of 10mg capsules, and more than a decade later it secured approval of 40mg and 60mg capsules.⁹⁵ Each was approved pursuant to a supplement.⁹⁶ Moreover, each strength is considered a separate *product* on the NDA, and each is numbered separately. Thus, within NDA No. 018936, for Prozac, the 20mg capsules are Product 001, and the

⁹¹ E.g., Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1016 (2010) (writing that “evergreening . . . refers to a drug company’s reformulation of its product”); Jordan Paradise, *Regulatory Silence at the FDA*, 102 MINN. L. REV. 2383, 2398 (2018) (writing that “evergreening” refers to “shifting market demand to a new formulation of a drug”); Robin Feldman & Evan Frondorf, *Drug Wars: A New Generation of Generic Pharmaceutical Delay*, 53 HARV. J. ON LEGIS. 499, 527 (2016) (writing that write that “product hopping” is a “variant of evergreening” that involves making a “small change” to an approved drug “right as its patents or regulatory exclusivities are about to expire, and introduc[ing] the new formulation as an entirely new drug generally protected by new patents”); Sarah Harding, *Perpetual Property*, 61 FLA. L. REV. 285, 305 (2009) (saying that “evergreening” is an “extension tactic” in which “pharmaceutical companies succeed in patenting new formulations and applications of a drug”).

⁹² For example, Zeneca reformulated Diprivan (propofol) in the 1990s by adding a new preservative, disodium edentate, to prevent microbial contamination. See *Zeneca, Inc. v. Shalala*, 213 F.3d 161, 165 (4th Cir. 2000).

⁹³ See 21 C.F.R. § 314.70(b)(1).

⁹⁴ Search Results for NDA No. 018936, Electronic Orange Book, https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm [<https://perma.cc/54YW-KDBZ>].

⁹⁵ See *id.*

⁹⁶ See BUNDLING GUIDANCE, *supra* note 85, at 4.

40mg capsules are Product 003.⁹⁷ Each strength is listed separately in the Orange Book with applicable patents and exclusivities.⁹⁸ A new strength may be associated with some of the same patents and exclusivity as the originally approved strength; classic examples would be the active ingredient patent and new chemical entity exclusivity, if they have not expired—but it could also be associated with additional patents and exclusivity.⁹⁹ In other words, the new strength could be protected by a newly issued patent. In addition, if approval of the new strength required clinical data (other than bioavailability data), that particular product will receive three years of clinical investigation exclusivity.¹⁰⁰ This will prevent approval of a generic drug for the change that required clinical data—the new strength—but it does not preclude approval for other strengths.¹⁰¹

In nearly every case, a new indication (a new medical use) may be proposed in a supplement to the approved new drug application. New indications are very common. Even at the outset of its pre-market clinical program, a brand company may foresee multiple possible uses for its new molecular entity; other potential uses may become apparent over time and indeed could emerge through serendipity.¹⁰² Some work on additional indications may begin before

⁹⁷ 43D ORANGE BOOK, *supra* note 19, at 3-205.

⁹⁸ Search Results for NDA No. 018936, Electronic Orange Book, https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm [<https://perma.cc/83FL-NJLW>].

⁹⁹ For example, FDA approved a new strength of Tambocor (flecainide acetate) after it initially approved the new drug application for the product and before the new chemical entity exclusivity had expired; the new strength was a discrete product and listed separately, with the same patents and new chemical exclusivity as the original two strengths as well as a separate three-year exclusivity period for being a new strength. *See* Orange Book (10th ed. 1990) at AD17.

¹⁰⁰ *See* 21 U.S.C. § 355(j)(5)(F)(iv).

¹⁰¹ *See id.* (stating that FDA “may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement”) (emphasis added).

¹⁰² A classic example would be the discovery that thalidomide could treat the cutaneous symptoms of leprosy. Thalidomide had been marketed in the late 1950s and early 1960s as a sedative and antiemetic, though never in the United States, until it was discovered to be a powerful “teratogen,” meaning it causes severe malformation of embryos and sometimes fetal death. *See generally* DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 213–97 (2010). The drug’s usefulness for treating the cutaneous symptoms of leprosy was discovered after

initial approval of the drug for its first use, but studying all uses at the same time (i.e., in parallel clinical programs) is prohibitively expensive, not to mention very risky.¹⁰³ As a result, brand companies often seek approval for new uses after initial approval, including sometimes even in the first year or two after initial approval.¹⁰⁴ Once approved, the new indication is simply added to the labeling of the already approved products to which it pertains.¹⁰⁵ Any relevant patents and statutory exclusivities will be added to the Orange Book at that time.¹⁰⁶ For instance, an inventor who discovers a new and non-obvious use for previously patented composition may obtain a separate narrower patent for that use.¹⁰⁷ And a new indication supplement will receive three years of exclusivity, preventing approval of a generic drug for that indication.¹⁰⁸ A new orphan indication will receive seven years of orphan exclusivity, preventing approval of

a physician administered some, for sedation purposes, to a patient with mania and leprosy. See Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of “New” Medicines*, 20 YALE J.L. & TECH. 1, 31–32 (2018).

¹⁰³ See Lietzan & Aciri, *Distorted Drug Patents*, *supra* note 34, at 1322.

¹⁰⁴ For a discussion of the incentives federal law provides for this new use research, see generally Erika Lietzan, *Paper Promises for Drug Innovation*, 25 GEO. MASON L. REV. 168 (2018) [hereinafter Lietzan, *Paper Promises*].

¹⁰⁵ In rare cases, the FDA may allow—or require—a separate NDA for a separate indication. This can happen at any time for a variety of reasons. For instance, the FDA “administratively split” the NDA for Lyrica (pregabalin) into one for treatment of neuropathic pain associated with diabetic neuropathy and one for treatment of post-herpetic neuralgia, because the agency review divisions and timelines were different. NDA Regulatory Filing Review from Lisa Malandro, Regulatory Project Manager, FDA, to Pfizer Global Research & Development (Mar. 05, 2004), in APPROVAL PACKAGE FOR: APPLICATION No. 21446, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021446_Lyrica%20Capsules_admincorres.PDF [https://perma.cc/VQ6K-TKU9]. To give another example, if a new use is fundamentally different (for instance, it involves a different type of healthcare practitioner and a significantly greater or lesser dose), the FDA might make an exception and permit or even require a freestanding application. In these cases, patient safety considerations might counsel a separate NDA and even a separate brand name. BUNDLING GUIDANCE, *supra* note 85, at 4.

¹⁰⁶ See 21 U.S.C. § 355(c)(2); 21 C.F.R. § 314.53(e); see also FDA, DRAFT GUIDANCE: ORANGE BOOK QUESTIONS AND ANSWERS 4 (May 2020), <https://www.fda.gov/media/138389/download> [https://perma.cc/DF9Y-GX3P].

¹⁰⁷ The Patent Act authorizes a patent for any “new and useful process.” See 35 U.S.C. § 101. The term “process” includes “a new use of a known process, machine, manufacture, composition of matter, or material.” *Id.* at § 100(b).

¹⁰⁸ See 21 U.S.C. §§ 355(c)(3)(E)(iv), 355(j)(5)(F)(iii).

the same drug for that same orphan disease.¹⁰⁹ These protections are narrower; they simply prevent, for a time, approval of generic drugs *for that use*. Moreover, a generic company can simply choose not to seek approval for a newer indication that is protected by patent or exclusivity.¹¹⁰

In addition to new indications, continuing research with the active moiety may lead to a variety of other changes to the labeling, all of which must be proposed in supplements to the NDA.¹¹¹ After the FDA approves the supplement, the revised labeling replaces the prior labeling for the relevant products marketed under the NDA.¹¹² Any patents or exclusivities associated with the new information will be added to the Orange Book entry for those products.¹¹³ For instance, when supported by clinical data, this new labeling—which is a new “condition of use”—receives three-year exclusivity.¹¹⁴ Examples might include new information about the onset of action, new guidance for specific populations such as those with renal impairment, clinical data from a new study, changes to the dosage and administration section (such as addition or removal of guidance to take with food), or removal of instructions that patients be monitored for a particular change in their blood chemistry.¹¹⁵ Any associated patent or exclusivity protections are again narrow; they simply prevent, for a time, approval of generic drugs for that condition of use. In other words, for the duration of the patent or

¹⁰⁹ See 21 U.S.C. § 360cc.

¹¹⁰ See, e.g., *supra* note 63.

¹¹¹ See CHANGES GUIDANCE, *supra* note 81, at 24–26; 21 C.F.R. § 314.70.

¹¹² For instance, after searching for “Prozac” on the Drugs@FDA website and selecting NDA 018936, which is Lilly’s original NDA, covering four discrete capsules, it is possible to review labeling changes for the NDA (i.e., all products on the NDA) over the years—including the revised labeling upon approval of a new indication in July 2000, the revised labeling upon approval of a new dosing regimen in June 2002, and revised labeling with a new patient population in July 2002. See <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018936> [<https://perma.cc/KL4R-3ZH5>].

¹¹³ See 21 U.S.C. § 355(c)(2); 21 C.F.R. § 314.53(e); see also FDA, DRAFT GUIDANCE: ORANGE BOOK QUESTIONS AND ANSWERS 4 (May 2020), <https://www.fda.gov/media/138389/download> [<https://perma.cc/84YF-H4WF>].

¹¹⁴ 21 U.S.C. § 355(c)(3)(E)(iv), (j)(5)(F)(iv).

¹¹⁵ These examples of labeling changes that have resulted in three-year clinical investigation exclusivity can be found in the Orange Book, 43D ORANGE BOOK, *supra* note 19, at ADB 38-49.

exclusivity, a generic drug's labeling may not include the new information. The FDA will approve a generic drug with the words carved from its labeling, however, unless the generic drug would be less safe and effective than the brand drug without the words.¹¹⁶

"Formulation" changes, that is, changes to the particular combination of active ingredient and inactive ingredients, may require supplements to the approved new drug application or separate new drug applications, depending on what is involved.¹¹⁷ As already noted, a new dosage form and a new route of administration will inherently have a different formulation.¹¹⁸ These new dosage forms and new routes of administration require standalone NDAs.¹¹⁹ But a brand company may also make formulation changes that do not require a separate marketing application. For instance, supply issues or pricing changes could drive it to reformulate with a different inactive ingredient. So could patient safety considerations or even environmental considerations. Or the company might devote resources to developing a formulation with a better adverse event profile, for instance, reducing the incidence of injection site reactions for an injectable product. These formulation changes are usually proposed in a supplement to the NDA.¹²⁰ The company must list patents claiming the formulation, which the FDA publishes in the Orange Book when it approves the supplement.¹²¹ There is no prospect for three-year clinical investigation exclusivity in these situations, as a formulation change on its own does not change the "conditions of use" of the product.

¹¹⁶ See *supra* note 63.

¹¹⁷ E.g., CHANGES GUIDANCE, *supra* note 81, at 7.

¹¹⁸ E.g., ANSEL'S PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS 90 (9th ed. 2011) (noting that different dosage forms reflect differing formulations that combine the active ingredient with inactive ingredients that "serve varied and specialized pharmaceutical functions" and in particular that "solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms").

¹¹⁹ BUNDLING GUIDANCE, *supra* note 85, at 3.

¹²⁰ See 21 C.F.R. § 314.70(b)(2)(i); see also CHANGES GUIDANCE, *supra* note 81, at 7.

¹²¹ See 21 U.S.C. § 355(c)(2); 21 C.F.R. § 314.53(e).

2. “Evergreening” Arguments

Continuing innovation by the brand company —changes to products, new versions of products, and new patents and exclusivities—lies at the heart of “evergreening” allegations. An earlier article explored the concept of “evergreening” in the literature, examining definitions, explanations, and examples, in order to articulate the concept as precisely as possible.¹²² In its simplest terms, the claim is that patents and exclusivities earned by brand companies *after* initial approval of their new drugs enable the companies to enjoy advantageous exclusivity-based pricing in the market for longer than they would have otherwise, and, by implication, for longer than they should.¹²³ The mechanism by which this is said to happen varies. Some use the term “evergreening” when a brand company holds patents or exclusivities that protect aspects of its product other than its active ingredient, even including new uses,¹²⁴ while many also use it to refer to the introduction of additional products containing the same active ingredient.¹²⁵ Often the underlying innovations are characterized as “slight variations” or “minor improvements.”¹²⁶ Ultimately, most who use the “evergreening” term claim that in these

¹²² See Lietzan, *Evergreening Metaphor*, *supra* note 3.

¹²³ See *id.* at 810.

¹²⁴ E.g., Noah, *supra* note 7, at 166–67 n.5 (pointing to a patent that claimed a new method of using gemcitabine (the active ingredient of Gemzar) in the treatment of cancer).

¹²⁵ E.g., Mark A. Lemley, *Ignoring Patents*, 2008 MICH. ST. L. REV. 19, 30 (2008) (“Evergreening” is “obtaining multiple patents covering the same product . . .”); Cynthia M. Ho, *A New World Order for Addressing Patent Rights and Public Health*, 82 CHI.-KENT L. REV. 1469, 1512 (2007) (“[E]vergreening” [is] a common practice used by drug companies to obtain additional patents for small improvements to previously patented compounds . . .”); Thomas F. Cotter, *Patents, Antitrust, and the High Cost of Health Care*, 13 ANTITRUST SOURCE 1, 3–4 (2014) (explaining that “evergreening” is the same as “product hopping” and occurs when a company obtains “a series of patents all relating to the same drug, with the later patents claiming merely minor variations in dosage and packing.”).

¹²⁶ E.g., Josef Drexler, *Real Knowledge Is to Know the Extent of One’s Own Ignorance: On the Consumer Harm Approach in Innovation-Related Competition Cases*, 76 ANTITRUST L. J. 677, 695 n.66 (2010) (“[S]light variations . . . with regard to the specific new uses of the compound, production methods, different crystalline forms, combinations with other drugs, the dosage regime or reformulations . . .”); Janet Freilich, *The Paradox of Legal Equivalents and Scientific Equivalence: Reconciling Patent Law’s Doctrine of Equivalents with the FDA’s Bioequivalence Requirement*, 66 SMU L. REV. 59, 74–75 (2013) (“[M]inor improvements to their drugs”); see also Feldman & Frondorf, *supra* note 6, at 527 (“[M]inor change”).

situations the brand company has “extended” something— for example, the drug’s patent coverage, its patent life, its exclusivity, or the company’s “monopoly” power.¹²⁷

Policy proposals to address this “evergreening” issue vary. One scholar, for instance, has argued for a “one-and-done” approach, under which a “drug” would “receive just one period of exclusivity,” a single patent, for instance, or a single period of data exclusivity.¹²⁸ If that policy were adopted, there would be no incentive for any further research once a company first introduced its new active moiety. To give another example, proposed legislation introduced in 2019 would have made it an “unfair method of competition in or affecting commerce” to obtain certain additional later-expiring patents in the same patent family or portfolio as an already issued patent that claims an approved drug.¹²⁹ Others have proposed new antitrust

¹²⁷ E.g., Robin Feldman, *Rethinking Rights in Biospace*, 79 S. CAL. L. REV. 1, 30 (2005) (describing “evergreening” as referring to “patent holders” attempts to refresh their patents by patenting updated versions, alternative delivery methods, or other variations of the original product.”); Robin Feldman et al., *Empirical Evidence of Drug Pricing Games—A Citizen’s Pathway Gone Astray*, 20 STAN. TECH. L. REV. 39, 50 n.39 (2017) (characterizing “evergreening” as a “practice of attempting to refresh one’s patents by patenting extended-release versions, alternative delivery methods, or other variations of the original product”); Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 354 (2007) (asserting that companies adopt “‘evergreening’ strategies that add new patents to their quivers as old ones expire” to “prolong their effective periods of patent protection.”); W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C.L. REV. 491, 522 (2014) (“‘Evergreening’ [is] a set of tactics used by firms to extend effective patent protection on a drug.”); Karshedt, *supra* note 9, at 1215 n.491 (stating the term “refers generally to strategies that brand companies use to maintain exclusivities for their products.”); Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 463 n.198 (2012) (defining “evergreening” as companies “making relatively minor changes to existing products in order to restart their monopoly protection clocks”).

¹²⁸ Robin Feldman, “*One-and-Done*” for New Drugs Could Cut Patent Thickets and Boost Generic Competition, STAT NEWS: FIRST OPINION COL. (Feb. 11, 2019), <https://www.statnews.com/2019/02/11/drug-patent-protection-one-done/> [<https://perma.cc/89A5-JX8V>].

