Identifying Extensions of Protection in Prescription Drugs: Navigating the Data Landscape for Large-Scale Analysis

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A. Overview

Patents and exclusivities have become an increasingly important component in the "life cycle management" strategies that are employed by pharmaceutical companies to prolong the period of market monopoly for their drugs. When a few additional months of exclusive marketing rights can be worth hundreds of millions of dollars, it is not altogether surprising that drug companies expend so much energy devising new ways to hold off generic competition. Though game-playing involving patents and exclusivities has been explored from a theoretical standpoint, and select case studies have been elaborated in the literature, there has yet to be a comprehensive, quantitative examination of such strategies across the industry. As such, we sought to compile a large volume of Food & Drug Administration (FDA) data that would allow us to examine the prevalence and specific contours of patent and exclusivity game-playing in a more empirically rigorous manner. We hypothesized that the behavior of repeatedly adding patents and exclusivities would be prevalent in a significant portion of drug products. Such a finding would contradict the traditional patent law narrative that each invention receives one period of exclusivity and that everyone in society has access to that invention as soon as the initial period of exclusivity expires.[4]

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[4] *See* Robin Feldman, *May Your Drug Price be Ever Green*, J. L. & THE BIOSCIENCES 2-4 (2018), available at https://academic.oup.com/jlb/advance-article/doi/10.1093/jlb/lsy022/5232981. U.S.

Our study hypothesized that we would find a picture quite different from the one painted in the traditional narrative. We expected to see many drug companies continually returning to the well, adding new patent and exclusivity protections to their reservoirs and artificially extending the period during which they can market and sell their product without any fear of competition. Additionally, we expected to see such behavior increasing in frequency over the course of the past decade. After all, ideas are easily copied, and as a technique becomes increasingly successful, others are likely to follow—unless, of course, one can have exclusive control over the idea of using strategies to extend the life of your drug's exclusivity.[5]

CONST. art. I, § 8, cl. 8 (the Intellectual Property Clause of the Constitution states that, "The Congress shall have Power … To promote the Progress of Science and useful Arts, by securing for *limited Times* to Authors and Inventors the exclusive Right to their respective Wrings and Discovers…" (emphasis added)); Pennock v. Dialogue, 27 U.S. (2 Pet.) 1 (1829) ("[The Constitution] contemplates … that this exclusive right shall exist but for a limited period…"); Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 146 ("Congress may not create patent monopolies of unlimited duration…"); Letter from Thomas Jefferson to Oliver Vans (May 2, 1807), in THE WRITINGS OF THOMAS JEFFERSON 200-202 (A.A. Lipscomb ed., Washington 1903) (Jefferson writing, "Certainly an inventor ought to be allowed a right to the benefit of his invention for some certain time. It is equally certain it ought not be perpetual; for to embarrass society with monopolies for every utensil existing, & in all the details of life, would be more injurious to them than had the supposed inventors never existed"; WILLIAM C. ROBINSON, I THE LAW OF PATENTS FOR USEFUL INVENTIONS42-43 (Boston, Little, Brown 1890) (arguing that "[t]he duty which the state owes to the people to obtain for them, at the earliest moment, the practical use of every valuable invention in the industrial arts is … a higher and more imperative duty than which it owes to the inventor"; Edward C. Walterscheid, *Defining the Patent and Copyright Term: Term Limits and the Intellectual Property Clause*, 7 J. INTELL. PROP. L. 315 (1999-2000) (exploring term limits on rights granted in the Intellectual Property Clause).

[5] At the height of patent trolling and the frenzy to obtain business method patents, some parties did, indeed, try to patent business methods of protecting inventions and advancing legal arguments. *See* Annie Lowrey, *Die, Patent Trolls!* SLATE (Jan. 19, 2011), www.slate.com/articles/business/moneybox/2011/01/die_patent_trolls.html (describing a patent filed by IBM for a system to defend the company's technologies against patent trolls); U.S. Patent No. 20100332285 (filed Dec. 30, 2010) (a patent filed by IBM claiming a "computerized system for providing an IP framework … [which] defines the decision process and plan of action to identify, create, and protect IP for defensive purposes"); Dan L. Burk & Brent McDonnell, *Patents, Tax Shelters, and the Firm,* 26 VA. TAX REV. 981 (2007) (describing the practice of patenting methods for sheltering income from taxation); Theo Francis, *Can You Get a Patent On Being A Patent Troll?* PLANET MONEY, NPR (Aug. 2, 2012), www.npr.org/sections/money/2012/08/01/157743897/can-you-get-a-patent-on-being-a-patent-troll (describing patents filed by IBM and Halliburton that seem to claim the patent troll strategy of accumulating patents and asserting them against other companies); U.S. Patent No. 20070244837 A1 (filed Apr. 3, 2007) (application to patent "a system and methods for extracting value from a portfolio of assets, for example a patent portfolio … by granting floating privileges

To quantitatively test our hypotheses, we set out to gather patent and exclusivity information published in the "Orange Book," which is a regular FDA publication containing information on approved drugs, their therapeutically equivalent generics, and the patents and exclusivities attached to approved drugs, among other drug-related data.[6] As was the case with our prior empirical dive into the realm of FDA citizen petitions,[7] compiling FDA data on patent and exclusivity additions into a format conducive to analysis was a formidable task. One would not expect this degree of difficulty, given that such data is relevant to the public interest and gathered by a government agency that ostensibly provides the interest to the public. The reality, however, is quite different from what one might hope. Copies of the Orange Book for our timeframe of January 2005 through December 2015 were not readily available because the FDA only posts the most recent edition of the Orange Book on its website.[8] Fortunately, we located a researcher

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described herein, a portfolio owner can extend an opportunity for obtaining an interest in selected assets from the portfolio to a client who lacks the resources to accumulate and maintain such a portfolio, in return for an annuity stream to the portfolio owner"); U.S. Patent No. 20080270152 A1 (patent filed by Halliburton on methods which "sometimes include offering a license of the patent property to the second party after the patent property issues as a patent with the claim. The methods sometimes include asserting infringement of the claim by the second party after the patent property issues as a patent with the claim"). This overly expansive notion of controlling ideas was shut down in a series of Supreme Court cases that vastly circumscribed method patents. *See* Bilski v. Kappos, 561 U.S. 593 (2010); Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012); Alice Corp. Pty. Ltd. vs. CLS Bank Int'l, 134 S.Ct. 2347 (2014).

[6] The full title of the Orange Book is "Approved Drug Products with Therapeutic Equivalence Evaluations." *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm. It has acquired the shorthand name of the "Orange Book," in reference to the orange cover of each printed edition of the document. There is also an electronic version of the Orange Book available at http://www.fda.gov/cder/ob/default.htm.

[7] *See* Robin Feldman, Evan Frondorf, Andrew K. Cordova, & Connie Wang, *Empirical Evidence of Drug Pricing Games – A Citizen's Pathway Gone Astray*, 20 STAN. TECH. L. REV. 39 (2017).

[8] On its Orange Book Frequently Asked Questions page, the FDA states that, "Over time, there will be an archive for the annuals and each year's December Cumulative Supplement." Thus, it appears that the FDA plans to make prior editions of the Orange Book available at some point in the future, but those prior editions are not easily accessible online at the present. Moreover, the FDA plans only to make the Cumulative Supplements from December available, excluding the Cumulative Supplements from the other months of the year. Using the December supplement, one would be able to see all the new patents and exclusivities added that year, but one would not be able to parse out in which month the patents and exclusivities had been added prior to December. For more details on the difference between "Annual Editions" and "Cumulative Supplements," and the information contained in each.

who had saved copies of the Orange Book over the years and were able to obtain the editions we needed. Had this resource not been available to us, however, we would have had no means of accessing Orange Books from prior to 2015 when we began our investigation, other than a Freedom of Information Act (FOIA) request, which could have taken years to be processed, given the backlog of FOIA requests at the FDA. Unfortunately, the copies of the Orange Book we obtained were all in PDF format, and as such, were effectively inscrutable to empirical analysis in their original state. Thus, we undertook the time and effort-intensive process of transferring the patent and exclusivity information from each of the PDF-format Orange Books to a spreadsheet format that could be run through a data program like Excel.

Once we compiled all the patent and exclusivity information from the eleven years of Orange Books included in our study, we had to go back through each entry to code what the actual nature of the addition or change was. This coding process, and why it was necessary, will be explained in more detail in Section B.2 below, but essentially, an Orange Book listing marked as a new addition does not, on its own, indicate whether the entire listing is new. It could be that only one or a few elements of the listing are new. Thus, one cannot tell whether a patent listed with a use code is an entirely new patent or simply a new use code added in reference to an existing patent, without examining the prior history of patents associated with the drug in question. This was one of the many laborious analyses we undertook. After all the data was properly compiled and coded, we were able to conduct a variety of analyses to help elucidate the prevalence and extent of game-playing involving patents and exclusivities in the U.S. pharmaceutical industry.

In the sections below, we will explain each step of our methodological process in greater detail. Consistent with our prior practices,[9] as well as our commitment to transparency and high ethical standards in data-driven academics,[10] we intend to make this dataset available to other academics and the general public. The degree of effort that was required to simply gather this set of FDA data and render it usable for empirical

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[9] *See* Robin Feldman, Evan Frondorf, Andrew K. Cordova, & Connie Wang, *Database from Empirical Evidence of Drug Pricing Games – A Citizen's Pathway Gone Astray* (Mar. 7, 2017), *available at* https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2924673 (the publicly available dataset from our prior paper on drug pricing games involving citizen petitions, Feldman et al., *Empirical Evidence*, *supra* note 7).