¹²⁹ Affordable Prescriptions for Patients Act of 2019, S.1416, 116th Cong. § 27(b)(1) (introduced May 9, 2019).

frameworks to evaluate whether continuing innovation is actually anti-competitive¹³⁰ or changes to the standards for issuing patents.¹³¹

In recent years, a variety of empirical studies and claims have been offered to support allegations of “evergreening” and the resulting policymaking proposals. Most count patents and exclusivities associated with new drugs, sometimes those associated with specific molecular entities or those associated with particular new drug applications. We refer the reader to an earlier Article for a full literature review.¹³² Before turning to the Hastings work in Part II, we note below two other studies of special interest from the literature review, as well as a newer and noteworthy contribution.

In *Polymorphs and Prodrugs and Salts*, Professor Amy Kapczynski and colleagues consider the 1,304 patents listed in the Orange Book for the 528 new molecular entities approved by FDA between 1988 and 2005.¹³³ Those with listed patents were more often associated with a “formulation” patent (81% of drugs) or a method of use patent (83%) than with a chemical compound patent (64%).¹³⁴ Patents lacking a chemical compound claim expired on average 4 to 5 years after the chemical compound patent for that new molecular entity.¹³⁵ They also expired an average of nine to eleven years after the NCE exclusivity term¹³⁶ and thus an average of fourteen to sixteen years after initial new molecular entity approval (because the NCE term is five years). Referring to non-compound claims as “secondary claims” and to patents without chemical compound claims as “independent secondary patents,” the authors conclude that (1) secondary claims are common, (2) independent

¹³⁰ E.g., Michael A. Carrier & Steve Shadowen, *Pharmaceutical Product Hopping: A Proposed Framework for Antitrust Analysis*, HEALTH AFFAIRS (June 1, 2017), <https://www.healthaffairs.org/doi/10.1377/forefront.20170601.060360/full/> [<https://perma.cc/E5SQ-V2P6?type=standard>].

¹³¹ E.g., Cynthia M. Ho, *Should All Drugs Be Patentable: A Comparative Perspective*, 17 VAND. J. ENT. & TECH. L. 295, 346–47 (2015) (suggesting a more stringent nonobviousness standard).

¹³² Lietzan, *Evergreening Metaphor*, *supra* note 3, at 848–53.

¹³³ Kapczynski, *supra* note 17.

¹³⁴ *Id.* at 3. The authors deemed “formulation” claims to be those asserting “specific pharmaceutical preparations to administer a product (e.g., tablets, dosage forms, sustained release forms).”

¹³⁵ *See id.* at 6.

¹³⁶ *See id.*

secondary patents are more likely to be filed after drug approval, and (3) independent secondary patents provide “incremental patent life” for drugs.¹³⁷ As to the latter point, for instance, they conclude that independent method-of-use patents provide, on average, 7.4 years of “incremental” patent life.¹³⁸

Dr. Aaron Kesselheim and Tahir Amin, a co-founder and co-executive director of the Initiative for Medicines, Access & Knowledge (I-MAK), also counted patents in *Secondary Patenting of Branded Pharmaceuticals*.¹³⁹ In addition to the Orange Book, the authors used a private database to identify patents and patent applications associated with ritonavir (marketed as Norvir), lopinavir, and the combination of the two (marketed as Kaletra), finding 82 patents and 26 patent applications.¹⁴⁰ The initial active ingredient patent for ritonavir was slated to expire in 2014, they noted, and for lopinavir in 2016.¹⁴¹ After sorting the patents and reviewing the claims, they construct what they call a “patent-related market exclusivity model” for the two active ingredients and project “generic entry delay due to life-cycle management” from 2016 to as late as 2028.¹⁴²

In 2018, I-MAK issued a fifteen-page report entitled *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices*.¹⁴³ Several other

¹³⁷ See generally *id.*

¹³⁸ *Id.* at 7 tbl.3; see also *id.* at 1 (“When present, independent formulation patents add an average of 6.5 years of patent life . . . independent method of use patents add 7.4 years . . . and independent patents on polymorphs, isomers, prodrug, ester, and/or salt claims add 6.3 years . . .”).

¹³⁹ See Amin & Kesselheim, *supra* note 4, at 2288.

¹⁴⁰ *Id.* at 2287–88 (noting that they also checked the Orange Book for patents and noting other searches run).

¹⁴¹ *Id.* at 2288.

¹⁴² *Id.* at 2290, Ex. 2.

¹⁴³ See *Overpatented, Overpriced: How Excessive Pharmaceutical Patenting is Extending Monopolies and Driving up Drug Prices*, I-MAK, 2 (2018) [hereinafter *Overpatented*], <https://www.i-mak.org/wp-content/uploads/2018/08/I-MAK-Overpatented-Overpriced-Report.pdf> [<https://perma.cc/WM3Y-3WAD>]. In January 2022, Professor Adam Mossoff published a policy memorandum with the Hudson Institute identifying a “serious concern” with the data and noting “serious discrepancies” between the numbers reported by I-MAK and information available in the Orange Book and court filings, while offering specific examples that raised questions about the data’s reliability and accuracy. See Adam Mossoff, *Unreliable Data Have Infected the Policy Debates over*

related reports now appear on the I-MAK website.¹⁴⁴ Most of the claims in these reports pertain to biological drug products, which are licensed under a different statute, subject to different patent listing and exclusivity rules, and beyond the scope of this Article. Their claims pertaining to drug products regulated under NDAs are,

Drug Patents, HUDSON INST., 1 (Jan. 2022), https://s3.amazonaws.com/media.hudson.org/Mossoff_Unreliable%20Data%20Have%20Infected%20the%20Policy%20Debates%20Over%20Drug%20Patents.pdf [https://perma.cc/6U8E-K3ZA]. Later that same month, Senator Thom Tillis (R-NC) wrote to I-MAK, citing Professor Mossoff's memo and requesting more information about the data and methodology. Letter from Thom Tillis, Ranking Member, United States S., to Tahir Amin, I-MAK, Co-Founder and Co-Executive Director, Initiative for Medicines, Access & Knowledge, 2 (Jan. 31, 2022), <https://ipwatchdog.com/wp-content/uploads/2022/02/1.31.2022-LTR-from-Senator-Tillis-to-IMAK-re-Patent-Data-Sources.pdf> [https://perma.cc/AA6Z-KX66]. I-MAK responded in March, claiming that the methodology was "clearly explained in the Methodology section" of its report, that the Orange Book and court filings "do not show all patents a company may have on a drug," and that it "stands by its findings." Letter from Tahir Amin, Co-Executive Director, Initiative for Medicines, Access & Knowledge, to Sen. Thom Tillis, 3–5 (Mar. 9, 2022), <https://www.i-mak.org/wp-content/uploads/2022/03/Letter-to-Senator-Tillis-re-I-MAK-Patent-Data-9-March-2022-1.pdf> [https://perma.cc/4WYX-JKWS]. The methodology section states that the organization searched for patents using the Orbit Intelligence patent database from Questel; this is a privately owned patent database marketed to industry for business intelligence. *See Overpatented*, *supra*, at 12. I-MAK conducted "exact structure searches in SciFinder," which is a database operated by the Chemical Abstracts Service (CAS) division of the American Chemical Society, and which permits a user to identify a chemical substance and its related chemical structures, and chemical names. *Id.* It then performed "extensive searches in Orbit Intelligence using exact drug names and fragmented chemical names," which was "supplemented with a sequence search in the open-source patent database Lens.org," and "results were refined using company names and other relevant entities." *Id.* This "patent landscaping" was intended to "identify issued patents (both current and expired) along with patent applications (both under review and abandoned)" for each drug. *Id.* Each patent application, including those abandoned and continued, was counted as a distinct application. *Id.* This was insufficient information for a researcher to replicate the study.

Recently, I-MAK issued a newer version of *Overpatented*, dated September 2022. This latest version drops discussion of some drugs and adds others. *See* I-MAK, *Overpatented, Overpriced: Curbing Patent Abuse: Tackling the Root of the Drug Pricing Crisis*, 1 (2022), <https://www.i-mak.org/wp-content/uploads/2022/09/Overpatented-Overpriced-2022-FINAL.pdf> [https://perma.cc/MV9X-XYMU]. I-MAK also released what it calls the "I-MAK Drug Patent Book," which lists the patents and patent applications counted for each drug covered in its reported. *I-MAK Drug Patent Book*, I-MAK, <https://www.i-mak.org/patent-methods/> [https://perma.cc/C97Z-8JFA].

¹⁴⁴ *E.g.*, I-MAK, *Overpatented: 2022 Key Findings Report* (2022), <https://www.i-mak.org/wp-content/uploads/2023/01/Overpatented-Overpriced-2023-01-24.pdf> [https://perma.cc/85K5-GCND].

however, within its scope. In addition to repeating the claims about ritonavir and lopinavir that appear in the *Secondary Patenting* article just mentioned, the I-MAK report discusses Revlimid (lenalidomide), Eliquis (apixaban), Xarelto (rivaroxaban), Eylea (aflibercept), Lyrica (pregabalin), and Imbruvica (ibrutinib).¹⁴⁵ As to each, it notes the initial approval date, states a number of “patent applications” and a number of “issued patents,” and then states a number of “years blocking competition.”¹⁴⁶ An example illustrates the approach: I-MMAK reports that Eliquis (apixaban) has been “on the market since 2012,” and is associated with forty-eight patent applications, twenty-seven issued patents, and thirty-four “years blocking competition.”¹⁴⁷

Professor Robin Feldman’s work counting both patents and exclusivities, discussed in the next part of this Article, rounds out the primary empirical literature on “evergreening” with which this Article engages.¹⁴⁸ We refer broadly to her paper and the subsequent public database and raw dataset as the “Hastings Project.”

II. THE HASTINGS PROJECT

A. *The Hastings Database and Dataset*

The Hastings Database traces its provenance to Professor Robin Feldman’s piece, *May Your Drug Price Be Evergreen*.¹⁴⁹ The Feldman paper presents the results of an exhaustive review of data entries in the Orange Book from January 2005 through December

¹⁴⁵ *Overpatented*, *supra* note 143.

¹⁴⁶ I-MAK explains that this represents the span of time from the earliest *filing* of a patent application to the latest *potential* expiration date (which they always add on an active patent application that is “not yet an issued/granted patent”). *See Overpatented*, *supra* note 143, at 12–13.

¹⁴⁷ *See id.* at 7.

¹⁴⁸ The text of this Article does not exhaustively list the relevant empirical papers. Other papers reach similar conclusions on the basis of different datasets. *See, e.g.*, Kate S. Gaudry, *Evergreening: A Common Practice to Protect New Drugs*, 29 NAT. BIOTECHNOLOGY 876, 876 (2011) (counting patents and exclusivities associated, by 2011, with new drug applications approved from 2000 to 2010).

¹⁴⁹ Feldman, *May Your Drug Price be Evergreen*, *supra* note 13.

2015.¹⁵⁰ The team recorded all patents and exclusivities listed in the Orange Book during that eleven-year window, noting the new drug applications with which they were listed, the dates they were added to the publication, and the expiration dates cited.¹⁵¹ On the basis of these data, the paper reports various trends over the eleven years. For instance, it states, the number of “drugs” with patents and exclusivities added after approval has been increasing.¹⁵² (The paper uses the common convention of referring to the number of “drugs” with patents and exclusivities, though in fact the count refers to the number of approved NDAs with patents and exclusivities.) So has the number of drugs with orphan drug exclusivity added after initial approval, as well as the number of drugs with new clinical investigation exclusivity tied to labeling for a new patient population.¹⁵³ *May Your Drug Price Be Evergreen* also presents data in various graphs and tables, for instance showing the number of drugs for which patents were added to the Orange Book each year and the number of drugs for which exclusivity was added each year.¹⁵⁴ The

¹⁵⁰ See *id.* The FDA historically issued the Orange Book in hard copy; now it releases the book electronically in PDF form at the beginning of every year, and it releases twelve cumulative supplements in PDF form over the course of each year. (In other words, each monthly supplement reflects all changes since the last annual edition.) In addition to listing reference drugs approved on the basis of safety and effectiveness, the Orange Book lists patents and statutory exclusivity associated with those drugs. See 43d ORANGE BOOK, *supra* note 19, at ADA1-ADA420. FDA maintains the same information in a searchable electronic database on its website. See FDA, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm> [<https://perma.cc/R4NS-EV7T>].

The print/PDF versions and database list only patents and exclusivity that have not expired. For instance, the most recent PDF publication (the 43d edition) and today’s database (link above) list no patents for Eli Lilly’s original Prozac product, which contained 20mg capsules of fluoxetine and was approved in December 1987 (NDA No. 18936), although the company listed patents at the time, each of which can be found in the annual print editions published before it expired. *E.g.*, 9th ORANGE BOOK (1989) at AD18.

The Hastings team compiled its dataset from a complete collection of the annual edition and monthly supplements of the Orange Book from 2005 through 2015, supplementing with NDA approval dates taken from the Drugs@FDA database on FDA’s website. Feldman, *May Your Drug Price be Evergreen*, *supra* note 13, at 590, 606.

¹⁵¹ Feldman, *May Your Drug Price be Evergreen*, *supra* note 13, at 605–11.

¹⁵² *E.g.*, *id.* at 597, 618–23.

¹⁵³ See *id.* at 623–26 (discussing orphan drug exclusivity), 626–28 (discussing new patient population exclusivity).

¹⁵⁴ *Id.* at 620 tbl.3, 621 tbl.4.

paper concludes with a series of claims that are both empirical and at least implicitly normative. Three are relevant here.

First, the paper presents a trend line showing the number of drugs each year for which brand companies added a “high quantity” of patents in that single year, defining “high quantity” as three or more.¹⁵⁵ “There was,” Feldman writes, “a clear increase in the number of drugs with three or more added patents in a single year between 2005 and 2015.”¹⁵⁶ Indeed, she notes, the number “more than doubles from 37 drugs in 2005 to 76 drugs in 2015.”¹⁵⁷

Second, the paper states the number of discrete “occasions” each drug’s Orange Book entry was amended to include a patent or exclusivity.¹⁵⁸ To be more precise, the author counted the number of *months* in which each drug’s entry was amended with a new patent or exclusivity, regardless of the number of additions in that month.¹⁵⁹ A table presents the number of drugs with one instance of amendment (267), the number with two (212), and so forth.¹⁶⁰ The author uses the term “serial offenders” to describe drugs that “repeatedly returned to the well.”¹⁶¹ She concludes that “a surprisingly large percentage of drugs returned to the well repeatedly.”¹⁶² Of the drugs that had at least one addition to the Orange Book (one month in which a protection, or more than one, was added), the paper reports, 80% had additions more than once, and 20% had additions on seven or more occasions.¹⁶³

Third, the paper concludes with a metric that forms the basis for the author’s “evergreening” thesis. It presents the percentage of the top 105 best-selling drugs from 2005 to 2015 that had “extensions” of their “protection cliffs.”¹⁶⁴ The author defines “extension” of the “protection cliff” as occurring if, after initial NDA approval, a new patent or exclusivity was added to the Orange Book and expired later

¹⁵⁵ *Id.* at 632.

¹⁵⁶ *Id.*

¹⁵⁷ *Id.*

¹⁵⁸ *Id.* at 634.

¹⁵⁹ *Id.*

¹⁶⁰ *Id.* at 635, tbl.7.

¹⁶¹ *Id.* at 634.

¹⁶² *Id.*

¹⁶³ *Id.*

¹⁶⁴ *Id.* at 638–39; *see* tbl.10.

than the “original” set of protections—meaning those listed within two months of initial approval.¹⁶⁵ After this table, she summarizes her findings: “Out of the 106 top-selling drugs from between 2005 and 2014, more than 70% had their protection cliff extended at least once and more than 50% had their protection cliff extended more than once.”¹⁶⁶ This, the paper asserts, “highlights the extent to which stifling competition has become the norm in the pharmaceutical industry.”¹⁶⁷

May Your Drug Price Be Evergreen was based on a dataset that included every new drug application listed in the Orange Book between 2005 and 2015.¹⁶⁸ In September 2020, the University of California Hastings College of Law launched the “Evergreen Drug Patent Database,” which covers an additional three years, i.e., 2015 through 2018.¹⁶⁹ Rather than raw data, however, this electronically searchable database contains analysis (data selection and interpretation) similar to that in the article. The website hosts refer to the database as an “aggregate dataset” rather than a “raw dataset.”¹⁷⁰ The launch page explains the significance of the database: it “reports drug patent extensions by pharmaceutical companies from 2005 to 2018 on brand-name drugs, listed in the [Food and] Drug Administration’s Orange Book, that may have been taken to prolong patents for trivial reasons.”¹⁷¹ We refer to this database as the “Hastings Database.”