[10] *See* Robin Feldman, Mark A. Lemley, Jonathan S. Masur, & Arti K. Rai, *Open Letter on Ethical Norms in Intellectual Property Scholarship,* 29 HARVARD J.L. & TECH. 339 (2016) (signed by dozens of professors). In further accord with the *Open Letter*, the University of California Hastings Institute for Innovation Law, which Robin Feldman directs, has made donation information available. *Donors*, Inst. for Innovation L.: UC HASTINGS COLLEGE OF L. (May 3, 2017), http://innovation.uchastings.edu/about/funding/funding-for-academic-year-2015-2016. No private or corporate donor accounts for more than 10% of the Institute's budget.

analysis was extensive. As pharmaceutical pricing gains focus in public policy debates, we hope to save others from the same amount of effort in future investigations into this crucial aspect of the pharmaceutical industry.

B. Methodology Details

1. Just What Are the Cumulative and Annual Editions of the Orange Book

Understanding the data sources begins with an understanding of the Orange Book editions themselves. At the beginning of each year, the FDA publishes an "Annual Edition" of the Orange Book, with information current up to the last day of the previous year. Thus, the Annual Edition lists all approved drugs, whether they are on the market as of that moment, had never been marketed, or have been discontinued from marketing. The patent and exclusivity section of the Annual Edition contains information on the active patents and exclusivities attached to approved drugs.[11] In addition to the annual editions, the FDA also publishes a "Cumulative Supplement" every month of the year, containing new information received and processed since the publication of that year's annual edition. To gain a full picture of the drug approval and patent and exclusivity landscape at any given time, one must read the annual edition from that year and the most recent cumulative supplement in concert. For example, if one wanted to compile a list of all the drugs with patent and exclusivity protections in the Orange Book as of March 2005, one would have to first consult the 2005 Annual Edition to compile all such drugs listed in the Orange Book up to December 31, 2004, and then examine the March 2005 Cumulative Supplement, to compile the drugs added between January 1, 2005 and March 2005.

The FDA explains in the Orange Book that the "goal" with the cumulative supplement is to publish an updated version "by the end of the following month's second work week (e.g., November's supplement will be updated by the end of the second full work week in December)" and that patent and exclusivity information is "current to the

[11] The Annual Edition lists all drug products that have been approved going back to those drugs that were marketed at the time when the first proposed Orange Book was distributed in January 1979. A separate list in the Orange Book exists for those drug products that were approved and marketed at some point, but have been discontinued by the time of publication. The patents and exclusivities section of the Annual Edition, however, lists only those drug products that have patent or exclusivity protections as of December 31 of the prior year. Thus, the patent and exclusivities section of the 2005 Annual Edition of the Orange Book lists only those drug products that have patents or exclusivity protections as of December 31, 2004.

date of publication." [12] Certain regulations require that drug companies submit information within a particular number of days, such as the requirement that companies submit patent information within thirty days of drug approval for the patents to be considered "timely filed."[13] Even if the official receipt date of a patent falls within thirty days, given internal delays in processing and transmitting information, the patent may not reach the Orange Book staff until after the thirty day period, and thus, a patent may still be timely filed even if the timing of its publication in the Orange Book seems to indicate otherwise.

Each cumulative supplement in a year lists both the new patents and exclusivities that were added in that specific month, as well as the patents and exclusivities added in earlier cumulative supplements from that year. For items that are entirely new as of that month, the relevant symbol is **>A>.** Thus, certain lines in the patent and exclusivity section in each cumulative supplement are marked with an **>A>** symbol (or **>ADD>** in earlier years), which indicates that the listing was added to the Orange Book that month and had not appeared in previous cumulative supplements of the Orange Book from that year. As such, all listings in the patent and exclusivity section from the January supplement of any given year are marked with the **>A>** symbol; there are no months that came before it during the year so all things new that year are also new that month. The December supplement, meanwhile, would contain all patents and exclusivities added between January and November of that year—listed *without* the **>A>** symbol—along

[12] *See, e.g., Cumulative Supplement 1: January 2015: Approved Drug Products with Therapeutic Equivalence Evaluations, 35th Edition*, DEPT. OF HEALTH AND HUMAN SERVICES, U.S. FOOD & DRUG ADMIN., at iv. This means that the cumulative supplement titled "November 2015," for example, will be published by the second full work week of December 2015. This lag in the publication of the Orange Book leads to some imprecision in terms of the date on which patent and exclusivity information was actually submitted and the date of the cumulative supplement in which it is published. If the Orange Book staff receives patent information on December 5, 2015, and the November cumulative supplement is not published until December 14, 2015 (at the end of the second full work week), then that patent information will be included in the November cumulative supplement, even though it was technically received by the Orange Book Staff in December. To complicate matters further, there may be some lag between when patent information is officially received by the FDA generally, and when it is received by the Orange Book staff specifically. The Orange Book explicitly states at the end of the patent and exclusivity section that, "Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5)." *See*, *e.g., Cumulative Supplement 1: January 2015*, *supra* note 12, at A-6.

[13] *See infra* note 47.

with any new patents and exclusivities added in December—listed *with* the **>A>** symbol.[14]

2. *Compiling the Patent and Exclusivity Data*

[14] There may be a few new additions to the patent and exclusivity section of the Orange Book that are added between the publication of the December cumulative supplement from one year and the annual edition from the next year (published at the very beginning of that next year). These new patents and exclusivities that happen to be added during this narrow window appear in the annual edition, but are not accounted for in the December or January cumulative supplements, and thus, are never marked as new additions with the **>A>** symbol. There was no way for us to systematically identify any such these cases without compiling the patent and exclusivity data from the annual edition of every single year in our study, which was infeasible from a time and resource point of view. We suspect that this situation of new patents and exclusivities falling through the cracks between years is extremely rare. Theoretically, there should be no gap between the December cumulative supplement of one year, and the January cumulative supplement of the next year. As noted in *supra text accompanying* note 12, the Orange Book aims to publish its cumulative supplement for one month by the second work week of the following month, and the cumulative supplement is "current to the date of publication." As such, if the December cumulative supplement is published on January 14th (at the end of the second work week of January), it should include all patent and exclusivity additions up until January 14. One would presume that any patent and exclusivities after January 14 would then be captured in the January cumulative supplement, published by the second work week of February. The only reason a new patent or exclusivity might fall through the cracks is if the December cumulative supplement was published ahead of schedule, perhaps before the end of December, and a patent or exclusivity that was added in the last few days of December did not make it into either the December or January cumulative supplements. This seems highly unlikely. We know that these unmarked new additions have occurred though, from individual examples we have identified. Consider the antipsychotic drug Seroquel (drug number 20639). In the December 2009 cumulative supplement, Seroquel is listed with six exclusivities: four added earlier in the year and two added that month. The four added earlier were indication exclusivity 560, pediatric exclusivity applied to indication exclusivity 560, indication exclusivity 503, and pediatric exclusivity applied to indication exclusivity 503. The two exclusivities marked as new additions for December 2009 were a new patient population exclusivity and a pediatric exclusivity applied to that new patient population exclusivity. In the 2010 annual edition, published at the very beginning of 2010, Seroquel is listed with *eight* exclusivities. In addition to the six that were listed in the December 2009 cumulative supplement, there is *another* new patient population exclusivity and a pediatric exclusivity applied to that new patient population exclusivity; these are distinct from the new patient population and pediatric exclusivity that were added in December 2009. Seroquel is nowhere to be found in the January 2010 cumulative supplement. Thus, the second new patient population exclusivity and its accompanying pediatric exclusivity are never accounted for as a new addition in any cumulative supplement. Again, we believe that such cases are quite rare and would not have any significant effect on our results. Also reassuring is that the only effect of these hidden patent and exclusivity additions would be to understate our results, creating the impression that there are fewer patents and exclusivities than in actuality.

The process of compiling data on patents and exclusivities added to drugs between 2005 and 2015 consisted of three general stages: 1) transferring all patent and exclusivity additions from the PDF cumulative supplement for each month between January 2005 and December 2015 to a spreadsheet); 2) transferring all patent and exclusivity information from the 2005 annual edition of the Orange Book to the spreadsheet to serve as a reference against which to analyze the additions after the 2005 annual edition was published; and 3) double checking all of the data entries in our spreadsheet to minimize the likelihood of human error.

a. Transferring Patent and Exclusivity Data from the Cumulative Supplements

The first step in our data gathering process was to transfer all patents and exclusivities marked as new additions from each month between January 2005 and December 2015 over to a comprehensive spreadsheet.

The spreadsheet included a wide range of information. For each patent or exclusivity, we recorded the active ingredient name, the product name, the New Drug Application (NDA) number, the month and year of the addition, whether the addition was a patent or exclusivity, the patent number (if applicable), the code(s) attached to the patent or the exclusivity code, the expiration date, the strength(s) of the drug to which the Orange Book addition applied, and whether a "delist request" flag was attached to the patent.[15] After transferring the above information available in the Orange Book, we used the Drugs@FDA database—an online repository of basic data on most drug products approved since 1939—to obtain the approval date for each New Drug Application in our dataset.[16] In all, the patent and exclusivity information from every month between

[15] A delist request flag indicates that the drug company has requested that the patent be removed from the Orange Book reference for their drug, but that the patent has remained listed because a first generic applicant may retain eligibility for 180-day exclusivity based on based on successfully asserting that the patent is invalid or should not be applied to the drug. *Orange Book Data Files*, U.S. FOOD & DRUG ADMIN. (last updated Feb. 24, 2017), https://www.fda.gov/drugs/informationondrugs/ucm129689.htm (providing descriptions of all data fields available in the Orange Book files, including the "patent delist request flag" data field).

[16] *See* Drugs@FDA: FDA Approved Drug Products, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/daf/. The approval date of any given drug can be found by searching for the NDA number or drug name, clicking on the page corresponding to that drug, and opening the "Approval Date(s) and History, Letters, Labels, Reviews for NDA #"

January 2005 and December 2015 amounted to 3,834 pages of data that we pored through by hand.