¹⁶⁵ *Id.* at 616 n.112.

¹⁶⁶ *Id.* at 638.

¹⁶⁷ *Id.*

¹⁶⁸ *Id.* at 590.

¹⁶⁹ *See About*, *supra* note 15 (“In her study, Feldman analyzed the patents filed with the United States Patent and Trademark Office between 2005 and 2015 for all brand-name, small-molecule drugs on the market, as identified by the Federal Drug Administration’s ‘Orange Book’ of approved drugs. The analysis required combing through 160,000 data points to examine every instance where a company added a new patent or exclusivity. The analysis plus additional data through 2018 are included in the Drug Patent Search Database.”).

¹⁷⁰ *Hastings Raw Dataset*, *supra* note 15.

¹⁷¹ HASTINGS DATABASE, *supra* note 14. This sentence claims that continuing innovations that merited a patent in the view of the U.S. Patent and Trademark Office or that required supporting clinical data (other than bioequivalence data) in the view of FDA were, nevertheless, “trivial.” We presume physicians and payers would reject newer more expensive medicines without clinically meaningful differences. *See infra* Part III.C.

For each approved NDA within the underlying dataset, the Hastings Database provides fifteen fields of information.¹⁷² Of particular interest here, it reports:

The “earliest protection end date after 2005,” which it explains as “the earliest expiration date of any of the protections granted for a drug”,¹⁷³

The “latest protection end date as of 2018,” which it explains as “the latest expiration date of any of the protections granted for a drug”,¹⁷⁴;

The “months added to the protection time via extensions and exclusivities,” which it explains as “the number of months between the latest and earliest protection end dates, rounded down to ensure a conservative estimate” and which it claims represents “the amount of additional time for which a company may have limited generic competition and monopolized a drug product”¹⁷⁵;

The “number of unique patents associated with a new drug application,” which means “the total count of all patents associated with an NDA”¹⁷⁶; and

The “total number of time extensions associated with a new drug application,” which it defines as “the number of protections that: 1) were added after the initial set of protections and 2) extended the

¹⁷² These fields appear when one uses the search tool on the Hastings website. The information in the Hastings Database fields can also be downloaded, but the fields in the download file are labeled slightly differently. *Id.*

¹⁷³ A footnote on the website clarifies that the records in the dataset “begin in 2005 and therefore do not include pre-2005 protection end dates.” *About, supra* note 15. In other words, the team worked with Orange Books beginning with the 2005 annual edition. For the most part, this edition would not have included patents or exclusivities expiring in 2004 or earlier. Therefore, the Hastings team would not have captured them.

That said, some expired patents and exclusivities remain listed in the Orange Book after their expiry, briefly, probably due to oversight at the FDA. The Hastings team appears to have captured them. Our audit indicates that the Hastings Raw Dataset actually *does* include protections expiring before 2005, and indeed the Hastings Database sometimes returns a pre-2005 date for the “earliest protection end date after 2005.” This is the case for NDA No. 21066, for instance; the Hastings Database returns 7/2/2004 (the end of NCE exclusivity) for the earliest protection end date. HASTINGS DATABASE, *supra* note 14.

¹⁷⁴ *About, supra* note 14, at col. 8.

¹⁷⁵ *Id.* at col. 9.

¹⁷⁶ *Id.* at col. 11.

time period of protection.”¹⁷⁷ A note explains that the initial set of protections comprises any patent or exclusivity added to the Orange Book within one month of approval.¹⁷⁸

After initial release of the Hastings Database, the website hosts added a link to the “Evergreen Raw Dataset,” which it describes as the “raw dataset used to create the aggregated dataset” (i.e., the searchable database).¹⁷⁹ The website explains that “the raw dataset is what we used as the basis for the calculations in the “Evergreen Patent Database,” but it does not include the calculations.”¹⁸⁰ We refer to this dataset as the “Hastings Raw Dataset.” Like the Hastings Database, the Hastings Raw Dataset can be searched online or downloaded.

B. The Hastings Inference

The “evergreening” claim relates to the fact that brand drug companies protect their brand drugs with what advocates view as too many patents and exclusivities. These patents and exclusivities are problematic, in the view of reform proponents, because they permit advantageous exclusivity-based pricing, i.e., in a market free of generic competition. (Advocates of reform generally discount the possibility of price competition from other branded products.) The sheer number of patents is problematic, some say, because each presents a hurdle that must at least be addressed by generic applicants.¹⁸¹ And, more relevant here, patents and exclusivity secured after initial approval are problematic, these advocates argue, because their later expiry dates push generic competition later and later.¹⁸²

An example illustrates the role that the Hastings Database plays in these policy discussions. Consider Gleevec (imatinib mesylate), initially approved by FDA in May 2001 for treatment of patients

¹⁷⁷ *Id.* at col. 14.

¹⁷⁸ As noted, the Feldman’s original paper defined the initial set of protections to include any listed in the Orange Book within the first two months after approval. *See supra* text accompanying note 165.

¹⁷⁹ *Hastings Raw Dataset*, *supra* note 15.

¹⁸⁰ *Id.*

¹⁸¹ *E.g.*, Feldman, *May Your Drug Price be Evergreen*, *supra* note 13, at 600.

¹⁸² Indeed, this is the essence of the “evergreening” argument. *See generally supra* part I.C.2.

with chronic myeloid leukemia, a type of blood cancer.¹⁸³ The Hastings Database contains a row for this initial new drug application (No. 21335). It tells us that the “earliest protection end date” was December 20, 2005, and that the “latest protection end date” was June 19, 2022.¹⁸⁴ And it tells us that Novartis therefore had 198 months (sixteen years and six months) of “additional” protection time, which it claims is “the amount of additional time for which a company may have limited generic competition and monopolized a drug product.”¹⁸⁵ In other words, an advocate of policy reform might say, an “Evergreen Drug Patent Search” on the Hastings website tells us that Novartis may have secured more than sixteen additional years of “monopoly.” The inference is that the “months added” field in the database reports the result of “evergreening.”

Curiously, though, a generic version of Gleevec launched in February 2016—quite a bit earlier than June 2022.¹⁸⁶ Indeed, this Article was prompted by intuition that the three key metrics (earliest protection end date, latest protection end date, and months “added”) might not be reliable indicators of anything, or at least anything consistent from one drug to the next, and that the proposed inference might be inherently unsound. This intuition stems from three observations about new drug regulation and innovation incentives, as follows.

First, the FDA approves finished products, rather than active ingredients. The statute requires approval of each “new drug,” but the term “drug” has more than one meaning at the agency.¹⁸⁷ Depending

¹⁸³ The price of Gleevec has attracted attention over the years. See, e.g., Robin Feldman, *Perverse Incentives: Why Everyone Prefers High Drug Prices—Except for Those Who Pay the Bills*, 57 HARV. J. ON LEGIS. 303, 305 n.3 (2020) (citing Michael G. Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, 39 AM. J. CLINICAL ONCOLOGY 210, 211 (2015) (discussing imatinib, a treatment for chronic myelogenous leukemia, which cost \$30,000 a year when it was introduced in 2001, but whose price had more than tripled to \$92,000 a year by 2012)).

¹⁸⁴ HASTINGS DATABASE, *supra* note 14.

¹⁸⁵ *Id.*

¹⁸⁶ See *Paragraph IV Patent Certifications*, FDA (Feb. 6, 2023), <https://www.fda.gov/media/133240/download> [<https://perma.cc/2BMC-GBDR>].

¹⁸⁷ Professor Feldman’s paper notes this issue. Feldman, *May Your Drug Price be Evergreen*, *supra* note 13, at 607–08 (“The term ‘drug’ can have several different meanings, depending on the chosen definition and context. For example, one can choose to define a drug on the level of the active ingredient, the branded product name, the specific

on the statutory provision or regulation at issue, the term may mean only a finished drug product, only an active ingredient, or both.¹⁸⁸ For instance, the statute requires FDA to publish a list of approved drugs, but the Orange Book actually lists approved products.¹⁸⁹ The pediatric exclusivity provision refers to extending various exclusivities relating to the “drug” studied, but the agency interprets this to mean extending any exclusivity applicable to any product containing the same active moiety.¹⁹⁰ And although approval is required for every new “drug,” if a product (drug) is new, it requires approval, even if the active ingredient (drug) has been approved before.¹⁹¹ Thus FDA approves discrete products—e.g., Prozac (fluoxetine) in 20mg capsules—rather than a “brand” writ large (all Lilly products marketed under the brand name “Prozac”) or an active ingredient (all Lilly products containing fluoxetine).¹⁹²

Further, each new drug application may cover more than one product. The FDA considers different strengths of what is otherwise the same presentation (active ingredient, route of administration, and dosage form) to be discrete products.¹⁹³ And it approves them

new drug application number, or the specific strength or formulation For our analysis, we chose to define ‘drug’ at the level of the new drug application number”).

¹⁸⁸ See Lietzan, *Evergreening Metaphor*, *supra* note 3, at 858. See *supra* Part I.A. for discussion of these terms.

¹⁸⁹ Compare 21 U.S.C. § 355(j)(7) (directing FDA to publish a list of “each drug which has been approved for safety and effectiveness”) with 43D ORANGE BOOK, *supra* note 19, at iv (stating that it “identifies drug products approved on the basis of safety and effectiveness”).

¹⁹⁰ See *Guidance: Qualifying for Pediatric Exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A)*, FDA (Mar. 1, 2023), <https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently> [<https://perma.cc/B96M-5SYF>].

¹⁹¹ See *supra* note 31 and accompanying text.

¹⁹² E.g., FDA, Approval Letter NDA No 21235, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2001/21235ltr.pdf [<https://perma.cc/4SNP-2YKE>] (approving Prozac Weekly delayed release 90 mg capsules for use in the treatment of depression).

¹⁹³ E.g., 43D ORANGE BOOK, *supra* note 19, at 2-1 (noting that discrete *products* are sorted by active ingredient, dosage form, route of administration, dosage form, route of administration, product name, applicant, and strength); FDA, GUIDANCE, REFERENCING APPROVED DRUG PRODUCTS IN ANDA SUBMISSIONS 5 (Oct. 2020) [hereinafter REFERENCING PRODUCTS], <https://www.fda.gov/media/102360/download> [<https://perma.cc/GRV5-JF8X>] (“Each strength of a drug is a distinct drug product and, therefore, a distinct listed drug.”).

as separately numbered products on the same approved NDA; for instance, the 20mg and 40mg capsules of fluoxetine marketed by Lilly under the name Prozac are discrete products (001 and 003) on a single new drug application (No. 018936).¹⁹⁴ A company might propose multiple strengths in its initial application, or it might seek approval of additional strengths over time in supplements. In either case, the result is a set of discrete products covered by the same approved application. As also noted earlier, in contrast with a differing strength, a different dosage form or route of administration results in a discrete product that must be the subject of its own NDA.¹⁹⁵ Thus, Lilly's extended-release capsules of fluoxetine required a separate NDA (No. 021235), as did its oral solution (No. 020101), and tablets at two different doses (two separate products on No. 020974).¹⁹⁶

Second, patents protect inventions, rather than products or active ingredients.¹⁹⁷ A single product may embody numerous discrete inventions and therefore be associated with multiple listed patents.¹⁹⁸ Conversely, multiple discrete products may embody the same invention and therefore be associated with the same listed patent.¹⁹⁹ Thus, a single approved application may cover multiple discrete products—which may be protected by some of the same patents as well as differing patents.²⁰⁰ Further, a brand company may hold multiple approved applications for products containing the same active ingredient (for instance, for differing routes of administration), and these might be protected by the same set of patents, or each might

¹⁹⁴ 43D ORANGE BOOK, *supra* note 19, at 3-205.

¹⁹⁵ 43D ORANGE BOOK, *supra* note 19, at 2-1

¹⁹⁶ See Search Results for “Prozac” on Drugs@FDA:FDA-Approved Drugs, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> [https://perma.cc/M2Z5-9ZNS].

¹⁹⁷ 35 U.S.C. § 101 (“inventions patentable”).

¹⁹⁸ Consider, for instance, “Product 001” on NDA No. 21908, which covers Amtiza (lubiprostone), for which there are four listed patents. See 43D ORANGE BOOK, *supra* note 18, at ADA258.

¹⁹⁹ To continue the example from the prior footnote, Product 002 on the same NDA is also covered by the same four listed patents, as well as a fifth patent. See *id.*

²⁰⁰ For example, in our dataset, NDA No. 20239, which covers Kytril (granisetron hydrochloride), was listed with U.S. Patent Nos. 4886808, 6294548 (products 1, 2, and 4), and 5952340 (products 1, 2, and 4), and Minivelle (estradiol), approved via NDA No. 203752, was listed with U.S. Patent Nos. 6841716, 5656286, 6024976, 8231906, 9730900, 9833419, and 9724310, but the last of these was listed only for product 5 on the NDA.

also have some unique patents.²⁰¹ The active ingredient patent (if there is one) would be listed with each product under each approved NDA, for instance, but the other patents might vary.²⁰² And whether they expire on the same day as the active ingredient patent, or later, may vary.²⁰³ A generic drug applicant chooses a single reference product, however, and will address only the patents that claim *that* drug (product) or approved methods of using *that* drug (product).²⁰⁴

Third, three-year statutory exclusivity—and seven-year orphan exclusivity, for that matter—protects *conditions of use*, rather than active ingredients.²⁰⁵ The initial new chemical entity exclusivity, much like the active ingredient patent, will protect every product on every relevant NDA until its expiry.²⁰⁶ But three-year exclusivity precludes approval of a generic drug only for the condition of use supported by the qualifying clinical data.²⁰⁷ It does not protect (prevent approval of a generic drug containing) the active ingredient for other conditions of use.²⁰⁸ For example, if the brand company obtains three years of exclusivity for a new strength, which will be listed as a new product under the same NDA, FDA may approve a generic version in the other strengths—copies of the other products—in the meantime. To give another example, if the brand company adds a new indication, or another new condition of use (such as a new patient population), to the labeling of its products under the NDA, FDA will generally approve generic drugs with labeling that omits these words.

To summarize, then: A single new chemical entity may be covered by multiple new drug applications, each of which in turn may

²⁰¹ For example, in our dataset, NDA No. 20978, which covers Ziagen (abacavir) oral solution, was listed with U.S. Patent Nos. 5089500, 5034394, 6294978, 6294540, and 6641843, while Ziagen (abacavir) tablets, approved via NDA No. 20977, was listed with only U.S. Patent Nos. 5089500, 5034394, and 6294540.

²⁰² See 21 C.F.R. § 314.53(b) (indicating that a patent meets the listing standard—“claims the drug . . . that is the subject of the NDA . . . and with respect to which a claim of patent infringement could reasonably be asserted”—if the patent claims the drug substance “that is the same as the active ingredient” of the product that is the subject of the application).

²⁰³ See *supra* Part I.B.1.

²⁰⁴ See 21 U.S.C. § 355(j)(2)(A)(vii).

²⁰⁵ See 21 U.S.C. §§ 355(c)(3)(E)(iii) & (iv); 355(j)(5)(F)(iii) & (iv); 360cc(a)(2).

²⁰⁶ See *supra* Part I.B.2.

²⁰⁷ See *id.*

²⁰⁸ See *id.*

cover multiple discrete products.²⁰⁹ Each product will be listed separately in the Orange Book with only the patents and exclusivities relevant to that product, and these protections will vary.²¹⁰ A generic applicant will cite a specific product (or more than one, in the case of strengths) in its own application.²¹¹ Patents and exclusivities relevant to other products on the NDA, or to other NDAs for the same chemical entity, are irrelevant; they have no effect on the timing of generic drug applications or approval.²¹² And some do not preclude generic drug approval at all.²¹³

From these points, we draw two conclusions that suggest not only that the Hastings inference is unsound but also that patent and exclusivity counting exercises, in general, are unhelpful. *First*, the very last date on which any patent or exclusivity expires for a particular NDA (or even for all products containing a particular active ingredient) is very unlikely to be the earliest point at which a generic drug might have entered the market, at least as far as patents and exclusivity are concerned. More than likely, other discrete products from the same brand company with the same active ingredient will have lost their protections sooner. *Second*, the last date on which a particular brand product's patents and exclusivity expire may itself not be the earliest a generic company might receive approval of an abbreviated application based on that very brand product. This is because many later-arising patents and exclusivities pertain only to specific indications or conditions of use and do not preclude generic drug approval²¹⁴. For both reasons, in our view, patent and exclusivity counting exercises tell policymakers very little about actual prospects for generic competition. The inference proposed in the Hastings Database seems inherently unsound.