Drug strengths pose particular recording challenges. In the Orange Book, each strength of a drug is listed separately. Thus, if a certain patent or exclusivity applies to multiple strengths of a drug, the patent or exclusivity will be listed multiple times. In most cases, we found that if a patent or exclusivity was applied to one strength of a drug, it was eventually applied to all strengths of the drug. As a result we felt that listing a patent or exclusivity multiple times in our dataset, for each corresponding strength, would amount to a form of double-counting and create an inaccurate picture of the level of patent and exclusivity activity. To choose the most conservative approach possible, we listed each patent and exclusivity that applied to a drug only once. In a column corresponding to that patent or exclusivity, we catalogued which strengths of the drug it had been applied to. This required extremely careful parsing of the Orange Book; in most cases, a list of added patents would be identical across all strengths of a drug, but occasionally, there were minute distinctions that could easily be missed, such as an extra patent added onto just one out of eight different strengths of the same drug.[17]

More generally, when considering an analysis of how many drugs are involved in a particular behavior—in our case, how many drugs added patents or exclusivities between 2005 and 2015—one must choose the level at which to conduct the analysis. 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 new drug application number, or the specific strength or formulation.

Consider the opioid addiction treatment drug, Suboxone. The active ingredients in Suboxone are buprenorphine hydrochloride and naloxone hydrochloride. There are,

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drop-down menu, under which an "action date" will be listed next to the "action type" of approval.

[17] For example, in September 2015, there were seven strengths listed for the drug Vyvanse (drug number 21977). In that supplement, there were five patents marked as new additions for all seven strengths. In addition, however, there were two patents marked as new additions for all strengths except strength 5. There was another patent marked as a new addition for all strengths except strength 5 and strength 7, and another patent marked as a new addition for only strengths 4, 5, and 6. Finally, there were ten patents that were marked as new additions for only strength 7. Another example would be the exclusivity additions to Risperdal (drug number 20272) in February 2007. The three exclusivities— indication number 509, indication number 413, and indication number 412—all with pediatric exclusivity attached, were added to strengths 1, 2, 3, 4, 7, and 8 of the drug. Indication numbers 413 and 412, with pediatric exclusivity, were added to strength 5, but indication number 509 was not. Strength 6 simply does not exist for that drug for some unknown reason.

however, brand-name drug products other than Suboxone that are identified with the exact same two active ingredients, including Bunavail and Zubsolv. Moreover, within the brand-name Suboxone itself, there are two different new drug application numbers: drug application 20733, approved in October 2002, and drug application 22410, approved in August 2010. And within Suboxone drug application 22410, there are four different strengths of the drug, corresponding to the same drug application number.

For our analysis, we chose to define "drug" at the level of the new drug application number, because many anecdotal reports suggest that pharmaceutical game-playing occurs at that level of granularity.[18] For example, if one version of a drug (at the new drug application level) is on the verge of losing patent protection, the pharmaceutical company might switch from a capsule to a tablet and submit a new drug application for the drug in tablet form, with new protections stemming from the revised formulation.[19] We did not go as far down as the level of strength, however, because we felt it could be misleading to define a 10mg strength and a 20mg strength of one drug as two separate drugs—resulting in counting two occurrences of strategic behavior—given the commonplace understanding of what "drug" means. Moreover, as noted above, a patent or exclusivity applied to one strength was applied to all strengths of the drug, in most cases.

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[18] *See generally* ROBIN FELDMAN & EVAN FRONDORF, DRUG WARS: HOW BIG PHARMA RAISES PRICE AND KEEPS GENERICS OFF THE MARKET 26-27 (Cambridge University Press 2017) (explaining how Abbreviated New Drug Applications, the generic counterpart to the New Drug Application, are the "battleground for many of the games that are played between brand-name companies and generics"); Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009, 1022-24 (2010) (noting how the drug company Cephalon introduced a new drug product, Nuvigil, with a different New Drug Application number, when it began to face generic competition on its sleep-disorder medication Provigil); Steve D. Shadowen, Keith B. Leffler & Joseph T. Lukens, *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 RUTGERS L.J. 1 (2009) (analyzing New Drug Application approval reports to examine anti-competitive product changes in the industry).

[19] *See, e.g.,* Jessie Cheng, *An Antitrust Analysis of Product Hopping in the Pharmaceutical Industry*, 108 COLUM. L. REV. 1471, 1491-92 (2008) (explaining how Abbott and Fournier, the drug companies that manufactured the cholesterol drug TriCor, began selling a tablet formulation shortly after Teva filed an application to sell a generic version of TriCor in its original capsule form); FELDMAN & FRONDORF, *Drug Wars*, *supra* note 18, at 541 (describing how Reckitt Benckiser developed a new film version of its opioid addiction drug Suboxone just as exclusivity was about to expire on its tablet version); Robin Feldman & Connie Wang, *A Citizen's Pathway Gone Astray—Delaying Competition from Generic Drugs*, 376 N. ENGL. J. MED. 1499, 1500 (2017) (describing how, on the eve of generic competition, Warner Chilcott began marketing a new version of its acne medication Doryx with two score lines as opposed to one).

The validity of measuring the data at this level was bolstered by the fact that other researchers in the field have adopted the same approach. For example, in an examination of generic challenges to brand-name patents, Hemphill & Sampat chose to measure such challenges at the new drug application level.[20] In their justification, the authors note that although technically, generic patent challenges are made in relation to the dosage strength level, their data showed that the first generic challenger received approval for all or nearly all strengths. In other words, the relevant activity was not occurring at the level of the dosage strength, but rather all dosage strengths were being swept together.

There may, indeed, be game-playing involving different strengths of the same drug. For example, for a generic drug to receive approval, it must match the brand-name product in dosage strength.[21] If a new formulation is not the same dosage or strength, pharmacists are not allowed to substitute the generic under most state drug substitution laws, and such substitution is the major pathway for generic drug companies.[22] Thus, although we do not count the same patent applied to different dosages as more than one occurrence, our spreadsheet does track instances in which a patent or exclusivity that had already been applied to one strength of a drug is applied to a new strength of that drug, so that future research can identify and analyze the behavior, if it is of interest.

We should also note that the definition of "drug" could include drugs listed in Abbreviated New Drug Applications (ANDAs). ANDAs are the applications filed by companies seeking approval for a generic version of a drug.[23] Generic applications are likely to be listed in the patents and exclusivities section of the Orange Book, however, only in relation to what the Orange Book calls, the "PC" or "patent challenge" exclusivity. The patent challenge exclusivity is a 180-day period of exclusivity awarded

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[20] *See* C. Scott Hemphill & Bhaven N. Sampat, *Evergreening, patent challenges, and effective market life,* 31 J. HEALTH ECON. 327, 329 (2012).

[21] Orange Book Preface: Approved Drug Products with Therapeutic Equivalence Evaluations, CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN. (36th ed. last updated June 10, 2016), http://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm.

[22] *See* Tobin Klusty, *A Legal Test for the Pharmaceutical Company Practice of "Product Hopping,"* 17 AM. MED. ASSOC. J. ETHICS 760, 760 (2015).

[23] Though the terms "NDA" and "ANDA" are commonplace in life science parlance, we use the terms "new drug application" and "generic drug application" in most places, to prevent confusion stemming from a paper littered with insider acronyms. As one of the authors has noted previously, writing in clear, straightforward language presses those in the legal field to be faithful to supportable logic, rather than subject to the whims of prejudice masked in obscurity. *See* ROBIN FELDMAN, THE ROLE OF SCIENCE IN LAW 180 (2009) (excerpted in Feldman, *Plain Language Patents*, 17 TEX. INTELL. PROP. L.J. 289 (2009) and discussing the dangers that arise when legal actors cloak themselves in scientific jargon); *see also* FELDMAN, THE ROLE OF SCIENCE IN LAW 5-7, 174-95 (exploring the issue further).

to the first generic drug to successfully challenge a brand-name patent under Paragraph IV of the Hatch-Waxman Act. Our research examines the use of exclusivities to obstruct generic entry. The 180-day exclusivity represents the exact opposite—the successful entry of a generic competitor—and thus, does not fall within the scope of our study. As such, we excluded all patent challenge exclusivities from our dataset and did not include generic drugs in our figures for the overall number of drug products. Once again, the goal was to choose a conservative approach and to avoid artificially inflating the relevant numbers.

Finally, for the purposes of this paper, we included only small-molecule drugs, rather than biologics, in our data set. Small-molecule drugs are simple, stable, single-molecule entities that are produced through chemical synthesis and are easy to replicate.[24] Commonplace drugs, such as aspirin, that are familiar to most people are small molecule drugs. In contrast, biologic drugs stem from a newer strain of biomedical research, and are large, complex products produced in living cell cultures for which it is currently impossible to create identical copies.[25] Examples of biologics include vaccines, blood products, and advanced gene therapies.[26] The FDA does not include biological products—or their generic counterparts termed "biosimilars" or "interchangeables"—in the Orange Book but has established a separate publication, colorfully known as the "Purple Book."[27]

Unfortunately, the Purple Book is much less comprehensive than the Orange Book and does not include a patent and exclusivity section. As a result, our analysis could not extend to biologics. If data on the patents and exclusivities attached to biological products

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[24] *See Small Molecule versus Biological Drugs*, GENERICS AND BIOSIMILARS INITIATIVE (June 29, 2012), http://www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs; *What Are "Biologics" Questions and Answers*, U.S. FOOD & DRUG ADMIN. (last updated Aug. 5, 2015), https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133077.htm. Also, the New Drug Application (NDA) format is distinct to small-molecule drugs. Biologics have a separate type of application called a Biologics License Application (BLA). *Biologics License Applications (BLA) Process (CBER)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/biologicsbloodvaccines/developmentapprovalprocess/biologicslicenseapplicationsblaprocess/default.htm.