²⁰⁹ See *supra* text accompanying notes 192–96.

²¹⁰ See *supra* Part I.B.

²¹¹ See 21 U.S.C. § 355(j)(2)(A)(vii); See also REFERENCING PRODUCTS, *supra* note 193, at 4–5.

²¹² See *supra* Part I.B.

²¹³ See *id.*

²¹⁴ See *supra* Part I.B.2.

III. OUR PROJECT

To explore our suspicion about the inference proposed in the Hastings Database, we decided to investigate whether the “latest protection end date” reported in the Hastings Database corresponds with the actual timing of generic competition. We describe our dataset, methodology, and findings below.

A. Dataset and Methodology

Generic market launch dates are hard to come by, if one is limited to public domain sources. We used the complete set of new drug applications for which the FDA has published the date of first commercial marketing by a generic applicant. These generic launch dates are published in connection with the agency’s administration of the 180-day exclusivity incentive for generic applicants who challenge brand patents.²¹⁵ The first company to submit a paragraph IV certification in an ANDA referencing a particular brand product is eligible for a 180-day exclusivity period during which the FDA will not approve subsequent ANDAs also containing paragraph IV certifications to the same brand product.²¹⁶ This generic company is known as the “first filer.” The FDA publishes a table that lists, product by product, the approval date for the first filer’s ANDA and the commercial launch date of the first filer’s generic drug.²¹⁷ We call this the “First Filer Table.”

²¹⁵ FDA publishes a table of the launch dates; see *Paragraph IV Patent Certifications*, *supra* note 186.

²¹⁶ See 21 U.S.C. § 355(j)(5)(B)(iv). The scheme has been amended since 1984, most notably in 2003. See generally Erika Lietzan & Julia Post, *The Law of 180-Day Exclusivity*, 71 FOOD & DRUG L.J. 327 (2016). Since 2003, this exclusivity has been awarded on a product-by-product basis; i.e., each brand product (thus each strength, on a single NDA) can produce a separate exclusivity period. *Id.* at 343.

²¹⁷ See *Paragraph IV Patent Certifications*, *supra* note 186. We used the version dated May 17, 2022. Although the First Filer Table generally proceeds product by product, if a single first filer sought to market two strengths (products) of a brand product and launched both at the same time, the FDA conveys this information in one row of the table. For instance, the two dosage forms of Fosamax (alendronate sodium)—oral solution and tablets—are distinct products and covered by separate NDAs. They are listed separately. The five strengths of Fosamax tablets are also distinct products, with distinct product numbers under the same NDA, but they were the subject of a single first filer ANDA, so FDA lists them together in the same row. *Id.*

The first filers for which the FDA had listed commercial launch dates as of May 17, 2022, formed the basis for our dataset. The Hastings Database does not distinguish among products on a single NDA, however. Rather, it offers patent and exclusivity information, new drug application by new drug application. Our dataset therefore comprises all 224 brand NDAs in the Hastings Database for which the FDA reported, by May 17, 2022, a first filer (generic drug) launch date.²¹⁸ Some brand drugs in our dataset are decades old; the earliest approved new drug application is NDA No. 012827 for Robinul Forte (glycopyrrolate), which took effect in August 1961. The latest approved application is NDA No. 208686 for Epaned (enalapril maleate), which the FDA approved in September 2016. The dataset contains seventy-nine new chemical entities, a complete list of which appears in the appendix. The first filer commercial launch dates range from June 15, 2006, for generic venlafaxine hydrochloride to January 4, 2022, for generic glycopyrrolate (based on the brand drug, Cuvposa).

For the NDAs in our dataset, we captured information from the First Filer Table: the NDA number, the brand name, the active ingredient(s), dosage form(s), and strength(s), as well as the date on which the FDA approved the first filer's ANDA and the date of first commercial marketing by the first filer. Using two databases on the FDA's website, we added the NDA approval dates and, where applicable, the product number(s) under the NDA that correspond to the strength(s) marketed by the first filer.²¹⁹

For each NDA, we then manually compiled a list of the patents and exclusivities listed in every annual Orange Book from the first edition to contain this information (the 6th Edition, in 1985) to the most recent annual edition available at the time we performed our

²¹⁸ In a few cases, different first filers applied for approval of different strengths of the same brand product, and the First Filer Table listed these first filers in separate rows (even though the brand NDA was the same in both cases). Because we are interested in the first launch of any generic drug based on a single NDA, we captured the earliest launching of these first filer drugs and ignored the additional rows.

²¹⁹ We used the Drugs@FDA database, available at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm> [https://perma.cc/8S76-39AY], to obtain the NDA approval dates and the electronic Orange Book database to correlate strengths with product numbers.

analysis (the 42nd Edition, dated 2022).²²⁰ If a patent or exclusivity did not attach to every product on the NDA, we recorded the subset to which it did attach. If the expiry date changed in subsequent editions of the Orange Book, we recorded the change. We also determined the reason for the change, using publicly available information from the PTO website. Most changes pushed the date later, and most of these reflected an award of patent term restoration (also called “extension”) under 35 U.S.C. § 156.²²¹ In some cases, a change reflected PTO’s recalculation of patent term adjustment under 35 U.S.C. § 154²²² or implementation of the 1995 change in the law governing calculation of patent terms.²²³ In a few other cases,

²²⁰ This was performed initially by a research assistant, and then one author (Lietzan) rechecked every entry. Some data entry errors remain a possibility.

²²¹ Section 156 of the Patent Act permits extension of a patent claiming a drug, a method of using the drug, or a method of manufacturing the drug, if the drug went through the NDA approval process. 35 U.S.C. § 156. Only one patent per NDA may be extended, and the extension is available only if the FDA has not previously approved the active ingredient (or its salt or ester) in another NDA. *Id.* The length of the extension depends on the length of the premarket clinical testing program and the amount of time FDA spent reviewing the application; it is capped at five years; and the extended patent may not expire more than fourteen years after NDA approval. *Id.* Various other products subject to premarket approval by the FDA and USDA are also eligible for patent term restoration. *Id.* For more information, see Lietzan & Acri, *Distorted Drug Patents*, *supra* note 34. To determine whether a change in the expiration date reflected application of section 156, we reviewed the patent’s Image File Wrapper available at the time through the PTO’s Public Patent Application Information Retrieval (PAIR) system. This usually contains the company’s request for patent term restoration, the Patent Office’s decision (“notice of final determination”), and the patent extension certificate. PTO retired the Public PAIR system in July 2022.

²²² Section 154(b) of the Patent Act governs patent term adjustment (PTA), which extends the term of a patent to accommodate delays in patent issuance caused by PTO during patent prosecution. All patentees—not just drug patent owners—are eligible for this. 35 U.S.C. § 154(b). The current provision, which dates to 1999, states various deadlines for stages in the patent prosecution—such as three years for completion of the entire process (subject to various exceptions)—and generally requires a day of adjustment for each day of delay beyond the stated deadlines. 35 U.S.C. § 154(b). For example, the entry for Veletri (epoprostenol sodium) (NDA No. 022260) includes U.S. Patent No. 8318802, which was initially listed as expiring on February 9, 2027. The expiry was later changed to March 15, 2027, which reflects the fact that PTO recalculated patent term adjustment under § 154.

²²³ In 1984, a patent lasted for seventeen years from its issuance date. 35 U.S.C. § 154 (1982). In the Uruguay Rounds Agreement Act (URAA) of 1994, Congress revised the provision of the Patent Act governing the patent term. For patents issued on applications filed on or after June 8, 1995, the term is twenty years from the patent application or, if the application refers to an earlier-filed application, twenty years from the date of that

the expiry date moved earlier, apparently due to a terminal disclaimer.²²⁴

Finally, we retrieved four fields from the Hastings Database for each NDA in our dataset: the earliest protection end date after 2005, the latest protection end date as of 2018, the “months added” to the protection time via extensions and exclusivities, and the number of unique patents associated with the application.²²⁵

B. Findings

As described below, we performed four analyses with our data.

First, we counted the number of patents listed in the Orange Book in connection with each new drug application. We made one adjustment to the apparent count, as follows. Sometimes the PTO reissues patents, including patents already listed in the Orange

application. Uruguay Round Agreements Act, Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4983-84. A change of expiry in the Orange Book reflects the fact that patents in force on June 8, 1995, and patents that issued on applications filed before that date, received the benefit of this change in the law—meaning that after June 1995 the expiry was recalculated using whichever formula was more favorable. *See* 35 U.S.C. § 154(c)(1). In other words, if a patent issued before June 1995, the Orange Book would initially list expiry seventeen years from issuance; but after June 1995, the Orange Book would show expiry twenty years from application, if that date was later. For example, the entry for Effexor (venlafaxine hydrochloride) (NDA No. 020151) includes U.S. Patent No. 4535186, which was originally slated to expire on August 13, 2022. After enactment of the URAA, the patent expiry changed to December 13, 2002. The change in patent term in 1994 applied to all patentees, not just drug patent owners.

²²⁴ A terminal disclaimer, which a patent owner files at the PTO and which can be filed at any time during the life of a patent, causes the patent to expire on the same date as an earlier patent and is typically filed to avoid invalidation of the patent on obviousness grounds. *See* Lietzan & Acri, *Distorted Drug Patents*, *supra* note 34, at 1344 n.135.

For instance, for NDA No. 020741, U.S. Patent No. 5216167 was initially listed as expiring on October 10, 2006, and then, after it received 921 days of extension under 35 U.S.C. § 156, listed as expiring on April 18, 2009. It later reissued as RE37035 with an expiry of March 14, 2009. This seems to reflect a terminal disclaimer to U.S. Patent No. 4863724 (leading to expiry on September 5, 2006) plus addition again of the 921 days of PTE (to reach March 14, 2009). To give another example, the Orange Book entry for NDA No. 207917 includes U.S. Patent No. 8445543, which was initially listed as expiring on July 12, 2027, and later listed as expiring on December 13, 2022. This, too, appears to stem from a terminal disclaimer.

²²⁵ To do this, a research assistant downloaded an Excel version of the Hastings Database and created an automatic “lookup” function in Excel. One author (Lietzan) then rechecked every entry using the online database search tool.

Book.²²⁶ In these cases, the Orange Book entry usually substitutes the new number for the old number, but sometimes it briefly contains both numbers. In either case, over time the Orange Book entry for the product shows two separate numbers for what is actually the same patent. In these situations, we counted the original patent and reissued patent as *one* patent.²²⁷ Otherwise, we counted every individual patent listed with an NDA.²²⁸ The new drug applications in our dataset averaged five listed patents (mean 5.07, median 4), and seventy-four (74) of the 224 (33%) had two or fewer listed patents. Twenty-two (22) (9.8%) had ten or more patents, and three (1%) had twenty or more listed patents.²²⁹

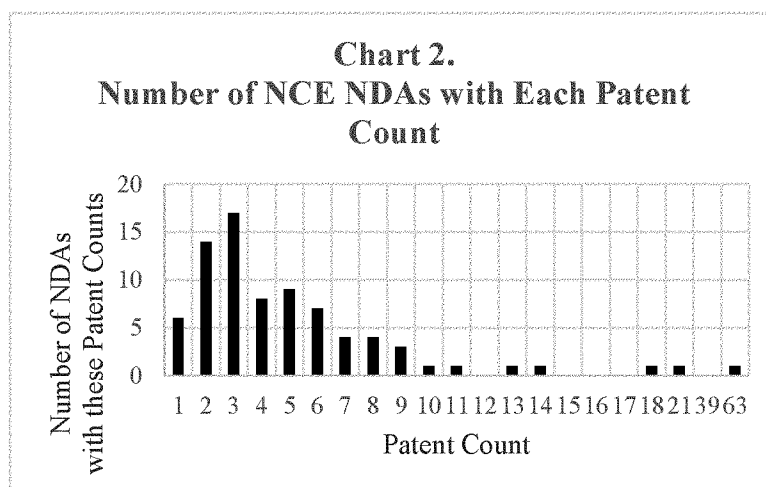
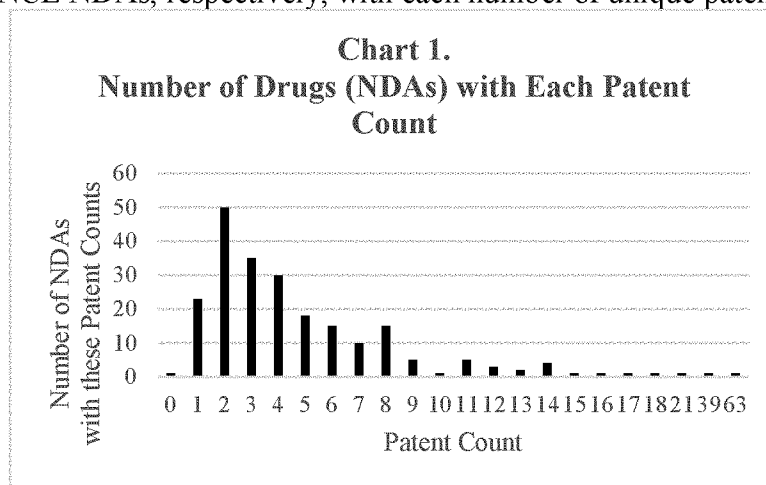
²²⁶ A patent may be reissued to correct certain types of error; in this case the patent number changes (and now begins with “RE”) but the term remains the same. *See* 35 U.S.C. § 251. Technically, the old patent has been surrendered and replaced with the reissued patent.

²²⁷ For instance, the Orange Book entries for Kuvan (sapropterin dihydrochloride) NDA No. 022181 include U.S. Patent No. 7947681, as well as RE43797, which is actually a reissue of the same patent. To determine whether a reissue patent was the same as an earlier listed patent, we looked at the reissue patents; under “Related U.S. Patent Documents” on the first page, a reissue patent identifies by number the patent it is reissuing.

²²⁸ We know, however, that at least two patent listings (which we counted) resulted from errors in the Orange Book. NDA No. 207917, for Epiduo Forte (adapalene and benzoyl peroxide), was initially listed with U.S. Patent 8809305, but this was corrected to U.S. Patent 8909305. NDA No. 020978, for Ziagen (abacavir), was briefly listed with U.S. Patent 6294978, which claims a high current fuse for vehicles. These are likely mistakes but because we did not systematically review the listed patents, we did not exclude them.

²²⁹ IMOmax (nitric oxide) (NDA No. 020845) had twenty-one listed patents, Hysingla (hydrocodone bitartrate) (NDA No. 206627) had thirty-nine, and Vascepa (icosapent ethyl) (NDA No. 202057) had sixty-three.

We analyzed the new chemical entities separately, because these application approvals represent the first-ever approval of the active ingredients in question and because much of the “evergreening” discussion relates to brand companies continuing to innovate with their new molecules. The new chemical entities in our dataset averaged six listed patents (mean 5.58, median 4) and ranged from one patent (six new chemical entities) to more than twenty (two new chemical entities). Charts 1 and 2 show the number of NDAs and the number of NCE NDAs, respectively, with each number of unique patents.



Second, after counting the number of patents in the Orange Book for each new drug application, we compared our number for each with the number identified in the Hastings Database. If our number

differed from that in the Hastings Database, we compared our raw data with the Hastings Raw Dataset to determine the basis for the difference. In most cases, the difference reflected the fact that we had captured patents that expired before 2005 as well as patents listed after 2018; in other words, the scope of our Orange Book review was broader. We also compared our raw dataset with the Hastings Database entries for the “earliest protection end date after 2005” and the “latest protection end date as of 2018” in order to determine *which* patent or exclusivity formed the basis for those entries in the database.²³⁰

Although we had not intended to audit the Hastings Database and Hastings Raw Dataset for actual error, this second step allowed us to identify a handful of errors and gives us a sense of the dataset’s reliability. For three of our 224 NDAs, we found minor mistakes in both the dataset and the database that probably reflect manual data entry errors.²³¹ For two others, we found patents listed in the Orange Book after 2005 and before 2018 that were not included in the Hastings Raw Dataset.²³² And for one NDA, the Hastings Raw Dataset did not pick up a change to an expiration date that was reflected in

²³⁰ In a few instances, we did not have a patent or exclusivity in our dataset with a corresponding expiry date, and review of the Hastings Raw Dataset revealed that a patent or exclusivity in our dataset had been briefly listed with a different (incorrect) expiration date—often only in a monthly supplement to the Orange Book. We verified these additional expiration dates using hard copies of the monthly supplements.