[25] *Id.*

[26] *See What Is a Biological Product?* U.S. FOOD & DRUG ADMIN. (last updated May 31, 2016), https://www.fda.gov/aboutfda/transparency/basics/ucm194516.htm.

[27] *Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, U.S. FOOD & DRUG ADMIN. (last updated June 9, 2017), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm.

can be obtained in the future, whether through the FDA deciding to make such data public in the Purple Book or through a FOIA request, conducting an analogous inquiry into activity in the biologics sphere would be a worthwhile endeavor. Biologics and their generic counterparts are also a younger phenomenon. Congress created a system for expedited approval of copies of biologic drugs in 2010,[28] and the first biosimilar was approved only in 2015.[29] Thus, the skirmishes over generic versions of biologics are in their infancy. Over time, however, greater FDA reporting and transparency will be critical for tracking and evaluating behavior in this increasingly important sector of the industry.

b. Transferring Patent and Exclusivity Data from the 2005 Annual Orange Book

The next step in assembling our dataset involved transferring over all patent and exclusivity information listed in the *annual* edition of the Orange Book from the year 2005 (as opposed to the cumulative supplements from 2005, which at this point, had already been entered into the dataset) in order to provide baseline information. Specifically, when a patent or exclusivity is marked as a new addition in a cumulative supplement, the Orange Book does not identify which component of the listing warranted the new addition flag. It could be that the entire listing—patent number, expiration date, patent codes, and all—is new, but it could also be that just one element is new. Thus, it was necessary to create baseline information to know which patents and exclusivities were already on the books at the start of our time period so that we could tease out which part of the listings flagged as new in any of the 2005 cumulative supplements constituted the addition. The annual edition for 2005 is published at the *beginning* of 2005, and it contains information that is current up to the last day of the previous year. Thus, entering the 2005 annual supplement provided the necessary baseline information for the initial year of our dataset.

Consider the multiple myeloma drug, Velcade. The March 2007 cumulative supplement of the Orange Book flags patent number 5780454, listed under Velcade, with the symbol for a new addition. The patent is shown in the listing as having an expiration date of May 3, 2017 and a drug product code, which indicates that the company believes

[28] Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, 124 Stat. 804, 807 (2009).
[29] *FDA Approves First Biosimilar Product Zarxio,* U.S. FOOD & DRUG ADMIN. (Mar. 6, 2015), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm.

the patent covers the formulation and composition of the drug.[30] Without having any context, one might categorize this as the addition of a new patent. In the 2005 *Annual* Orange Book from the start of 2005, however, which is the oldest annual Orange Book from which we obtained data, patent 5780454 is already listed for Velcade, with expiration date October 28, 2014 and no patent codes. Thus, one can tell that the March 2007 listing is marked as new, not because it is an entirely new patent, but because the expiration date has been extended and a new drug product code has been attached to the patent.

Thus, creating baseline information required entering every patent and exclusivity listing from the 2005 Annual Orange Book into our dataset. The annual book consists of a much larger volume of data than any of the individual cumulative supplements that had been entered previously. For those cumulative supplements, we were only entering information for the patents and exclusivities that had been added that month (i.e., those marked with the **>A>** symbol). For the 2005 Annual Orange Book, we entered *all* listings for every drug on the market with patents and/or exclusivities attached as of the start of that year, to create a full record of what patents and exclusivities were listed at the beginning of our period of interest. Specifically, the PDF version of the 2005 Annual Orange Book contained a total of 134 pages of patent and exclusivity data. All listings from this annual edition were clearly marked as being from "pre-2005" in our dataset, so that they would not be confused with patents and exclusivities that had been added from January 2005 onward. It is worth emphasizing again that those patents and exclusivities from the 2005 Annual Orange Book were used only as a reference from which to interpret patents and exclusivities added between 2005 and 2015—they were not included in our count of how many patents and exclusivities were added to the Orange Book in our study timeframe.

c. Verifying the Accuracy of the Patent and Exclusivity Data

Ultimately, this process of collecting patent and exclusivity data for the eleven years from 2005 to 2015—both the monthly supplements and the 2005 annual edition—yielded 16,141 individual rows of data, with nine to eleven data field columns per each row. This amounts to over 160,000 individual cells of data, all entered by hand.

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[30] *See Orange Book Data Files,* U.S. FOOD & DRUG ADMIN. (last updated Feb. 24, 2017), https://www.fda.gov/drugs/informationondrugs/ucm129689.htm (providing descriptions of all data fields available in the Orange Book files, including the "patent delist request flag" data field). 21 CFR 314.53(b).

Any process of manually compiling over 160,000 individual items of data, many of which were random strings of numbers, is subject to human error. Thus, we went back through a second time and double-checked every entry from the monthly supplements and the 2005 annual edition for accuracy, comparing what was listed in the PDF Orange Books with what was listed in our spreadsheets. A small number of errors were found and corrected.

We are optimistic that by double-checking every Orange Book listing in our dataset, we were able to catch the overwhelming majority of errors. There exists the possibility, however, that there were a few remaining errors that we did not catch upon second review. Given the massive volume of data, we are confident that the overall conclusions would remain unchanged even if there were a small number of data entry errors that were not caught. Some of the most likely mistakes—such as mistyping one number in the random, seven-digit string that composes a patent number—would be largely inconsequential, as for the most part, the information of note is that a patent was added, not that patent 6789039 rather than 6789038 was added. Moreover, the coding process, which is described in the section below, effectively required us to go through the data line-by-line a third time, further reducing the possibility of significant inaccuracies in our dataset.

3. Coding the Patent and Exclusivity Data

After entering and double-checking each individual addition to the patent and exclusivities section of the Orange Book, we proceeded to the analysis stage. Before we could process the data and derive results, however, we needed to code each entry in our dataset to reflect the nature of the addition or change to the Orange Book in a concise and consistent manner.

As noted in the section above,[31] Orange Book entries do not explicitly identify whether the entire listing is new or whether just one element of the listing is new, and if so, which component of the patent or exclusivity is new. Consequently, a level of human expertise and interpretation is required to parse the data and translate patent and exclusivity information from the Orange Book into meaningful categorizations.

Consider the heartburn relief medication Nexium.[32] The drug was approved in October 2006. In November 2006, the company added ten patents, one of which was patent number 4738974, which included the expiration date of April 19, 2007, a drug substance code, a drug product code, and the use code 773. This patent was applied to

[31] *See supra* note 30 and accompanying text.
[32] Nexium has the new drug application number 21957.

strengths 1 and 2 of the drug. Immediately below this entry, patent number 4738974 was listed yet again, with the same expiration date, the same drug substance and drug product codes, and applied to the same strengths. The only difference was that instead of use code 773, use code 729 was listed. Taken in isolation, this second patent listing could appear as the addition of an entirely new patent; in reality, it was simply a patent being listed twice to account for two different use codes. Additionally, below that second occurrence of patent number 4738974, the patent number was listed a third time, just with the letters "*PED" affixed to the end, with the expiration date October 19, 2007 (rather than April 19, 2007), and no drug product, substance, or use codes. This third listing indicates that the drug had received a pediatric exclusivity, which was applied to the patent, and thus, extended the effective expiration date by six months.[33] Thus, reading these three patent listings in context, one can deduce that what was added to strengths 1 and 2 of this drug was a single patent (with a drug substance code, a drug product code, and *two* different use codes) and a pediatric exclusivity, extending the expiration date of that patent out to October 19, 2007.

To complicate matters further, five months later, in the April 2007 supplement to the Orange Book, patent number 4738974 is again listed three times, once for each of the two use codes, and once with the "*PED" annotation for pediatric exclusivity. This time, the expiration date for the first two has been changed to September 1, 2007, and the expiration date for the third has been changed to March 1, 2008. If one had not seen the earlier entries from November 2006, one might assume that what was added in April 2007 was a new patent (with a drug substance code, a drug product code, and two different use codes), and a pediatric exclusivity, but that would be inaccurate. Knowing the prior Orange Book history, we can deduce that what was added in April 2007 was simply a patent term extension of some sort, pushing out the original expiration date of

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[33] To incentivize the collection of safety and efficacy data on drug use in pediatric populations, the FDA grants a six-month period of protection to companies that perform pediatric clinical trials. Pediatric exclusivity applies to both patent rights and exclusivities, such that each existing patent and exclusivity is separately extended by six months. *See Patents and Exclusivity,* FDA/CDER SBIA CHRONICLES, U.S. FOOD & DRUG ADMIN. (May 19, 2015), https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf. This pediatric exclusivity right applies to all formulations and uses of drugs, including those for adult populations. There are questions as to whether the benefit received by drug companies that conduct these pediatric trials is proportionate to the societal benefit, as the company receives the benefit even if the trials are unsuccessful. *See* Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM J.L. & ARTS 53, 85-87 (2016) (describing the pediatric benefit in detail, along with critiques of the program) [hereinafter, "*Regulatory Property"*].

April 19, 2007 to September 1, 2007 (which was then extended to March 1, 2008 in light of the pediatric exclusivity six-month addition).[34]

Other cases exist in which a patent listing appears identical to another previous listing. The only change is that while the patent was applied previously to strengths 1 and 2, for example, it is now being applied to strengths 3 and 4, as well. Although this might initially appear to be a new patent, to categorize it as such would be misleading, given that the substance of the change involves adding an existing patent to new strengths.

Due to the interpretation needed to accurately represent each Orange Book addition or change, we had to go through each line in our dataset, reading every entry in the context of the patents and exclusivities that came before. We assigned each type of Orange Book addition or change a specific shorthand code, a full index of which is available at *Appendix A*. For example, a new patent with a use code attached would be coded as P:UC, pediatric exclusivity applied to a patent would be coded as P:PED, and a new orphan drug exclusivity would be coded as ODE. The changes we tracked that we considered to be significant for our analysis of pharmaceutical game-playing included:

- Patents added for the first time, regardless of whether the addition included any drug substance, drug product, and/or use codes;[35]
- The addition of drug substance, drug product, and/or use codes to existing patents;
- Exclusivity additions (a full list of the exclusivities tracked can be found in *Appendix A*);

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[34] *See* Feldman, *Regulatory Property, supra* note 33 (describing the way in which the exclusivity for pediatric drug testing applies to extend all other patents and exclusivities by six months).

[35] A drug substance code indicates that the company believes the patent covers the active ingredient. A drug product code indicates that the company believes the patent covers the formulation and composition. A use code indicates the company believes the method-of-use patent covers a particular indication or use of the drug product—use codes can apply across multiple applications, multiple products, and multiple patents. *See Orange Book Data Files, supra* note 30; 21 CFR 314.53(b). This means that the same use code can be applied to two or more different patents, new drug application numbers, and/or drug products. For instance, use code 257 indicates that drug company is asserting that their method-of-use patent covers "treatment of HIV infection." *See Approved Drug Products with Therapeutic Equivalence Evaluations: 35th Edition*, U.S. FOOD & DRUG ADMIN. at ADB 32 of 67 (2015). In our dataset, use code 257 is attached to numerous different patents, new drug application numbers, and drug products, which should not be altogether surprising given that HIV infection is a medical problem that has spurred much innovation in the pharmaceutical realm. For instance, use code 257 is attached to five different patents under the drug Epzicom (drug number 21652) and several patents under two different drug numbers corresponding to the product Agenerase (drug number 21007 and drug number 21039).

- Patents marked with a "delist request" flag;[36]
- Cases in which existing patents or exclusivities were added to a new strength of the same drug.

There were other changes that we tracked but excluded from our analysis because it was unclear whether these changes were relevant to strategic pharmaceutical game-playing. These changes include cases in which:

- The patent term increased or decreased;
- A drug substance, drug product, and/or use code was removed;
- A change to a patent was applied to another use code listing of the same patent;[37]
- A listing was determined to be an error in the Orange Book, whether made on the part of the company or the Orange Book staff—a category we call "errors";
- A listing was determined to be a correction of a previous error on the part of the company or the Orange Book staff—a category we call "corrections";
- The Orange Book listing was ambiguous.[38]

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[36] As noted earlier, *see supra* note 15, a delist request flag indicates that the company has requested that the patent be removed from the Orange Book reference for that drug, but that the patent has remained listed because a first generic applicant may retain eligibility for a 180-day exclusivity based on successfully asserting that the patent is invalid or should not be applied to the drug.

[37] As noted earlier, *see supra* note 35, when a single patent has more than one use code attached to it, the patent is listed separately for each use code. For instance, Imbruvica (drug number 205552) was approved on February 12, 2014. That month, Imbruvica added patent number 8476284 to the Orange Book. In the supplement for that month, the patent was listed once with use code 1456 attached. Immediately after that listing, the patent was listed again with use code 1491 attached. Rather than the patent being listed once, with both use code 1456 and use code 1491 listed under the patent codes column, the patent was listed two separate times—once for each use code. Thus, some tracked listings do not represent a new change to the patent, but rather, a change already made to the patent with one use code, being applied to the same patent with a different use code.

[38] There were several listings for which we could not definitively determine the nature of the Orange Book addition or change. In the interest of erring on the conservative side, we simply classified these listings as "ambiguous" and excluded them from our analysis. For example, in June 2014, patent number 8746242 was added to the drug Incruse Ellipta (drug number 205382). The next month, the same patent number 8746242 was listed under the same drug number 205382 once again, with the expiration date increased by one day to October 11, 2030. The marginal change to the expiration date, as well as how soon after the initial listing the new expiration date was published, cast doubt on whether this was truly a patent term extension or adjustment or if it was simply a correction of an Orange Book error. Thus, we classified the re-listing of the patent with the revised expiration date as ambiguous, and excluded it from our analysis.

In terms of cases in which the patent term increased or decreased, there are several plausible explanations. A patent term increase could be attributable to a patent term extension or a patent term adjustment. A patent term extension is governed by 35 U.S.C. §156 and is meant to compensate for delays in the regulatory approval process for pharmaceuticals and other products subject to pre-market approval. Essentially, the formula for calculating the length of a patent term extension is half of the testing phase plus the approval phase, with a maximum patent term extension term of five years, and a limit on the total remaining patent term of fourteen years. The drug company must file its application for a patent term extension before the patent expires and within fifty days of drug approval. On the other hand, a patent term adjustment is governed by 35 U.S.C. § 154(b) and applies to *all* patents—not just those attached to products subject to pre-market approval, such as drugs. The patent term adjustment is meant to compensate for delays at the Patent Office in examining and issuing patents, as opposed to FDA delays in approving drug products. The basic formula is the number of days of Patent Office delay minus the number of days of applicant-caused delay. This adjustment is meant to ensure that "no applicant diligently seeking to obtain a patent will receive a term of less than 17 years." Approximately 80% of patents receive patent term adjustments due to Patent Office delay, and of that group, the average adjustment is about 600 days.[39]

We categorized a listing as an error when we found an original entry line that might appear to be a separate addition of new patent or exclusivity information, but in reality, was entered in error by the company or the Orange Book staff. Whether something is an error is, unsurprisingly, not indicated explicitly in the Orange Book. We were able to surmise which entries were most likely errors by observing patterns in the Orange Book data. For example, in the November 2013 supplement, patent number 7053902 with use code 839 is added to Abilify (drug number 21436). This patent is only listed with the use code, however, for strength 1. For strength 2, 3, 4, 5, and 6, the same patent is listed as a new addition, but without the use code. The patent mysteriously does not appear at all in the next supplement, December 2013. In the 2014 annual edition of the Orange Book—published at the very beginning of 2014—the drug (number 21436) shows that patent listed with the relevant use code for all strengths. Thus, we can be confident that the listing of the patent without use code 839 for strengths 2-6 in the November 2013 supplement was an error, corrected in the annual edition a month later. In other words, the original entries at first glance could appear to be two separate additions: 1) an addition of a new patent generally applied to all but one strength of the drug and 2) the addition of that new patent interpreted as protecting a particular new use

[39] *See* Dennis Crouch, *Patent Term Adjustment (PTA) Statistics,* PATENTLYO (July 27, 2011), http://patentlyo.com/patent/2011/07/pta.html.

only for the remaining strength. Nevertheless, the listing should simply have been one single addition, consisting of a new patent interpreted to apply to a particular use added to all strengths of the drug. Having two slightly different entries in the Orange Book was an error.

Another example of an error is a listing in the June 2008 supplement for Vytorin (drug number 21687). There are four strengths of the drug listed. Strengths 1, 2, and 4 show the addition of miscellaneous exclusivity number 54 with expiration date June 5, 2011 and a pediatric exclusivity added onto that exclusivity with expiration date December 5, 2011. For strength 3, miscellaneous exclusivity number 54 is also listed with the same expiration date of June 5, 2011, but the pediatric exclusivity is listed as changing that expiration date to December 5, 2008—years shorter than the December 5, 2011 expiration date listed with the pediatric exclusivity for the other strengths. If that were accurate, it would suggest that the pediatric exclusivity for that one strength had the effect of actually shortening the expiration date of the patent from June 2011 to December 2008. That, however, cannot be accurate. Application of a pediatric exclusivity adds six months; it does not decrease the expiration date by two-and-a-half years. Thus, we could be confident this was an error in the Orange Book. Our classification of this entry as an error is confirmed by the supplement in the following month of July 2008. That supplement once again lists four strengths for Vytorin, but this time, the pediatric exclusivity expiration date for all of them is December 5, 2011, including for strength 3.

We only classified listings as errors in obvious cases such as these. Otherwise, we classified entries as ambiguous.

As noted above, we categorized a listing as an error when we found an original entry line that might appear to be a separate addition of patent or exclusivity information, but in reality, was merely a separate line entered in error by the company or the Orange Book staff. The mirror image of these are new listings added to the Orange Book that do nothing but correct previous Orange Book errors. The difference between the two categories is essentially that with errors, two entries appear that would only be one, if they had been entered correctly. The proper information can be seen in later additions of the Orange Book, but in a way that the information is not flagged as a new addition. With corrections, a new entry appears flagged as an addition, but the new entry is simply a correction of a previous Orange Book error. Either way, our goal was to avoid double counting those things that were merely the result of errors by the company or the Orange Book staff, whenever we could identify them.

Some of the changes in the second list—changes we tracked but excluded from our analysis—could conceivably be related to pharmaceutical game-playing in one way or another. For example, there are cases in which a single drug product can receive

multiple patent term extensions by strategically having two new drug applications approved on the same day and then extending a different patent for each.[40] Despite this possibility, our overarching philosophy in making methodological decisions was to err on the side of caution and make the conservative choice, with the result that, if anything, we are understating as opposed to overstating the results.

As noted earlier,[41] there was one type of Orange Book listing that we excluded from our dataset entirely: the "PC" or "patent challenge" exclusivity. Because the patent challenge exclusivity represents the successful attempt of a generic to challenge a brand-name company's patent and enter the market, it does not fall within the scope of our inquiry into the use of exclusivities by brand-names to extend the lifecycle of their drugs and prevent generic entry.

After completing the coding process, our data consisted of a complete set of every patent and exclusivity added to the Orange Book between January 2005 and December 2015, with each line neatly categorized into a specific type of Orange Book addition or change. With this dataset in hand, we moved on to establishing a set of metrics for drawing conclusions from the large volume of data we had compiled and organized.