²³¹ For NDA No. 021742, the Hastings Raw Dataset and Database include U.S. Patent No. 5758590, which claims a stacking device for sheet material and appears unrelated to the NDA. They also include, correctly, U.S. Patent No. 5759580, and we assume manual entry error (last four digits of 8590 versus 9580). For NDA No. 019881, the Hastings Raw Dataset and Database include U.S. Patent No. 5993859 (in addition to U.S. Patent No. 5993856, which is correct). The Hastings Raw Dataset states that the patent ending in 859 was added in the November 2009 monthly supplement and the patent ending in 856 in the December 2009 monthly supplement, but we found only the 856 patent in both supplements. For NDA No. 204063, the Hastings Raw Dataset and Database state the wrong expiration date for U.S. Patent 8399514. They state it as February 7, 2018, but it is February 7, 2028.

²³² For NDA No. 206627, the Hastings Raw Dataset and Database omit U.S. Patent Nos. 6488963 (June 24, 2017), 6733783 (October 30, 2021), 8309060 (November 20, 2023), 8361499 (October 30, 2021), 8529948 (August 6, 2022), 8551520 (October 30, 2021), 8647667 (October 30, 2021), and 10369109 (June 16, 2023). For NDA No. 21641, the Hastings Raw Dataset and Database omit U.S. Patent Nos. 5457133 (February 7, 2012) and 6126968 (September 18, 2016).

the Orange Book.²³³ Finally, for eleven NDAs, the Hastings Database counts a patent that reissued as two patents, and the Raw Dataset lists the two patent numbers as if they are separate patents.²³⁴ We found no other errors.

Although we found at least one error in the Dataset entries for seventeen of the 224 new drug applications in our study (7.6% of the applications), the Dataset contains dozens of data entries for each application. Our findings therefore suggest the percentage of data entries that are erroneous is likely to be quite small.²³⁵ Another researcher working from the Orange Books—indeed, even if working from only the annual editions as we did—would by and large generate the same raw dataset. Moreover, not only is the underlying Hastings Raw Dataset essentially accurate, but as a general rule the Hastings Database correctly reports information *from* that dataset, such as, for each NDA, the number of discrete patents (putting aside the problem of double-counting reissued patents) and the patent or exclusivity expiring the earliest after 2005. That said, there might be at least one data error in the Hastings Raw Dataset for around 7.6%

²³³ For NDA No. 20114, the Hastings Raw Dataset did not pick up a correction to the expiration date for the company's three-year exclusivity (coded by FDA as "D-102" for a particular new dosing regimen). The Dataset notes correctly that this exclusivity was recorded in the February 2006 monthly supplement as expiring on February 17, 2007. The March 2006 Orange Book supplement corrected this to February 17, 2009, which was three years after approval of the new dosing regimen, and only the correct 2009 expiration appears in the annual editions. The Hastings Raw Dataset did not capture the change.

²³⁴ These are: NDA No. 021743 (U.S. Patent Nos. 5747498 and RE41065), NDA No. 20554 (U.S. Patent Nos. 5763426 and RE39706), NDA No. 050802 (U.S. Patent Nos. 5721275 and RE41134), NDA No. 022181 (U.S. Patent Nos. 7947681 and RE43797), NDA No. 021852 (U.S. Patent Nos. 5763426 and RE39706), NDA No. 021588 (U.S. Patent Nos. 7544799 and RE43932), NDA No. 020611 (U.S. Patent Nos. 5763426 and RE39706), NDA No. 021540 (U.S. Patent Nos. 5273995 and RE40667), NDA No. 22012 (U.S. Patent Nos. 5760069 and RE40000), NDA No. 021704 (U.S. Patent Nos. 6004582 and RE39069), and NDA No. 022532 (RE37564 and RE38253).

²³⁵ Professor Feldman touches on the likelihood of errors in her 2018 paper, noting that her team manually transferred over 160,000 individual data points from FDA PDFs to its database. The Hastings team double-checked every entry and, in coding the data, reviewed every entry a third time. Feldman, *May Your Drug Price be Evergreen*, *supra* note 13, at 611. This was an appropriate and appropriately robust quality check for a project of this magnitude.

of the NDAs in the database, and some of these will affect the key metrics in and proposed inference from the Hastings Database.²³⁶

Third, after counting the number of patents and assessing any changes in their expiry dates, we calculated each product's actual exclusivity in the market, meaning the number of months from the brand product's approval until the commercial launch of the first filer's generic drug based on that brand product. The 224 new drug applications in our dataset averaged 11.3 years of actual market exclusivity (mean 11.30, median 10.80). The new chemical entities averaged 13.34 years (mean 13.34, median 13.75). This is slightly higher than the finding in our earlier study using a different dataset but generally consistent with that and other studies.²³⁷

Tables 1 and 2 show our market exclusivity results. I-MAK claims that brand companies "abuse" the patent system "to extend

²³⁶ For instance, for NDA No. 204063, the Hastings Raw Dataset records the expiry date of U.S. Patent No. 8399514 as February 7, 2018, when in fact the expiry was February 7, 2028. (The dataset cites the April 2013 monthly supplement to the Orange Book, but our copy of that supplement contains the correct expiration date.) As a result of this error, the Hastings Database uses February 7, 2018, as the earliest protection end date; it should have instead used March 27, 2018, which was the expiry of NCE exclusivity.

²³⁷ E.g., Lietzan and Acri, *Distorted Drug Patents*, *supra* note 34, at 1363 (finding a mean of 12.62 years and a median of 13.28 years for 227 new drugs that received an award of patent term restoration under § 156 between 1984 and 2018, using generic market launch dates purchased from IQVIA); Reed F. Beall et al., *Patent Term Restoration for Top-Selling Drugs in the United States*, 24 DRUG DISCOVERY TODAY 20, 20 (2019) (reporting average exclusivity in the market—time to generic market entry—as 13.75 years for eighty-three top-selling drugs, and identifying a quarter of generic market entry as the one in which a prescription for a therapeutically equivalent generic drug appeared in Medicaid prescription data aggregated by the Centers for Medicare and Medicaid data); Bo Wang et al., *Research Letter: Variations in Time of Market Exclusivity Among Top-Selling Prescription Drugs in the United States*, 175 JAMA INTERNAL MED. 635, 635 (2015) (finding median market exclusivity period of 12.5 years for the 175 drugs that experienced generic competition by the end of 2012, out of the 437 top-selling drugs by sales in the United States between 2000 and 2011, also using Medicaid prescription data as proof of generic competition); Henry Grabowski et al., *Updated Trends in US Brand-Name and Generic Drug Competition*, 19 J. MED. ECON. 836, 839 (2016) (finding that non-biologic drugs experiencing initial generic entry in 2011–2012 had enjoyed 12.9 years of actual exclusivity in the market, and using IQVIA data to confirm generic launch); Henry Grabowski et al., *Continuing Trends in U.S. Brand Name and Generic Drug Competition*, 24 J. MED. ECON. 908, 911 (2021) (finding that new molecular entities experiencing initial generic entry in 2017–2019 had enjoyed 14.1 years of actual exclusivity in the market, and those with sales over \$250 million in 2008 dollars the year before generic entry had enjoyed 13.0 years, using IQVIA data to confirm generic launch).

their monopolies far beyond the twenty years of protection intended under United States patent law.”²³⁸ But 95% of the new drug applications in our dataset (216 of 224) had generic drug competition in the market before twenty years had passed, and 70% (157 of 224) enjoyed fewer than fourteen years of exclusivity.²³⁹ Of the new chemical entity NDAs, 96% (76 of 79) had generic competition before twenty years had passed, and 53% (42 of 79) had generic competition before fourteen years had passed.

Table 1 Actual Market Exclusivity All 224 NDAs in Our Dataset			
Actual Years of Exclusivity	Number of NDAs	Percentage of NDAs	Cumulative Percentage of NDAs
$0 \leq \text{years} < 1$	0	0.00	0.00
$1 \leq \text{years} < 2$	1	0.45	0.45
$2 \leq \text{years} < 3$	0	0.00	0.45
$3 \leq \text{years} < 4$	13	5.80	6.25
$4 \leq \text{years} < 5$	9	4.02	10.27
$5 \leq \text{years} < 6$	13	5.80	16.07
$6 \leq \text{years} < 7$	16	7.14	23.21
$7 \leq \text{years} < 8$	14	6.25	29.46
$8 \leq \text{years} < 9$	25	11.16	40.63
$9 \leq \text{years} < 10$	11	4.91	45.54
$10 \leq \text{years} < 11$	13	5.80	51.34
$11 \leq \text{years} < 12$	12	5.36	56.70
$12 \leq \text{years} < 13$	16	7.14	63.84

²³⁸ *Overpatented*, *supra* note 143, at 14.

²³⁹ This may be of particular interest in light of the 1984 legislative decision that patent term restoration would be structured to make it possible for drug innovators to enjoy fourteen years of effective patent life. *See generally* Erika Lietzan, *The History and Political Economy of the Hatch-Waxman Amendments*, 49 SETON HALL L. REV. 53, 103 (2018); Lietzan & Aciri, *Distorted Drug Patents*, *supra* note 34, at 1352, 1364–65.

Table 1 Actual Market Exclusivity All 224 NDAs in Our Dataset			
Actual Years of Exclusivity	Number of NDAs	Percentage of NDAs	Cumulative Percentage of NDAs
$13 \leq \text{years} < 14$	14	6.25	70.09
$14 \leq \text{years} < 15$	26	11.61	81.70
$15 \leq \text{years} < 16$	12	5.36	87.05
$16 \leq \text{years} < 17$	10	4.46	91.52
$17 \leq \text{years} < 18$	4	1.79	93.30
$18 \leq \text{years} < 19$	2	0.89	94.20
$19 \leq \text{years} < 20$	5	2.23	96.43
years > 20	8	3.57	100.00
Average	11.3 years		
Median	10.8 years		
Total	224 drugs		

Table 2 Actual Market Exclusivity NCEs (79 NDAs in Our Dataset)			
Actual Years of Exclusivity	Number of NDAs	Percentage of NDAs	Cumulative Percentage of NDAs
$0 \leq \text{years} < 1$	0	0.00	0.00
$1 \leq \text{years} < 2$	0	0.00	0.00
$2 \leq \text{years} < 3$	0	0.00	0.00
$3 \leq \text{years} < 4$	0	0.00	0.00
$4 \leq \text{years} < 5$	0	0.00	0.00
$5 \leq \text{years} < 6$	1	1.27	1.27
$6 \leq \text{years} < 7$	1	1.27	2.53

Table 2 Actual Market Exclusivity NCEs (79 NDAs in Our Dataset)			
Actual Years of Exclusivity	Number of NDAs	Percentage of NDAs	Cumulative Percentage of NDAs
$7 \leq \text{years} < 8$	5	6.33	8.86
$8 \leq \text{years} < 9$	8	10.13	18.99
$9 \leq \text{years} < 10$	2	2.53	21.52
$10 \leq \text{years} < 11$	4	5.06	26.58
$11 \leq \text{years} < 12$	4	5.06	31.65
$12 \leq \text{years} < 13$	8	10.13	41.77
$13 \leq \text{years} < 14$	9	11.39	53.16
$14 \leq \text{years} < 15$	17	21.52	74.68
$15 \leq \text{years} < 16$	7	8.86	83.54
$16 \leq \text{years} < 17$	2	2.53	86.08
$17 \leq \text{years} < 18$	3	3.80	89.87
$18 \leq \text{years} < 19$	0	0.00	89.87
$19 \leq \text{years} < 20$	5	6.33	96.20
$\text{years} > 20$	3	3.80	100.00
Average	13.34 years		
Median	13.75 years		
Total	79 drugs		

Fourth, to investigate our ultimate question, we calculated the number of months between the first filer generic launch date and the “latest protection end date” cited in the Hastings Database. In one instance, involving Jalyn (dutasteride and tamsulosin hydrochloride) (NDA No. 022460), the first filer launched on the actual day projected by the Hastings Database. This product was not a new chemical entity; it had no statutory exclusivities and only three listed patents, each of which had little patent life remaining when the FDA

approved the NDA. A generic drug launched when the last patent expired, 5.4 years after NDA approval. In every other instance in our dataset, the first filer launched its generic drug before the latest protection end date cited by Hastings and sometimes years before that date; the average was eighty-four months (seven years) earlier (mean eighty-four months, median seventy-nine months). Further, fifty-nine (26%) had generic competition ten or more years earlier, and eleven (5%) had generic competition fourteen years earlier. Two had generic competition more than twenty years earlier (twenty-two years and twenty-four years). Table 3 aggregates these results.

Table 3 Timing of First Filer Generic Market Entry All NDAs	
First Filer Entry Date	Number of NDAs
On or after the Hastings Latest End Protection Date	1 (0.5%)
1 to 60 months (5 years) before Hastings Latest End Protection Date	88 (39.2%)
More than 60 months (5 years) to 120 months (10 years) before Hastings Latest End Protection Date	76 (33.9%)
More than 120 months (10 years) to 180 months (15 years) before Hastings Latest End Protection Date	48 (21.4%)
More than 180 months (15 years) before Hastings Latest End Protection Date	11 (4.9%)
Total	224 (100%)

The new chemical entity NDAs in our dataset faced generic competition on average sixty-eight months (5.7 years) (mean sixty-eight months, median sixty-three months) earlier than the latest protection end date cited by Hastings. Fifteen (19%) had generic competition only in the final year before the Hastings Database projection, but fifty-six (71%) had competition more than two years

earlier. Approximately half (thirty-nine) had generic competition in the market more than five years earlier than the latest protection end date cited by Hastings. Table 4 aggregates these results.

Table 4 Timing of First Filer Generic Market Entry New Chemical Entity NDAs	
First Filer Entry Date	Number of NCE NDAs
On or after the Hastings Latest End Protection Date	0
1 to 60 months (5 years) before Hastings Latest End Protection Date	39 (49.4%)
More than 60 months (5 years) to 120 months (10 years) before Hastings Latest End Protection Date	26 (32.9%)
More than 120 months (10 years) to 180 months (15 years) before Hastings Latest End Protection Date	12 (15.2%)
More than 180 months (15 years) before Hastings Latest End Protection Date	2 (2.5%)
Total	79 (100%)

These results confirm our suspicion that the “latest protection end date” should not be used as a proxy for the likely generic entry date. Instead, they suggest that for a new chemical entity NDA, actual generic competition will more likely than not launch at least five years earlier, and nearly 18% of the time it will launch more than ten years earlier. This in turn confirms our suspicion that the Hastings inference—that the “months of additional protection time” field in the Hastings Database refers to a period during which the brand company may have “limited generic competition and monopolized a drug product”—is not sound.²⁴⁰

²⁴⁰ See *About*, *supra* note 15.

C. *But Why?*

The Hastings Raw Dataset makes a significant contribution that can improve empirical scholarship and advance efforts to base policymaking in relevant evidence. But the Hastings Database—and the inference that the number of months between the earliest and latest expiries corresponds to the amount of time the brand company may have limited generic competition and extended its “monopoly”—is problematic. In the end, this is because the Hastings inference is sound only if the earliest protection end date and latest protection end date are valid proxies. But the proxies are not valid. The inference uses the earliest protection end date as a proxy for the date on which generic drug approval might have initially been expected; that is, the date on which a generic company might have reasonably expected to enter the market based on what was known at the time of initial NDA approval.²⁴¹ It uses the latest protection end date as a proxy for the true and final date on which generic drug approval can be expected, given the alleged “evergreening” that occurred after initial approval.²⁴² These proxies fail, for the following reasons.

First, the Hastings Database does not account for the fact that some patents and exclusivity will preclude generic entry, while others will not. This is because it does not distinguish between different types of statutory exclusivity, even though they differ in scope and legal effect. Nor does it consider the fact that patents vary in scope and type and therefore in practical effect, given the legal framework governing generic drug approval. Some protections are broad, while others are narrow. The active ingredient patent and new chemical entity exclusivity are broad in coverage, meaning that they protect *every* product on the NDA and *every* NDA with the active ingredient in question.²⁴³ A patent claiming a new use of an existing compound, in contrast, is narrow—protecting only that use of the compound.²⁴⁴ Differing protections have different legal functions, as well; orphan exclusivity prevents *approval* for seven years, for

²⁴¹ See *id.*

²⁴² See *id.*

²⁴³ See *supra* note 243; *supra* part I.B.2.

²⁴⁴ E.g., THOMAS, *supra* note 44, at 46 (“Although inventors are allowed to obtain process patents on newly discovered uses, the patent law limits the scope of protection to the particular method claimed.”).

instance, while NCE exclusivity prevents *submission* but not approval.²⁴⁵ And differing protections interact differently with the regulatory framework; the statute requires a generic drug to have the same active ingredient, for instance, but not the same formulation (combination of active and inactive ingredients).²⁴⁶

Second, the Hastings Database does not distinguish between discrete products approved under a single NDA, even though they are legally distinct *and* function independently of each other with respect to generic drug approval. Different strengths of the same dosage form—e.g., 10mg, 20mg, and 40mg capsules of Prozac (fluoxetine)—are separately numbered products on a single NDA.²⁴⁷ A generic company may seek approval of all three strengths, also under a single ANDA, but it need not. The differing products on a single NDA could have different exclusivities and patents; this is likely if dosages are added later and especially likely if they are tied to new indications.²⁴⁸ The Hastings Database treats any patent or exclusivity listed on the NDA as applicable to every product, but in our dataset of seventy-nine new chemical entities, thirteen (16.5%) had multiple products under the same NDA with differing patents or exclusivity. The Hastings Database does not account for the fact that a generic company might not choose to reference (copy) the product under the NDA with the “latest protection end date.”

In sum, the Hastings Database treats all patents and exclusivities as equivalent in power, simply reporting the earliest expiring and the latest expiring. And it treats all products on an NDA as a single product, assigning every expiry date to every product, when this may not

²⁴⁵ Compare 21 U.S.C. § 360cc (stating that upon approval of a drug designated for a rare disease, FDA “may not *approve* another application” for the same drug and disease for seven years) (emphasis added) with 21 U.S.C. § 355(j)(5)(F)(ii) (stating that upon approval of a new chemical entity, “no application may be *submitted*” that relies on the drug for five years) (emphasis added).

²⁴⁶ See 21 U.S.C. § 355(j)(2).

²⁴⁷ See *supra* notes 94–97.

²⁴⁸ In our dataset, NDA No. 21992, which covers Pristiq (desvenlafaxine succinate), was listed with three exclusivities: new chemical entity exclusivity expiring in 2013, a new indication exclusivity expiring in 2016, and a miscellaneous three-year exclusivity expiring in 2021. The new indication exclusivity was listed only with product 1 (50 mg tablet) and 2 (100 mg tablet), but not with product 3 (25 mg tablet).

be true.²⁴⁹ Together, these decisions mean that the earliest and latest protection end dates are not reliable proxies for the potential timing of generic competition.

The earliest protection end date is really just the first expiration date after 2005 of any patent or exclusivity associated with any product under the particular new drug application.²⁵⁰ The decision to consider only patents and exclusivities expiring after 2005 essentially guarantees that for a large percentage of the database, this date has no relationship to what a generic company would have predicted when the NDA was first approved. Most drugs marketed between 2005 and 2015 (i.e., most drugs in the Database), were approved before 2005,²⁵¹ and for many the initial patents and exclusivity are omitted from the Database (because they would have expired before publication of the 2005 Orange Book, which is the first the Hastings team consulted). In addition, even for the NDAs first approved in 2005 or later, the earliest expiry date in the Hastings Raw Dataset may have nothing to do with the earliest date a generic company could reasonably expect to enter the market, on the basis of information available at NDA approval. For instance, for a new chemical entity, the Hastings Database reports the NCE exclusivity expiry date, even if the active ingredient patent—which generally precludes generic drug approval—expires later.²⁵² To give another example, if the brand company with NCE exclusivity secures approval of a new indication one year after initial approval, that exclusivity will expire before the NCE exclusivity and will be reported by

²⁴⁹ In other words, each entry in the Hastings Database is for an entire NDA—meaning all products on the NDA—and one answer is provided for the entire NDA for each field such as “latest protection end date.” See HASTINGS DATABASE, *supra* note 14.

²⁵⁰ See *About*, *supra* note 15.

²⁵¹ We base this assertion on examination of each Orange Book from 2005 (the 25th edition) to 2015 (the 35th edition).

²⁵² Again, the Hastings Database selects the *first* expiration date (after 2005) of any patent or exclusivity associated with the NDA. See *id.* By definition, then, it does not select patents or exclusivities that expire *later*. See *id.* To give an example, the Hastings Database identifies November 20, 2006, as the earliest protection end date for Avodart (NDA No. 21319), and our dataset shows that (1) this was the date, five years after NDA approval, on which new chemical entity expired, and (2) U.S. Patent No. 5565467, which was listed in the Orange Book as a drug substance patent, was slated to expire on October 15, 2013, and then later, by virtue of patent term restoration, expired on November 20, 2015.

Hastings instead.²⁵³ That expiry date will be earlier than any reasonable generic company would expect approval. For that matter, if a new chemical entity is also an orphan drug, the statute will prevent approval of a generic for the same use for seven years,²⁵⁴ but the Hastings Database will report the earlier NCE expiry date—even though no generic could be approved until expiry of the orphan protection (unless there is an additional unprotected indication).

The latest protection end date is, similarly, just the last expiration date of any patent or exclusivity associated with the new drug application.²⁵⁵ But this date may have nothing to do with the actual date on which a generic drug might obtain approval and enter the market. For instance, if the patent or exclusivity protects a new indication, it will not preclude generic drug approval. As noted, FDA will almost always permit the new indication to be omitted from the generic drug labeling.²⁵⁶ So, too, if the patent or exclusivity protects another condition of use; usually the generic company may obtain approval of earlier and now-unprotected conditions of use.²⁵⁷ In addition, if the patent or exclusivity pertains to one product under the NDA (for instance, a new strength), it will not preclude approval of a generic drug based on the other products under the NDA.²⁵⁸ This is not to say that patents and exclusivity listed in the Orange Book after the initial set of protections are irrelevant. They do provide exclusivity in the market; that is their purpose. But the point is that these subsequent protections relate to discrete products or to conditions of use that can (generally) be carved from a generic drug's labeling, allowing generic entry before expiry of the last protection period.

²⁵³ This is because NCE exclusivity lasts for five years from initial approval of the active moiety and new indication exclusivity lasts for three years from approval of the new indication. *See supra* part I.B.2. Exclusivity for a new indication approved one year after initial approval of the active moiety will therefore expire four years after initial approval of the active moiety (because $1+3=4$), which is earlier in time than five years after initial approval of the active moiety (because $4<5$).

²⁵⁴ *See* 21 U.S.C. § 360cc(a)(2); *see supra* Part I.B.2.

²⁵⁵ *See supra* note 174.

²⁵⁶ *See supra* note 62.

²⁵⁷ *See* 21 U.S.C. § 355(j)(5)(F)(iii)–(iv); *see supra* Part I.B.2.

²⁵⁸ *E.g.*, REFERENCING PRODUCTS, *supra* note 193, at 5 (“Each strength of a drug is a distinct drug product and, therefore, a distinct listed drug.”).

Finally, the Hastings Database does not distinguish corrections from true changes. The field for the “earliest” protection end date simply reports the earliest of any expiration date printed in the Orange Book.²⁵⁹ The field for the “latest” protection end date simply reports the latest of these dates.²⁶⁰ As noted above, these dates change over time; a patent’s expiration date might move later because of modifications to patent term adjustment under § 154, a patent term restoration under § 156, or the 1995 change in the underlying patent term law.²⁶¹ Sometimes, however, the changes reflect correction of an obvious error. The Hastings Database does not distinguish these from true changes; instead, it relies on the erroneous date. To give an example, for a “latest” expiry, the Hastings Database uses U.S. Patent No. 5846976 for NDA No. 021319, which covers Avodart (dutasteride). This patent was briefly listed in the Orange Book with an expiration date incorrectly calculated as seventeen years from its issuance. But the patent application was filed in August 1996, and the patent was (always) subject to a twenty-year patent term from its filing date. The correct expiration date for this patent was (always) more than two years *earlier* than the expiration date used in the Hastings Database to calculate the “months added” metric for Avodart. In our dataset of 224 NDAs, we found nine corrections in the Orange Book affecting a protection used by the Hastings Database to calculate the months added metric, and in each case using the corrected date would have returned a lower number of months added.²⁶²

²⁵⁹ See *About*, *supra* note 15.

²⁶⁰ *Id.*

²⁶¹ 35 U.S.C. §§ 154, 156; Uruguay Round Agreements Act, Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4983-84; see *supra* note 223.

²⁶² These are: (1) NDA No. 20114, a correction to the expiry for three-year exclusivity D-102; (2) NDA No. 20978, a correction to the expiry of U.S. Patent 6641843; (3) NDA No. 20990, a correction to the expiry of U.S. Patent 7067555; (4) NDA No. 21319, a correction to the expiry of U.S. Patent No. 5846976; (5) NDA No. 21516, a correction to the expiry of U.S. Patent 6645963; (6) NDA No. 21875, a correction to the expiry of U.S. Patent 4927855; (7) NDA No. 22430, a correction to the expiry of U.S. Patent 8273795; (8) NDA No. 50741, a correction to the expiry of U.S. Patent 5466446; and (9) NDA No. 201373, a correction to the expiry of U.S. Patent 8933097. Again, the Hastings Database did not use the corrected date, which means that it returned a higher number of months than accurate. Moreover, in two of the nine cases, the Hastings Raw Dataset did not even catch the correction made by FDA.

Because these two dates are not reliable proxies for anything else, and the reason each fails will vary from application to application, the months between them is not standardized and has no meaning. A few examples, in Table 5, illustrate these problems.

Table 5 (Selected) False Proxies in the Hastings Database		
NDA	False Proxy	Explanation
Exjade (defer- asirox) (NDA No. 21882)	Latest protection end date: 1/23/2020	This is the expiration date for an orphan exclusivity awarded eight years after initial drug approval. It protects a single new orphan indication and can be carved from a generic drug's labeling. A generic drug launched ten months before this exclusivity expired.
Reyataz (ataza- navir sulfate) (NDA No. 21567)	Earliest protection end date: 7/6/2007	This is expiry of a three-year exclusivity period that protects a new dosing schedule approved in 2004, one year after the new drug application. But a generic company would not need to seek approval of a newer dosing schedule, and in any case the NCE exclusivity would not itself expire until June 2008.

Table 5 (Selected) False Proxies in the Hastings Database		
NDA	False Proxy	Explanation
Lunesta (eszopiclone) (NDA No. 21476)	Latest protection end date: 4/10/2016	This is expiry of a three-year exclusivity period protecting a new condition of use — specifically, revisions to the labeling based on data submitted in response to a pediatric written request (i.e., to earn pediatric exclusivity). But section 505A(o) of the statute directs FDA <i>not</i> to deny generic drug approval on account of exclusivity deriving from the addition of pediatric information to the labeling. And a generic drug launched two years earlier, in 2014.
Tarceva (erlotinib hydrochloride) (NDA No. 21743)	Earliest protection end date: 11/2/2008	This is expiry of three-year exclusivity that was awarded for a new indication approved in November 2005, one year after initial NDA approval. But a generic company would not need to seek approval of its drug for that indication, and in any case the new chemical entity exclusivity would not expire for another year (in November 2009).

Table 5 (Selected) False Proxies in the Hastings Database		
NDA	False Proxy	Explanation
Micardis (telmisartan) (NDA No. 20850)	Earliest protection end date: 10/16/2012	<p>This corresponds to expiry of a three-year exclusivity period awarded — long after initial approval — for a new indication associated with one strength of the product. This is Product 2, which contains 80 mg.</p> <p>This example illustrates the problem with capturing only exclusivities and patents that expired after 2005. FDA approved this NDA on 11/10/1998. Its NCE exclusivity expired on 11/10/2003, and the single patent initially listed in the Orange Book expired on 1/7/2014. A rational generic company might have concluded that (absent scientific or regulatory challenges) it would enter the market in January 2014. In fact, a generic drug launched on 1/8/2014.</p>

Table 5 (Selected) False Proxies in the Hastings Database		
NDA	False Proxy	Explanation
Actonel (risedronate sodium) (NDA No. 20835)	<p>Earliest protection end date: 5/17/2005</p> <p>Latest protection end date: 11/6/2023</p>	<p>This example illustrates the problem with capturing only exclusivities and patents that expired after 2005 <i>and</i> the problem with failing to distinguish between products on an NDA.</p> <p>FDA has approved five products: (1) 30 mg in March 1998, (2) 5 mg in April 2000, (3) 35 mg in May 2002, (4) 75 mg in April 2007, and (5) 150 mg in April 2008. NCE exclusivity expired in 2003 and was not captured by Hastings.</p> <p>The Hastings “earliest” date corresponds to expiry of three-year exclusivities associated with the Product 3 dosing schedule. The Hastings “latest” date corresponds to expiration of two patents plus pediatric exclusivity, listed only for Product 5.</p> <p>A generic copy of Products 1, 2, and 3 launched 101 months (8.4 years) earlier.</p>

IV. A PATH FORWARD TO RELEVANT DATA

A. *Limitation to Our Research*

There are three significant limitations to our research.

First, our data are incomplete. Our dataset does not even have commercial launch dates for all first filers, meaning all generic companies that became eligible for 180-day exclusivity by challenging brand company patents. It has only the commercial launch dates for those who enjoyed the exclusivity upon commercial launch (and in fact, only those who launched in 2006 or later); other first filers may have forfeited or waived the exclusivity but nevertheless launched at one point or another.²⁶³ We do not know whether we would reach the same results for the brand products whose first filers did not enjoy exclusivity, i.e., whether these generic companies still launched before the “latest protection end date” cited by the Hastings Database. Further, other first filers listed in FDA’s table are still holding their exclusivity eligibilities; these companies have neither launched nor forfeited.²⁶⁴ We do not know whether they will launch before the “latest protection end date.”

Second, our data pertain to a distinctive subset of brand products. To begin with, these are products for which there *is* a generic drug in the marketplace. Moreover, each company that launched had challenged at least one patent owned by the brand company; that is, by definition it sought to market its generic drug before a stated expiration date. And then it launched, which means in turn that (1) the brand company did not sue for patent infringement, (2) it sued but the 30-month stay expired, and the generic company launched at risk, (3) it sued and reached a settlement permitting the generic company to market before patent expiry, or (4) it sued and lost. And in each scenario, the generic company could (and probably would) have launched before the stated expiration date. Indeed, doing so was the purpose of the company’s paragraph IV certification.

²⁶³ Exclusivity can be forfeited for a variety of reasons, including failure to launch by deadlines specified in the statute. See 21 U.S.C. § 355(j)(5)(D).

²⁶⁴ In other words, there are entries in the table *without* any first commercial marketing date listed and also *without* any indication that the exclusivity was extinguished or forfeited. *E.g.*, entry for Balsalazide Disodium Tablets, *Paragraph IV Patent Certifications*, *supra* note 186, at 7.

Focusing on brand products that, by definition, experienced generic competition before the “latest protection end date” biased our findings toward earlier generic entry dates.

There is, however, good reason to expect broadly similar results with a larger dataset. Our point is that the key metric in the Hastings Database is fundamentally flawed. Again, the “earliest protection end date” and the “latest protection end date” for an NDA in the database are not standardized. The Hastings Project does not differentiate between discrete products on a single new drug application, even though they may be subject to differing patents and exclusivities and may be vulnerable to generic competition at different times. Nor does it distinguish among patents on a single product, or among different forms of statutory exclusivity, even though these protections vary in scope, and some do not preclude generic approval. Thus, our finding—that on an NDA-by-NDA basis, the “latest protection end date” does not correspond to the actual generic launch date—should largely be true in the broader dataset as well. We do not, however, have generic launch dates to confirm this.