4. Establishing Key Metrics

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[40] Patents are eligible for a patent term extension (PTE) if patent life was lost during the "regulatory review period." The patent term extension statute at 35 U.S.C. §156(c)(4) states that "in no event shall more than one patent be extended … for the same regulatory review period for any product." The FDA, however, considers each regulatory review period for different new drug applications to be distinct, even if they share the same regulatory review period dates, and thus, each new drug application is eligible for its own patent term extension. Thus, if a single drug product is covered by multiple patents, it may receive a different patent term extension for each new drug application approved on the same first day. *See* Kurt Karst, *Looking a Gift Horse in the Mouth – Why Would a Company Refuse a Patent Term Extension?* FDA LAW BLOG (May 1, 2008), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2008/05/looking-a-gift.html. Examples of products that have used this multiple patent term extension strategy to their advantage include Omnicef, Lyrica, Mycamine, and Vimpat. *See* Kurt Karst, *False Friends: FDA's "Gift" on NESINA – Present or Poison? It May Depend on Which Hatch-Waxman Language is Spoken,* FDA LAW BLOG (May 2, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/05/false-friends-fdas-gift-onnesina-present-or-poison-it-may-depend-on-which-hatch-waxman-language-is-.html. This strategy can lead to what appear to be multiple patent term extensions for a single new drug application, because it is common for multiple new drug applications corresponding to the same drug product to share patents, and to benefit from a patent term extension that stemmed from regulatory review period delays from a related, but separate, new drug application.

[41] *See text accompanying notes* 22-24.

As described above, our goal in assembling the dataset was to quantitatively evaluate the use of patents and exclusivities as a lifecycle management strategy for pharmaceutical products. To accomplish this task, we created metrics including the following:[42]

- The number of drugs that added patents or exclusivities to the Orange Book between 2005 and 2015, compared to the total number of drugs available between 2005 and 2015;
- The number of drugs that added patents or exclusivities to the Orange Book, broken down by year for each year between 2005 and 2015;
- The number of drugs that added an exclusivity, broken down by type of exclusivity;
    - Exclusivities examined on this more granular level include orphan drug exclusivity, new patient population exclusivity, new product exclusivity, pediatric exclusivity, and indication exclusivity.[43]

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[42] As a reminder, the use of the term "drug" and the measurement of "number of drugs" in our study refers to drugs at the New Drug Application (NDA) level, *supra* text accompanying notes 18-20.

[43] There is one exclusivity for which the notation in the Orange Book, and consequently the coding in our dataset, requires some additional explanation. For most exclusivities, there is a one-to-one relationship between the number of exclusivities that a drug receives and the number of times that exclusivity appears in the Orange Book. For example, if a drug receives an orphan drug exclusivity, that means that the FDA is barred from approving any other application for the same orphan disease for seven years, and that is noted in the Orange Book with the abbreviation ODE appearing once with the expiration date of the exclusivity printed next to it. Pediatric exclusivity, however, is not a one-and-done situation. It appends six months of market protection to the end of *all* patents and exclusivities listed in the Orange Book that contain the same active moiety on which the pediatric studies were conducted. *See Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN., *supra* note 33. Thus, when a drug company receives a grant of pediatric exclusivity, that one grant can manifest multiple times in the Orange Book, appearing once for each patent and exclusivity to which it is applied. Specifically, for each patent to which pediatric exclusivity is applied, the original patent and original expiration date are listed, and immediately below that line, the original patent number with "*PED" appended to the end is shown, with the original expiration date extended by six months printed next to it. For exclusivities to which pediatric exclusivity is applied, the original exclusivity and original expiration date are listed, and below, the letters "PED" are printed in the exclusivities column, with the original expiration date extended by six months printed next to the letters "PED." Inconveniently, the Orange Book does not explicitly indicate which "PED" exclusivity notation corresponds to which original exclusivity, so one has to infer which original exclusivity each "PED" applies to by matching up the expiration dates. Essentially, the Orange Book notates each individual time pediatric exclusivity is applied to a different patent or exclusivity, rather than the number of pediatric exclusivity grants from which those applications to specific patents or exclusivities stemmed. As such, in our analysis, we employed the same system as the Orange Book and counted the number

- The total quantities of patents and exclusivities added between 2005 and 2015;
- The number of drugs that added a high quantity of patents in a single year between 2005 and 2015;
- The number of separate times that each drug added something to the Orange Book (a measure of "serial offenders");
- The number of drugs newly approved in a year compared to the number of drugs that added something to the Orange Book in that year;
- Percentage of the approximately 100 top-selling, non-biologic drugs from between 2005 and 2015 that extended the initial "protection cliff."

To examine the landscape of evergreening behavior, we assembled a large volume of FDA data that would allow us to analyze the prevalence and specific contours of patent and exclusivity game-playing in an empirically rigorous manner. However, before diving deep into the data analysis process, we had to test the hypothesis of whether a widespread pattern of additions—of patents and exclusivities—across drug products is detectable or not. For this purpose, we created a table that contains the drugs we collected and the number of additions of each drug. In order to find whether a parametric or non-parametric one sample test is appropriate for hypotheses testing, we need to examine normality. We used a significance level of 0.05 while exploring our data. The p-value of the Shapiro-Wilk normality test is less than 2.2e-16. Since this p-value is smaller than our significance level, then we can say that our data is not normally distributed. Therefore, a non-parametric method is preferable to be used for hypothesis testing. Thus, we chose Wilcoxon Signed Rank test to examine out two hypotheses as follows:

- The null hypothesis states that drugs usually have two additions or less.

$$H0: m \pounds m0$$

- The alternative hypothesis states that drugs have more than two additions.

$$HA: m > m0$$

Where m0 is a hypothesized upper bound of the true population median μ.

The p-value of our hypotheses test is less than 2.2e-16 with sample median estimation of 7.5. Hence, the p-value is less than our significance level of 0.05, so we have evidence to reject the null hypothesis H0, and explore more in depth the hypothesis of multiple drug additions.

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of times that pediatric exclusivity was applied to a patent and the number of times that pediatric exclusivity was applied to an exclusivity, rather than the overall number of pediatric exclusivities that were granted by the FDA.

To provide a broad sense of the types of metrics we are using, there are some that could be characterized as "intensity" measures, which capture the breadth and depth of patent and exclusivity activity in the industry. Another set of our metrics can be characterized as "temporal" measures, which evaluate whether there are any trends in the behavior under examination across time during our eleven-year timeframe from 2005 to 2015. Below, we will provide details on each metric and the relevance of each metric to our overall inquiry.

a. The number of drugs that added patents or exclusivities to the Orange Book between 2005 and 2015, compared to the total number of drugs available between 2005 and 2015

This metric provides the total number of drugs that added a patent or exclusivity, or made any other relevant change to the Orange Book (as listed above in Section 2), relative to the overall number of drugs in existence and listed in the Orange Book in the eleven years between 2005 and 2015.

The denominator in this metric—the overall number of drugs—required an immense amount of effort and many hours of sleuthing through online data repositories to acquire. As with so many other crucial pieces of FDA data, figures for the total number of drugs (at the level of new drug applications) listed in the Orange Book each year are not readily available.[44] One way to obtain these figures would be to go through each PDF annual edition of the Orange Book and hand count the relevant number of drugs. One would have to not only count the number of drugs, but also keep track of the specific new drug application numbers in each edition, to compare the new drug application numbers

[44] Each supplemental version of the Orange Book does contain a section entitled, "Report of Counts for the Prescription Drug Product List Counts Cumulative by Quarter." It contains a number for "drugs products listed." The FDA defines "drug products" for this report, however, at the level of strengths. As explained *supra* text accompanying notes 18-20, the most useful measurement of drugs lies at the level of the initial approval for the drug itself—that is the new drug application—rather than counting the same drug repeatedly for different strengths. Thus, trying to compare the number of drugs that added patents and exclusivities to the number of drug products reported in the Orange Books would be like comparing apples to oranges. Moreover, the number reported in the Orange Book is not separated by whether the drug product is a new drug (NDA) or a generic application (ANDA). It would be inaccurate to include generics in our overall count to serve as the denominator in this measure. As described above, the only reason a generic might be included in the Orange Book's patent and exclusivity section is if the generic received the 180-day "patent challenge" exclusivity, something that represents successful entry of, rather than obstruction of, generics. *See supra* text accompanying notes 21-22.

from year to year and eliminate duplicates. Given that the list of drug products in each Orange Book is hundreds of pages long—with generic drug applications interspersed among new drug applications, and each strength listed separately—this would have required an extraordinary amount of additional time and resources.

The FDA does make available a copy of the Orange Book in ASCII text, tilde-delimited format.[45] Files in this format can easily be imported into Excel, and using Excel functions, one could obtain an overall figure for the number of drugs with significantly less effort than hand-counting would require. Unfortunately, the FDA only makes the ASCII text file Orange Book from the most recent month available online. Thus, since historical archives of the ASCII text file Orange Books from 2005 through 2015 are not provided by the FDA, theoretically, the existence of this format would not have been of much help to us. However, using a tool called Wayback Machine, we were eventually able to obtain ASCII text file versions of the Orange Books published between 2005 and 2015. Wayback Machine is a digital archive of webpages and information available on the Internet created by a non-profit called Internet Archive. Every few weeks, Wayback Machine archives cached pages of websites as they exist at that point in time; the tool also allows visitors to capture and enter webpages into the archive. As a result, one can enter a website URL into the Wayback Machine search engine and find archived versions of how that website appeared at previous points in time.

The current URL for Orange Book data files made available by the FDA is https://www.fda.gov/drugs/informationondrugs/ucm129689.htm. Entering that URL into Wayback Machine, brings up saved versions of the webpage from present day going back until June 2009. If one clicks on the link to a captured webpage, one can see the page as it was at that particular point in time and download any files available on the webpage, including the Orange Book ZIP file that contains the ASCII text file version of the Orange Book. Having downloaded the ASCII text file Orange Book, we imported it into Excel for analysis. We then had to filter the list of drug products to include only those relevant to our inquiry—namely, we filtered out any drug products labeled as generic drug applications, leaving only new drug applications, and we filtered out those drug products labeled as discontinued. Also, in the files, each separate strength of a new drug is listed separately, so we then had to filter the list for unique new drug applications. From there, we could obtain a figure for the total number of drugs available at the time that copy of the Orange Book was made public.

[45] ASCII stands for American Standard Code for Information Interchange, and an ASCII, tilde-delimited file is, in simple terms, a plain text file in which the different data fields are separated by tildes (~). Such files are easily imported into Excel and can be separated into appropriate data columns by specifying in the Excel importation settings that the file is tilde-delimited.

Using the current FDA URL and Wayback Machine only allowed us to obtain electronic copies of the Orange Book going back to June 2009, while our study goes back to 2005. Fortunately, we were able to access the older data by tracking down the URL that the FDA used in the past to post its Orange Book data files prior to June 2009: http://www.fda.gov/cder/orange/obreadme.htm. By entering the former URL into Wayback Machine, we were able to access links to the FDA webpages containing the Orange Book files going back to October 1999.[46]

Orange Book text files prior to December 11, 2009, do not include a data field indicating whether a drug product is a generic or a new drug. Thus, we could not easily filter out generic drug products, which are irrelevant to our analysis. To solve this problem, we compared the list of new drug numbers from the files prior to December 11, 2009 to the list of new drug numbers from the files after that period, using the later files to determine whether entries in the earlier files were generics or new drugs. For the most part, drugs in the pre-December 11, 2009 files were also listed in later files. For a few drugs, however, we had to look up the drug individually on Drugs@FDA to determine whether the drug was a generic or a new drug. We went through this process for every copy of the Orange Book available through Wayback Machine going back to February 7, 2005 (the earliest file available for the year 2005).

The next step in determining the overall number of drugs approved between 2005 and 2015 involved grappling with the fact that internet archiving and timing for updating the Orange Book ACSII text files did not necessarily happen on the same schedule, and neither happened on a precisely predictable schedule. Although currently, the FDA updates the ASCII text file version of the Orange Book every month, that has not been the case across time. The Wayback Machine versions show periods in which months go by without a single change occurring in the ASCII text file versions of the Orange Book, while we know from the hard copy versions that dozens, or even hundreds, of changes occur each month.

On the flip side, the number of dates on which the Wayback Machine captured the FDA's webpage, and the distribution of those dates across any given year, appears to be somewhat random. For example, for the year 2014, the webpage was captured once in February, once in April, twice in September, and three times in December. Meanwhile, in

[46] Files prior to August 2006 are only available in .exe file format as opposed to .zip file format—.exe is an old Microsoft Windows file format that cannot be opened on Macs, and many of the .exe files containing copies of the Orange Book were so old they could not even be opened on modern Windows operating systems. We were able to access these files using a program called "The Unarchiver," that can be installed on Mac computers and be used to access very old .exe files.

2011, the webpage was captured every month of the year, at least two times each month. In September 2011, the number of days the webpage was captured reached a high of seven times, and there were a few occasions in 2011 that the webpage was captured more than one time in a single day. Thus, we compared each internet archived version of the Orange Book ASCII text files with the versions immediately before and after to cull out those archived versions that were mere duplicates. For the benefit of future researchers who may want to follow the same internet archive path, *Appendix B* contains a list of the dates of the non-duplicated Wayback Machine archived versions between 2005 and 2015.

Finally, we note that the comprehensiveness of our collection of Orange Book text files was at the mercy of whatever was available through Wayback Machine. It is possible that there was a gap between two of our Wayback Machine webpages during which a certain drug was added and then removed. We would have no record of this drug's existence in the Orange Book and consequently, it would not have been included in our count of unique drugs listed in the Orange Book between 2005 and 2015. This possibility is unlikely, however, given that there was rarely much of a temporal gap between the various versions we obtained through Wayback Machine. Moreover, most drugs would remain listed in the Orange Book for longer than the one-week or two-week periods for which we occasionally did not have any Wayback Machine-supplied versions of the Orange Book.

With the archived versions in hand, we were able to obtain a figure for the total number of drugs (at the new drug application level) available in each year. We then combined the yearly information, sorting for unique new drug numbers among that aggregate list of new drug numbers, resulting in a figure for the total number of drugs available in our entire 2005-2015 timeframe. We compared the number of drugs that added patents or exclusivities, or made any relevant change to the Orange Book, between 2005 and 2015, to the total number of drugs available in those eleven years, to get a sense of how prevalent the behavior is in the overall universe of pharmaceutical products. The outcomes of this analysis will be detailed in the results section below.

It should be noted that these figures include many drugs that were approved decades prior to the 2005-2015 window in which we were examining patent and exclusivity behavior. Many of those drugs may have added patents and exclusivities long ago, those patents and exclusivities may have expired long ago, and those drugs may simply be dormant listings in the Orange Book with little relevance to current pharmaceutical market activity. Which is to say that our figure for the total number of drugs available certainly errs more on the side of overbroad than overly narrow. In other words, the results in our paper could be understated, given that the volume of behavior may have been measured against an overbroad pool of drugs.

b. The number of drugs that added patents or exclusivities to the Orange Book, broken down by year for each year between 2005 and 2015

The previous section described the metric of the number of drugs that added patents or exclusivities to the Orange Book between 2005 and 2015 compared to the total number of approved drugs during those years. The next metric was similar to the first, except that rather than presenting an aggregate picture of Orange Book activity between 2005 and 2015, this metric breaks down activity for each individual year between 2005 and 2015. Through this analysis, we were able to examine if there were any trends over time in terms of the level of patent and exclusivity activity within the pharmaceutical industry.

We used the figures for the overall number of drugs available each year, obtained through the process described in the section above, as a comparison figure for the number of drugs that added to the Orange Book in each year.

c. The number of drugs that added an exclusivity, broken down by type of exclusivity

The third metric delved more deeply into the exclusivity numbers. Our figure for the number of drugs that added an exclusivity involved nineteen different exclusivities, including well-known and highly significant ones, such as the orphan drug exclusivity and the pediatric exclusivity, but also lesser known exclusivities, such as the GAIN (Generating Antibiotic Incentives Now) exclusivity. Again, a full list of the exclusivities included in our study is available at *Appendix A*. The trend for drug company activity in the exclusivity realm across our eleven-year time frame could be obscured by underlying trends—and perhaps opposing trends—within individual exclusivities. Thus, we conducted an analysis of how many drugs added each individual type of exclusivity to obtain a more granular picture of various types of activity.

d. The total quantities of patents and exclusivities added between 2005 and 2015

An important distinction exists between the number of drugs that added a patent or exclusivity and the total *quantity* of patents and exclusivities added. An individual drug could have added just one patent or one exclusivity, but it also could have added dozens

of different patents and exclusivities. Looking at total quantities of patents and exclusivities across the time period provides a picture of the amount of Orange Book activity at the level of sheer numbers of patents and exclusivities added, rather than at the level of the specific drugs responsible for those patents and exclusivities. Similar to the previous metrics, we provide an aggregate figure for the entire time frame and then also break down the numbers by year between 2005 and 2015.

e. The number of drugs that added a high quantity of patents in a single year between 2005 and 2015

The next metric we established was the number of drugs that added a high quantity of patents in a single year, for each year between 2005 and 2015. This metric provides insight into whether the activity of throwing a large collection of patents at a single drug to see what sticks over time is prevalent, as well as whether, and the extent to which, there has been any increase in such behavior across time. In addition, by looking at how many drugs add large quantities of patents, we gain a better sense of whether the total quantity of patents added in any particular year is due to a large number of drugs, each adding a small number of patents, or if it is due to a smaller number of drugs, each adding multiple patents. The increments we chose for this metric were the number of drugs that added three patents or more in a given year, and the number of drugs that added five patents or more in a given year.

f. The number of separate times that each drug added something to the Orange Book (a measure of "serial offenders")

In our dataset, there were some drugs that added to the Orange Book once, and then never made another addition to the Orange Book during our eleven-year timeframe. There were other drugs, however, that repeatedly returned to the well, adding one set of patents and exclusivities, then adding another set a few months later, coming back with another round a few years after that, and so on. Thus, we sought to create a metric to capture the activity of these "serial offenders," who added to the Orange Book with high frequency between 2005 and 2015. We went through our dataset and counted by hand the number of separate instances that each drug added to the Orange Book, with an "instance" being defined as all activity during a particular month. For example, if a drug added three patents in February 2009 and then two exclusivities in April 2010, that would be counted as two instances. Through this metric, we could assess how common it was

for drugs to add to the Orange Book on more than one occasion, or more than four occasions, or more than eight occasions, etc. between 2005 and 2015.

g. The number of drugs newly approved in a year compared to the number of drugs that added something to the Orange Book in that year

This next metric is an attempt to capture how much Orange Book activity represents true innovation, as opposed to mere recycling and repurposing of old drugs. Specifically, we aimed to compare the number of drugs that are approved in any given year to the number of drugs that added a patent or an exclusivity to the Orange Book in that year. Theoretically, if patents and exclusivities were granted solely to reward occurrences of new innovation in the pharmaceutical field, then you would expect each new drug to receive just one set of patent and exclusivity protections, granted at the time of approval. If that were the case, and each drug company submitted the protections attached to its new drugs for Orange Book listing shortly after approval as the "timely-filed" requirement dictates,[47] then you would expect the number of drugs adding patents