Third, we focus on protections (and generic competition) at the level of individual products or of individual new drug applications. This is more significant limitation to our research, and indeed to the Hastings research and other counting exercises as well. As a reminder, though, (1) a single active ingredient may be spread across multiple NDAs, whether approved at the same time or sequentially, and (2) a single NDA may cover discrete products that serve as discrete reference products for a single ANDA or indeed competing ANDAs.²⁶⁵ Further (3) a patent claims an invention, which might be embodied in one or more products under one or more NDAs, just as (4) a statutory exclusivity usually protects research, which might have supported one or more products under one or more NDAs.²⁶⁶ And finally, (5) a generic drug company cites one product and deals with the patents and exclusivities associated only with that product.²⁶⁷

²⁶⁵ See *supra* Part III.C.

²⁶⁶ See *supra* Parts I.B.2, I.B.3, & III.C.

²⁶⁷ See *supra* Parts I.A. & I.B.

As a result, counting patents and exclusivities tied to an active ingredient or NDA overlooks the fact that a generic company copies a specific product. Counting patents and exclusivities tied to a specific product overlooks the fact that a generic company could copy a different product, including a different product on the same NDA.²⁶⁸ Finding the latest protection end expiry for an NDA overlooks the fact that a generic company copies a specific product on the NDA *and* the fact that some patents and exclusivities do not preclude generic entry. These considerations *also* make considering first filer generic launch dates tied to NDAs (or specific products on particular NDAs) problematic: this approach, *our* approach, overlooks the fact that other generic companies may have already launched copies based on products containing the same active ingredient. This limitation should bias our results—and the results of any counting exercise tied to an active ingredient or NDA—in the other direction, i.e., towards later dates; actual generic entry is likely to be *earlier*.

B. Additional Considerations

The real question is how quickly less expensive versions of important, expensive new medicines become available for physicians to prescribe and patients to use—not just approved, but launched and available in the marketplace. Even assuming the results are normatively unacceptable (that is, policymakers conclude these versions should be available for use *sooner*), another question must be answered before evidence-based patent and exclusivity policymaking can occur: what, exactly, drives the timing?

Before describing the path to answer these questions, we must make two additional points. *First*, a generic company has more choices than the simple ANDA that proposes a purported duplicate. In some cases, a generic company may file an ANDA for a generic drug that has a different strength or, even, a different route of

²⁶⁸ For example, NDA No. 21038 covers four strengths (products) of Precedex (dexmedetomidine). The Hastings Database cites, for the latest protection end date, July 4, 2032, which is when pediatric exclusivity expires on six patents that are listed for products 2 through 4. But product 1's last protection period ended in 2019, and in any case a generic (of product 1) launched in 2014.

administration and dosage form.²⁶⁹ In other cases, the generic company can file an abbreviated application that falls under a different provision of the FDCA, section 505(b)(2). This application relies on the brand company's safety and effectiveness data, but the generic company can add whatever safety and effectiveness data are required to justify the changes it has made.²⁷⁰ The applicant might make changes to avoid infringing a patent held by the innovator, for instance, or it could propose innovations to create a competitive branded product in the market.²⁷¹ This leads to an additional conclusion. Focusing on the first filer generic drug launch date tied to a particular NDA, or specific products on a particular NDA, overlooks the fact that other generic companies may have launched versions that are *nearly* copies based on 505(b)(2) applications.²⁷² Drugs approved on the basis of these applications are not eligible for 180-day exclusivity and are therefore never considered first filers.²⁷³ Their launch dates do not appear in the FDA Table. And yet these may provide meaningful price competition for the brand drug and options for patients and their healthcare providers, and their (potentially earlier) entry should not be overlooked by policymakers.

²⁶⁹ See 21 U.S.C. § 355(j)(2)(C) (describing a process in which the generic company files a suitability "petition," which the FDA must grant unless it determines that more safety or effectiveness data are required); see also 21 U.S.C. § 355(j)(2)(A) (requiring the strength, route of administration, and dosage form of a generic drug to be the same, unless a suitability petition has been granted, and also allowing the labeling to be different to reflect the changes approved in the petition). An ANDA submitted after approval of a suitability petition is known as a "petitioned" ANDA.

²⁷⁰ See 505(b)(2) GUIDANCE, *supra* note 37.

²⁷¹ *Id.* at 3 (describing a range of possibilities, from a change of dosage form that cannot be accommodated in a petitioned ANDA to a change in active ingredient (such as a different salt), a new indication, or even a switch from prescription to nonprescription status).

²⁷² Again, an application under section 505(b)(2) is abbreviated—relies on the safety and effectiveness data that supported the referenced brand product—and simply contains the additional data needed to substantiate whatever changes (whether minor or major) the generic applicant proposes. See 505(b)(2) GUIDANCE, *supra* note 37. But these could be minor differences: drugs approved through section 505(b)(2) might differ from their reference products simply because current scientific understanding and technology do not permit a finding that the active ingredients are identical, for instance, or because of certain changes made to the inactive ingredients. *Id.* at 7–10.

²⁷³ The statute provides 180-day exclusivity only for applications filed under section 505(j). See 21 U.S.C. § 355(j)(5)(B)(iv).

Second, focusing on patent and exclusivity expiry overlooks the fact that timing of generic drug approval and launch turns also on business considerations as well as scientific and regulatory challenges faced by the generic company. A variety of circumstances can make it expensive, risky, difficult, or impossible to prepare an abbreviated application, secure FDA approval, and launch as early as hoped. To give one example, some new drugs are hard, or impossible, to characterize, precluding the use of the ANDA pathway altogether. Sometimes this is clear at the outset, but other times it only becomes clear *after* the generic company starts developing a copy or even *after* it submits an ANDA.²⁷⁴ This was long the case for insulin, for instance; FDA eventually determined that a 505(b)(2) application could be filed, but for many years there were no “copies” in the market.²⁷⁵ It was long thought impossible to show that one recombinant protein is the “same” as another (precluding use of the

²⁷⁴ For example, in September 1994 and July 1995, Duramed Pharmaceuticals and Barr Laboratories submitted ANDAs for conjugated estrogens, citing Premarin. *See* Opportunity for a Hearing Notice, 62 Fed. Reg. 42,562, 42,562 (Dep’t of Health and Hum. Servs. Aug. 7, 1997). Derived from the urine of a pregnant mare, Premarin has been marketed under an NDA since the 1940s for treatment of various symptoms associated with menopause. *See* Highlights of Prescribing Information, Wyeth Pharms. Inc., Prescribing Information for Premarin (Nov. 2017). In 1997, while those ANDAs were pending, FDA concluded that the product and its various estrogenic ingredients were not sufficiently characterized for a sameness finding, which is paired with bioequivalence in an ANDA to justify bypassing testing requirements. *See* Opportunity for a Hearing Notice, 62 Fed. Reg. 42,562, 42,563–65 (Dep’t of Health and Hum. Servs. Aug. 7, 1997). FDA did not approve the Duramed ANDA or the Barr ANDA, and indeed it has still not approved an ANDA for conjugated estrogens. *See* Search Results for “conjugated estrogens,” Drugs@FDA, FDA-Approved Drugs, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> [https://perma.cc/E3KY-C8FZ]. Instead, generic firms must file abbreviated applications under section 505(b)(2)). *E.g.*, FDA Approval Letter from Lisa D. Rarick, Dir. Div. of Reprod. and Urologic, Ctr. for Drug Evaluation and Rsch., to John R. Rapoza, Vice President, Regul. Affs, Duramed Pharms, Inc., NDA No. 20-992 (Mar. 24, 1999), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/1999/20992ltr.htm [https://perma.cc/AZX5-FVH9] (approving 505(b)(2) application filed by Duramed).

²⁷⁵ The FDA signaled early that a generic applicant would need to use section 505(b)(2) rather than an ANDA to copy any recombinant insulin product, but the showing that would be needed and the studies that would be required were not clear until well after European regulators issued their own first guidance document on biosimilar insulins. Meanwhile the FDA itself did not approve the first follow-on recombinant protein product until it approved Omnitrope in 2006. *See generally* Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 685–86 (2010).

ANDA), and FDA had not determined what should be shown, instead, in an abbreviated application.²⁷⁶ To give another example, some innovative drugs are difficult to manufacture, complicating generic drug development, which adds expense and risk and sometimes delays approval or launch.²⁷⁷ Drugs with novel delivery mechanisms have been hard to copy, due to challenges with characterization and bioequivalence showings.²⁷⁸ The FDA believes the complexity of making these drugs is slowing generic drug development.²⁷⁹ Some new drugs require raw materials that are hard or expensive to source or that are in short supply. Sometimes raw material suppliers make changes to their manufacturing process or make mistakes in manufacturing, affecting generic drug development, a pending application, or supply after approval.²⁸⁰ Dependence on a third

²⁷⁶ E.g., *USP Human Growth Hormone Monographs Issued; Generics Status Unresolved*, THE PINK SHEET (May 16, 2005), <https://pink.pharmaintelligence.informa.com/PS045827/USP-Human-Growth-Hormone-Monographs-Issued-Generics-Status-Unresolved> [<https://perma.cc/8DKC-R4UK>] (noting that an existing USP monograph for human insulin had not yet led to approval of follow-on products, and that the agency was “developing materials that could build a framework for generic biologics, but the process appears to be a lengthy one.”); Kathryn Phelps, *505(b)(2) Resurrection, FDA Guidance to Bless Follow-On Biologics Pathway*, THE PINK SHEET (Apr. 2, 2007), <https://pink.pharmaintelligence.informa.com/PS048186/505b2-Resurrection-FDA-Guidance-To-Bless-Follow-On-Biologics-Pathway> [<https://perma.cc/JCX5-75S6>] (noting that over time FDA had said it would issue a white paper, general guidance, and then specific guidance on insulin, and describing some of the technological issues the agency was grappling with).

²⁷⁷ For example, Mylan Pharmaceuticals found itself unable to manufacture 100mg phenytoin sodium in capsules that would be bioequivalent to Warner Lambert’s Dilantin and famously ended up stuffing a tablet inside a capsule shell, explaining to a court that it was “unsuccessful in formulating an ordinary capsule that would satisfy FDA and USP requirements, and only succeeded after it had compressed the material to the point that it actually comprised a tablet.” Brief for Appellant Warner-Lambert Company at 9, *Warner-Lambert Co. v. Donna E. Shalala*, No. 99-5048, 1999 WL 34835355 (D.C. Cir. Apr. 15, 1999).

²⁷⁸ Joanne S. Eglovitch, *US FDA Pushing for Generic Alternatives to Long-Acting Injectables, Implants*, THE PINK SHEET (Mar. 21, 2017), <https://pink.pharmaintelligence.informa.com/PS120259/US-FDA-Pushing-For-Generic-Alternatives-To-LongActing-Injectables-Implants> [<https://perma.cc/F9K2-MRN2>] (“Officials are concerned that the complexity posed in manufacturing these drugs is delaying the development of generic alternatives.”).

²⁷⁹ See *id.*

²⁸⁰ To give an example, Perrigo secured approval of a generic guaifenesin tablet in 2011, based on Mucinex, but twice had to stop distributing—once when raw material sourcing did not meet specifications (leading to a two-year wait), and once when problems emerged

party supplier always introduces an element of risk.²⁸¹ Some generic companies fall out of compliance with current good manufacturing practices and fail facility inspections, which may affect regulatory approvals or require manufacturing lines to be slowed or even shut

with an excipient. *See Private Label Mucinex March Reaches Two Formulations*, HBW INSIGHT (May 4, 2016), <https://hbw.pharmaintelligence.informa.com/RS123166/Private-Label-emMucinexem-March-Reaches-Two-Formulations> [https://perma.cc/X2A9-VQ9E].

²⁸¹ For example, Amphastar ended up suing FDA when the agency detained shipments of semi-purified heparin from China, after the supplier had been cited in a warning letter for violation of current good manufacturing practices. Amphastar had planned to use this intermediate raw material, used to make heparin USP (the starting material for the active ingredient in its generic enoxaparin product), for which an ANDA was pending. *See Sue Sutter, Amphastar Lawsuit Over Heparin Shipments Suggests Lovenox ANDA Approval May Be Far Off*, THE PINK SHEET (Nov. 1, 2010), <https://pink.pharmaintelligence.informa.com/PS052765/Amphastar-Lawsuit-Over-Heparin-Shipments-Suggests-iLovenoxi-ANDA-Approval-May-Be-Far-Off> [https://perma.cc/N9SA-E8BC] (“Amphastar says it needs the detained material to perform proof of process development and validation studies necessary to qualify the company’s Chinese and California subsidiaries as raw material and active pharmaceutical ingredient suppliers for its pending ANDA. . . . Amphastar told ‘The Pink Sheet’ that such qualification studies normally would take four to five months. The amount of time involved suggests that ANDA approval will not be forthcoming in the near term, even if FDA were to release the detained material.”). The agency released the materials shortly after the suit was filed. *See Derrick Gingery, Drug Shipments into U.S. Could Depend on Facility Inspection; FDA Mulls Import Alerts*, THE PINK SHEET (Nov. 22, 2010), <https://pink.pharmaintelligence.informa.com/PS052851/Drug-Shipments-Into-US-Could-Depend-On-Facility-Inspection-FDA-Mulls-Import-Alerts> [https://perma.cc/DVM3-3B8Z].

down.²⁸² These factors may push generic entry later, even when patents and exclusivity have long since expired.²⁸³

C. A Better Study

There is a better way to explore the relationship between patent and exclusivity policy, on the one hand, and the length of time brand companies might enjoy supra-competitive pricing with their new molecular entities, on the other hand. This study would focus on each new molecular entity approved since 1984, and not on brand

²⁸² For example, after generic drug company Apotex received a series of warning letters arising out of inspections, the FDA decided it would withhold approval of any new ANDAs from the company until the violations were corrected. *See Apotex Manufacturing Violations Could Delay Launch of Taxotere Generic*, THE PINK SHEET (Apr. 19, 2010) (“In a newly released letter dated March 29, FDA’s Office of Compliance in the Division of Manufacturing and Product Quality told Apotex it would recommend that the agency withhold approval of the firm’s pending applications until the violations are corrected. Sanford C. Bernstein analyst Tim Anderson pointed out in an April 15 research note that this could derail Apotex’s ability to launch Taxotere, depending on whether the drug is manufactured by Apotex or an entity not covered in the warning letter.”). To give another example, after running into manufacturing problems, Sandoz voluntarily slowed manufacturing at several sites, prompting the agency to mention the risk of shortages in an unusually stern warning letter at the end of 2011. *See Martin Berman-Gorvine, Sandoz GMP Warning Letter: Is the Problem Documentation, or Leadership?*, THE PINK SHEET (Dec. 6, 2011), <https://pink.pharmaintelligence.informa.com/PS073134/Sandoz-GMP-Warning-Letter-Is-The-Problem-Documentation-Or-Leadership> [<https://perma.cc/VY72-2P9A>] (“In a new development for a CGMP warning letter on finished pharmaceuticals, FDA asked Novartis/Sandoz to contact CDER’s Drug Shortages Program as soon as internal discussions begin if the companies are considering decreasing the number of finished drug products or bulk drug substances produced by the affected manufacturing facilities.”); *see also* M. Nielsen Hobbs, *Managing the World’s First Blockbuster Generic: An Interview with Sandoz’s George*, THE PINK SHEET (Feb. 20, 2012), <https://pink.pharmaintelligence.informa.com/PS054204/Managing-The-Worlds-First-Blockbuster-Generic-An-Interview-With-Sandozs-George> [<https://perma.cc/GZ49-EGMD>] (“Manufacturing will continue to be a challenge for many Novartis products as the company responds to an unusually pointed GMP warning letter from FDA sent late last year. . . . Sandoz ‘continues to produce in each of our three sites in North America that were under the warning letter,’ George noted on the earning call. ‘We had imposed a number of areas of slowdown at those sites prior, and we made significant progress over the year.’”).

²⁸³ *See Darrow & Mai, supra* note 24, at 64 (concluding that, after finding that patent expiration was not followed by generic drug approval in 32% of cases, “greater research is needed to determine why generic entry does not always occur after patent expiration”).

names (“Prozac”), individual new drug applications, or individual products.

For each new chemical entity, one would identify and distinguish among every product on every new drug application, as well as the patent and exclusivity protections in the Orange Book associated with each. Corrections to the Orange Book—for instance, because of manual data entry errors or because the law governing the patent term changed—would result in corresponding corrections to the dataset. (We would consider both patent term adjustment and patent term restoration after initial Orange Book listing as amendments to a specific patent’s expiration date and replace the old expiry with the new expiry, but others might want to investigate the impact of these changes and thus note the changes and reasons.) Patents that reissue would be counted only once.

Two dates would then be of interest.

First, one would calculate what we call the Initial Protection End Date. One would start with the first approved brand product containing the new chemical entity. Using the patents and exclusivities associated with that product—those listed in the Orange Book as covering the initially introduced product(s) for the initially approved use(s), even if they issued after its approval—one would estimate the date on which a reasonable generic company might have expected to enter the market with a true duplicate of the product, assuming no scientific or regulatory challenges. This would assume each patent was valid and would be infringed by generic copy.

Second, one would determine the NCE Competition Date—the commercial launch date for the first product, approved on the basis of an abbreviated application (relying on the brand company’s research), to contain that same new chemical entity for the same indication(s). For this, any abbreviated application, citing one of the brand products as its reference listed drug and relying on the brand company’s research data, would count. The product might be a true duplicate, or it could be an alternative with a different route of administration, dosage form, and strength, or even an alternative approved through a 505(b)(2) application.

Thus, we recommend the preparation of a database—perhaps covering the entire period since enactment of the generic drug

pathway in 1984 so that trends can be examined—that allows policymakers to see exactly how long brand companies with new chemical entities enjoy a market without competition from another company marketing the *same* chemical entity for the *same* use on the basis of the brand company's *own* research.

The most important step of the proposed study would follow: if the Generic Competition Date (actual commercial launch date) is later than the Initial Protection End Date, one would need to determine the *reason* for its timing. Perhaps, for instance, the generic company chose not to duplicate the initially approved product but proposed instead a generic version of a newer strength or dosage form that had a later expiring protection. Or perhaps the generic company had difficulty making a bioequivalent version using the brand company's initial dosage form. Or perhaps it faced manufacturing difficulties. Or the market for the brand product is small and, for a while, no generic companies pursued the development of duplicates. This information might be difficult to find in some cases, but in others it would not be, and in others it still might be possible to make a reasonable assumption informed by careful research.

Although we have not calculated the Initial Protection End Date for any applications in our dataset, it is worth asking whether actual generic competition dates may be later than the date on which a reasonable generic company might have initially expected to enter the market (assuming a business case to enter the market and no scientific or regulatory challenges). Reform advocates and policymakers have for too long simply *assumed* that later-expiring protections explain the delta.²⁸⁴ Understanding the true reason is important. And then, if actual market exclusivity periods are indeed viewed as normatively too long, understanding what drives the length is the first step toward an evidence-based policymaking response. Further, it is a necessary step. It would be irresponsible to make major changes to patent law, competition law, or drug regulatory law without documenting a problem that can be solved only this way.

In response to this proposal, some will argue that only the launch of perfect duplicates counts, because only these will be automatically substituted for the brand product under state law. Automatic

²⁸⁴ E.g., *About*, *supra* note 14; *see generally* Part I.C.2.

pharmacy substitution stems from an interaction between FDA practices and state pharmacy law. The agency will deem a generic drug that is approved under an ordinary ANDA to be “therapeutically equivalent.”²⁸⁵ Every state then permits or requires pharmacists to dispense a therapeutically equivalent generic product when a prescriber specifies the brand product, unless the prescriber has said not to.²⁸⁶ Some will argue, in other words, that the only market entry that counts is the launch of a substitutable drug, not another drug approved on the basis of an abbreviated application. Therefore, a third date should probably be captured: the launch date for the first generic product deemed therapeutically equivalent to the first-approved brand product. But we reject the assumption that less expensive drugs (approved on the basis of abbreviated applications) do not—or cannot—provide meaningful price competition unless they are automatically substituted at the point of sale. Whether they do is an empirical question, and whether they could is an entirely separate one.

²⁸⁵ See U.S. DEP’T OF HEALTH & HUM. SERVS., FDA & CENTER FOR DRUG EVALUATION & RSCH., EVALUATION OF THERAPEUTIC EQUIVALENCE: GUIDANCE FOR INDUSTRY 6 (July 2022), <https://www.fda.gov/media/160054/download> [<https://perma.cc/6SK6-ZU8X>] (“In general, with the exception of a drug product approved in a petitioned ANDA, when FDA approves a drug product under an ANDA it is therapeutically equivalent to its RLD because the requirements for ANDA approval include the data and information that establish therapeutic equivalence.”). An ANDA that is not petitioned shows that the generic drug has the same active ingredient, route of administration, dosage form, and strength as the reference drug and that the two drugs are bioequivalent. See *supra* I.A. The FDA deems two products therapeutically equivalent if they are bioequivalent and “pharmaceutical equivalents” (same active ingredient, route of administration, dosage form, and strength). 43D ORANGE BOOK, *supra* note 19, at vii. This means that most generic drugs approved through ordinary ANDAs are deemed therapeutically equivalent to their reference drugs.

²⁸⁶ See *New York ex rel. Schneiderman v. Actavis PLC*, 787 F.3d 638, 645 (2d Cir. 2015) (stating that every state either “permit[s] or require[s] pharmacists to dispense a therapeutically equivalent, lower-cost generic drug in place of a brand drug absent express direction from the prescribing physician that the prescription must be dispensed as written”); see also Brief for Amicus Curiae Federal Trade Commission Supporting Plaintiff-Appellant at 5, *Mylan Pharms. Inc. v. Warner-Chilcott PLC*, 838 F.3d 421 (3d Cir. 2016) (No. 15-2236) (“Since the late 1970s, state legislatures throughout the country have sought to address the prescriber-payor pricing disconnect by enacting laws that enable (and sometimes require) a pharmacist to substitute a therapeutically equivalent generic drug (known as an ‘AB-rated’ drug) when presented with a prescription for a brand-name drug, unless a physician directs or the patient requests otherwise.”); Erika Lietzan, *Ignoring Drug Trademarks*, 56 WAKE FOREST L. REV. 945, 1004–05 (2021) [hereinafter, Lietzan, *Trademarks*].

Some will also argue that when a brand company introduces a newer product with the same active ingredient—such as a controlled release capsule after having previously marketed just an immediate release capsule—only a perfect duplicate of this *later* product counts. Whether or not the brand company withdraws the earlier product from the market, the argument would be that healthcare providers will prescribe the newer version. The generic company copied the older version, however, so its product will not be substituted. And so, the argument would go, this generic copy of the older product does not really provide meaningful price competition for the brand product actually capturing sales the market. This is, in the end, the “evergreening” argument in its purest form. The problem with this argument, and its corollary that only substitutable generic drugs count, is that it ignores the roles of and decisions that can be made by actual and autonomous participants in the process, specifically, healthcare providers and payers. The brand company’s newer products simply create new choices for them.

Prescribers are licensed under state medical practice laws and expected to exercise informed clinical judgments about the best treatment options for their patients.²⁸⁷ A prescriber may specify either brand drugs or generic drugs. If the prescriber specifies the older brand drug (even if it is not marketed), a pharmacist will generally dispense the generic equivalent.²⁸⁸ If the prescriber specifies the active ingredient, the pharmacist will generally dispense one of the available generic products.²⁸⁹ In theory, the prescriber could

²⁸⁷ E.g., American Medical Association Code of Medical Ethics § 1.1.1 (“The relationship between a patient and a physician is based on trust, which gives rise to physicians’ ethical responsibility to place patients’ welfare above the physician’s own self-interest or obligations to others, to use sound medical judgment on patients’ behalf, and to advocate for their patients’ welfare.”). Federal law requires that prescription drugs be dispensed only upon the prescription of a practitioner licensed by law to administer the drug, but state law dictates who is licensed to do so. See 21 U.S.C. § 353; Peter Barton Hutt et al., FOOD AND DRUG LAW 1045 (5th ed. 2022).

²⁸⁸ Every state’s pharmacy law either requires or permits the pharmacist to dispense the therapeutically equivalent generic drug, and payers usually require its substitution. See *New York ex rel. Schneiderman v. Actavis PLC*, *supra* note 286; Lietzan, *Paper Promises*, *supra* note 104, at 188–89.

²⁸⁹ State pharmacy laws require a pharmacist to dispense the drug specified by the prescriber, and in this case the prescriber has specified only the active ingredient rather than a particular company’s product; either the state pharmacy law, or the payer, or both,

even identify a particular generic company's drug containing a particular active ingredient. Conversely, if the prescriber specifies the newer brand product, the pharmacist will dispense it rather than generic copies of the older brand product.²⁹⁰ A physician might shift to prescribing a newer brand product for many reasons, including the view that there are benefits to the newer product, perhaps informed by research, or advertising and promotion by the brand company (which the FDA regulates and requires be truthful and not misleading), or experience treating patients with the two options. And while generic drug companies rarely promote generic drugs to doctors and patients, nothing prevents them from doing so.²⁹¹ They do promote their therapeutically equivalent generic drugs to pharmacies and payers, focusing on the lower prices they offer, and they could do so to prescribers as well.²⁹² Based on this advertising (or for other reasons, such as experience with the older brand product that the generic company copied) a doctor might *not* select the newer brand product. The payer, too, plays a profound role in product selection. If a payer perceives the newer brand product as less cost effective than the available generic drugs that contain the same active ingredient, it may decline to cover the product. A rational payer will adopt strategies that steer doctors and patients to less expensive products that are equally or adequately effective; not just those that are therapeutically equivalent, but also those that are not. In these cases, even if a prescriber specifies the brand product, the patient's insurance might prompt a conversation among the doctor, pharmacist, and patient, ultimately leading to modification of the

will steer the pharmacist towards an inexpensive option. *See generally* Lietzan, *Trademarks*, *supra* note 286, at 1015–18.

²⁹⁰ This is because state pharmacy laws require a pharmacist to dispense the drug specified by the prescriber; generic substitution laws provide an exception if there is a generic equivalent to the drug specified (which there would not be, if the prescriber specified the newer brand product). *See generally* Lietzan, *Trademarks*, *supra* note 286, at 1004; *see also* Office of the Assistance Secretary for Planning and Evaluation, Department of Health and Human Services, *Expanding the Use of Generic Drugs* (Dec. 1, 2010), <https://aspe.hhs.gov/sites/default/files/private/pdf/76151/ib.pdf> [<https://perma.cc/598V-8CTU>] (exploring how generic prescribing results in significant cost savings for the U.S. health care system).

²⁹¹ *See* Lietzan, *Trademarks*, *supra* note 286, at 1015–16.

²⁹² *See id.*

prescription and dispensing of the generic copy of the brand company's initial product.

Those who complain about the introduction of newer brand products are, in essence, assuming prescribers are helpless automata who cannot resist the siren call of new brand drugs, and they are assuming insurers—despite operating for profit in a heavily data-driven market—do not act rationally or in their own economic interests. On this basis, they would argue that our proposed study will not document the “evergreening” that concerns them. However, neither does the Hastings Database, nor the myriad other patent and exclusivity counting projects. In the end, this “evergreening” argument really amounts to a claim that patients should *not* be treated with newer products because the older ones are, objectively, good enough, given their lower prices. This is a normative claim, not an empirical claim. And policymaking on the basis of such a normative claim—taking steps to effectively deny this access by discouraging this innovation—raises philosophical and ethical issues that would need to be addressed carefully by proponents of reform.

CONCLUSION

This Article grew out of concern that policymakers considering significant reforms to domestic pharmaceutical policy have been working from an incorrect assumption that “evergreening” has been empirically documented. The essence of the “evergreening” argument is that brand drug companies protect their drugs with what advocates view as too many patents and exclusivities. Patents and exclusivity secured after initial approval are problematic, the argument goes, because their later expiry dates push generic competition later and later. But this has *not* been empirically documented. Although the Hastings Raw Dataset can serve as a tool for policymakers and scholars, there is no basis for the inference proposed by the Hastings Database, and our study indicates that, as a factual matter, it is likely wrong. Other, similar, counting exercises suffer from the same conceptual infirmities.

New drug approval by the FDA—our standards for both brand drugs and generic drugs—represent the “gold standard” for both protecting and promoting the health of patients. And the American

biopharmaceutical industry leads the world in medical research. Its success is understood to depend in large part on the strong intellectual property protections of U.S. law. We have a profound interest in continuing pharmaceutical innovation—the development and introduction of safe and effective medicines to treat previously untreatable diseases and to offer more, or better, options for currently treatable diseases. Consequently, fundamental changes striking at the heart of domestic pharmaceutical policy—the complex of federal and state laws and policies relating to brand and generic drug approval, and incentives to innovate—should not be undertaken lightly. Reforms based on supposed “evergreening” would not, at this stage, be evidence based.

APPENDIX

New Chemical Entities in Our Dataset

Brand Name	New Chemical Entity	NDA #
Accolate	Zafirlukast	20547
Actonel	Risedronate Sodium	20835
Aldara	Imiquimod	20723
Amitiza	Lubiprostone	21908
Ampyra	Dalfampridine	22250
Astelin	Azelastine Hydrochloride	20114
Atacand	Candesartan Cilexetil	20838
Avapro	Irbesartan	20757
Avodart	Dutasteride	21319
Azilect	Rasagiline Mesylate	21641
Banzel	Rufinamide	21911
Baraclude	Entecavir	21797
Boniva	Ibandronate Sodium	21455
Bystolic	Nebivolol Hydrochloride	21742
Chantix	Varenicline Tartrate	21928
Cialis	Tadalafil	21368
Clolar	Clofarabine	21673
Copaxone	Glatiramer Acetate	20622
Crestor	Rosuvastatin Calcium	21366
Cymbalta	Duloxetine Hydrochloride	21427
Effexor	Venlafaxine Hydrochloride	20151
Effient	Prasugrel Hydrochloride	22307
Elestat	Epinastine Hydrochloride	21565
Emend	Aprepitant	21549
Emtriva	Emtricitabine	21500
Enablex	Darifenacin Hydrobromide	21513

Brand Name	New Chemical Entity	NDA #
Entereg	Alvimopan	21775
Epivir	Lamivudine	20596
Ethyol	Amifostine	20221
Exjade	Deferasirox	21882
Ferriprox	Deferiprone	21825
Fosrenol	Lanthanum Carbonate	21468
Frova	Frovatriptan Succinate	21006
Gemzar	Gemcitabine	20509
Geodon	Ziprasidone Hydrochloride	20825
Hepsera	Adefovir Dipivoxil	21449
INOmax	Nitric Oxide	20845
Inspira	Eplerenone	21437
Integrilin	Eptifibatide	20718
Kerydin	Tavaborole	204427
Kuvan	Sapropterin Dihydrochloride	22181
Kytril	Granisetron Hydrochloride	20239
Levitra	Vardenafil Hydrochloride	21400
Lotronex	Alosetron Hydrochloride	21107
Lunesta	Eszopiclone	21476
Maxalt-MLT	Rizatriptan Benzoate	20865
Micardis	Telmisartan	20850
Mycamine	Micafungin Sodium	21506
Naropin	Ropivacaine Hydrochloride	20533
Plavix	Clopidogrel Bisulfate	20839
Prandin	Repaglinide	20741
Precedex	Dexmedetomidine	21038
Pristiq	Desvenlafaxine Succinate	21992

Brand Name	New Chemical Entity	NDA #
Razadyne	Galantamine Hydrobromide	21169
Renexa	Ranolazine	21526
Reyataz	Atazanavir Sulfate	21567
Rozerem	Ramelteon	21782
Saphris	Asenapine Maleate	22117
Sustiva	Efavirenz	20972
Tarceva	Erlotinib Hydrochloride	21743
Targretin	Bexarotene	21055
Tecfidera	Dimethyl Fumarate	204063
Tekturna	Aliskiren Hemifumarate	21985
Temodar	Temozolomide	21029
Teveten	Eprosartan Mesylate	20738
Tikosyn	Dofetilide	20931
Tykerb	Lapatinib Ditosylate	22059
Uloric	Febuxostat	21856
Ultiva	Remifentanyl Hydrochloride	20630
Uroxatral	Alfuzosin Hydrochloride	21287
Vascepa	Icosapent Ethyl	202057
Vfend	Voriconazole	21266
Viagra	Sildenafil Citrate	20895
Virazole	Ribavirin	18859
Viread	Tenofovir Disoproxil Fumarate	21356
Zaditor	Ketotifen Fumarate	21066
Zetia	Ezetimibe	21445
Ziagen	Abacavir Sulfate	20977
Zytiga	Abiraterone Acetate	202379