[47] In almost all cases, the original patents protecting a drug are issued prior to the drug receiving FDA approval. The FDA requires that drug companies submit patent information for publication in the Orange Book on FDA Form 3542. The form must be submitted within thirty days of the approval of the drug for the patent information to be considered "timely filed." Patent information can be submitted beyond the thirty-day timeframe, but those patents will not be considered timely filed. (For patents issued after the date of drug approval, the patent information must be submitted within thirty days of the issuance of the patent for it to be considered timely filed, but given that most drugs receive their core set of patents months, if not years, before the drug is even approved, this should be the exception rather than the rule.) Generic drug makers are not required to certify to patents that are not timely filed if the generic application is submitted before the patent. *See Patents and Exclusivity*, *supra* note 33; 21 CFR 314.53. For an example of how failure to timely file can result in undesirable consequences for a brand-name company, consider the case of the ADHD medication Focalin XR. Focalin XR (drug number 21802) has eight strengths listed in the Orange Book. For most of the strengths, the drug company submitted patent information in a timely manner. For the 30mg strength, however, the drug company failed to submit its patent information within thirty days, and thus, the patents were not considered to be "timely filed." According to 21 CFR § 314.94(a)(12)(vi), generic applicants who have submitted their applications before the submission of brand-name patent information that is not "timely filed," do not have to amend their applications to certify to the late-listed patents. In the case of Focalin XR, there were two generic applicants that had submitted their materials before the brand-name submitted its untimely filed patents for the 30mg strength. There was one other generic, Mylan, that submitted its application after the late patents for the 30mg strength were added, and thus, it certified to those patents and became eligible for a period of 180-day exclusivity. Theoretically, with that 180-day exclusivity, Mylan would be the only generic competitor allowed on the market. However, because the two other

or exclusivities to the Orange Book each year to roughly match the number of drugs that were approved that year. If the number of drugs adding patents and exclusivities to the Orange Book in a year dwarfs the number of drugs approved that year, however, that would be an indication that many drugs are receiving patents and exclusivities—not for innovation represented by a newly approved drug—but rather for changes made to old drugs that were approved previously.

Such recycling and repurposing of old drugs may be sufficient to garner new patents and exclusivities for the drug company, but the changes may not be therapeutically significant or valuable to patients and society in general. The changes may represent instances of evergreening,[48] where therapeutically minimal changes are made to delivery mechanism or formulation in a way that leads to new protections and extends the lifecycle of the drug, but undermines the intent of the system to operate as an incentive and reward for societally beneficial innovations in the pharmaceutical field.

h. The number of top-selling, non-biologic drugs that extended the initial "protection cliff."

Our final metric involves extension of what is commonly referred to as the "patent cliff." We have expanded the notion to include both patents and exclusivities, and have thus, renamed it the "protection cliff."

The "patent cliff" is a term used by industry insiders, academics, and journalists alike to refer to the point at which patent protection ends for a particular drug, or commonly, a set of blockbuster drugs.[49] When facing an impending patent cliff, pharmaceutical companies often scramble to find ways to extend the patent cliff out

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generics had applied prior to the submission of the late-listed patents on the 30mg strength, they were not subject to Mylan's 180-day exclusivity and were permitted to enter the market. Thus, as a result of its failure to timely file patents, the brand-name company was faced with three generic competitors rather than the one it would have had if it had timely filed, further diluting the brand-name's market share. *See* Kurt Karst, *One Sponsor's Failure is Another Sponsor's Fortune: The Importance of Timely Listing (and Challenging) Orange Book Patents,* FDA LAW BLOG (Nov. 25, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/11/one-sponsors-failure-is-another-sponsors-fortune-the-importance-of-timely-listing-and-challenging-or.html .

[48] *See* Feldman *supra* note 4 at 7.

[49] *See, e.g.,* Mike May, *Pharma Positions to Survive the Impending Patent Cliff*, 15 NATURE MEDICINE 1243 (2009); Eric Sagonowsky, *Big Pharma faces $26.5B in Losses this Year as Next Big Patent Cliff Looms, Analyst Says*, FIERCEPHARMA (Apr. 21, 2017, 8:04 AM), http://www.fiercepharma.com/pharma/big-pharma-faces-26-5b-patent-loss-threats-year-analyst-says; Jessica Hodgson, *Big Pharma Tries to Look Past "Patent Cliff,"* WALL STREET J. (Oct. 24, 2012), https://www.wsj.com/articles/SB10001424052970203897404578076173187345806.

further into the future, given that falling off that ledge can portend millions, or even billions of dollars, in lost profit. One method of circumventing an approaching patent cliff is to add a new patent or a new exclusivity with a later expiration date, thus rendering the drug product safe from competition for another several months or even years. With our data, we can empirically evaluate whether drugs are, in fact, engaging in this behavior of extending the patent cliff. We take the latest expiration date in the original set of protections added and then determine if a new protection was subsequently added with a later expiration date.[50] We refer to this benchmark as the "protection cliff" rather than the "patent cliff," given that many of the relevant "cliffs" apparent in our dataset stemmed from exclusivities, not patents.

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[50] In defining the "original" set of protections, we chose to examine those patents and exclusivities that were added within the two months following the month of drug approval. Our logic was the following: Patents that are attached to a drug prior to approval must be submitted to the Orange Book within 30 days (one month) of approval to be considered "timely filed," which has relevance for staving off generic competition, *supra* note 47. We added an additional month on top of the "timely filed" month as a buffer to account for possible Orange Book staff delays in publishing a patent or exclusivity once it has been submitted by the drug sponsor. The Orange Book explicitly states at the end of the patent and exclusivity section that, "Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5)." *See*, *e.g., Cumulative Supplement 1: January 2015*, *supra* note 12, at A-6. Thus, if a drug was approved in January 2015, we would define anything added in January, February, or March 2015 as part of the "original" set of protections. We added the extra two months to err on the side of over-including patents and exclusivities within our definition of "original," thereby avoiding the possibility of inflating the amount of strategic behavior.

For many drugs that were approved prior to 2005, the first patents and exclusivities we have in our dataset are simply drawn from the 2005 Annual Edition of the Orange Book. As such, we do not have specific month and year information for when those patents and exclusivities were added. Rather, the best we can say is that they were added prior to 2005. In those cases, we considered all of the "pre-2005" patents and exclusivities to be the original set. Once again, we erred on the side of conservatism, given that there could easily have been protection cliff extensions prior to 2005 that we are not counting. For those drugs that were approved between 2005 and 2015, but for which no patent or exclusivity was added within the first two months after the approval month, we used the first month that any patent or exclusivity was added to define the original set, even if that month was past our general two-month marker. This conceivably could represent an extension of exclusivity in some cases. For example, a drug whose formulation is not sufficiently novel to receive a patent—perhaps because a patent on something too similar was granted to another party in the past and has expired—could receive FDA approval. Thus, new patents or exclusivities added arguably could be described as an extension of the old patent protection. Nevertheless, we considered such possibilities either too remote or impossible to determine, and thus chose to benchmark the first month of any patent or exclusivity as the approval month, in those cases.

We focused this analysis on the best-selling, drugs from the time period between 2005 and 2015, and, as with the entire study, we focused on non-biologic drugs. The high profit margins for Blockbuster drugs provide a strong incentive for drug companies to invest in finding ways to extend protection. Thus, in addition to making the analysis more manageable, we chose the subset of our data for which we believed the protection cliff analysis would be most relevant.

To assemble a list of best-selling drugs from our study timeframe, we consulted the lists available through Drugs.com (for the years 2005-2012) and Medscape.com (for the years 2013-2014). These websites obtain information from Verispan's Vector One National (VONA) database and from the IMS Health database.[51] From those lists, we selected the top fifty, non-biologic drugs by unique name from each year.[52] In the event that a drug's unique name corresponded to multiple NDAs, we only included the NDA with the least number of cliff extensions in our analysis.[53] We then eliminated any duplicate drugs that overlapped in the top fifty from one year to the next.

We also chose to leave out the best-selling drugs from 2015. Our study only goes up through 2015, and examining extension of a patent cliff requires having a sufficiently long period of the drug's lifecycle that one can analyze movement across time. For those drugs that did not add a first set of patents or exclusivities until 2015, it would be impossible to analyze *any* future extension of the protection cliff. One could argue that

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[51] *Pharmaceutical Sales 2005*, DRUGS.COM, https://www.drugs.com/top200_2005.html (Drugs.com is the largest independent medicine information website. It makes available lists of the top 100 or 200 best-selling drugs from each year between 2003 and 2012. It sources its data from either Verispan's Vector One National (VONA) Database, which pulls data on prescription activity from national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefit managers, etc., and has been used by the FDA itself in its reports, *see Memorandum: Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Drug Use Data Update*, CTR. FOR DRUG EVAL. & RESEARCH, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4295b_05_03_Xenical%20Use%20Review%202007.pdf. The other source of data used by Verispan is IMS Health, which provides information and technology services to the healthcare industry); Megan Brooks, *Top 100 Most Prescribed, Top-Selling Drugs*, MEDSCAPE (Aug. 1, 2014), http://www.medscape.com/viewarticle/829246 (data also sourced from IMS Health).

[52] As explained earlier, biologics are outside the scope of our study, though they have come to represent an increasingly large percentage of the best-selling drugs in recent years and would be an interesting avenue for future research, *supra* text accompanying notes 28-29.

[53] For example, the drug Aricept is attached to three different NDAs: 22568, 21719, and 20690. While our dataset shows that 22568 did engage in one instance of patent extending behavior, the other two NDAs did not. Therefore, our analysis reflects that Aricept did *not* engage in any patent extending behavior. This was done to compensate for the fact that Drugs.com and Medscape only identified top selling drugs by their unique names and not by NDA and maintain the study's conservative approach.

the later years in the data set would be less fruitful for the same reason, thereby understating the results, but at least there would be some possibility of relevant activity to analyze. In addition, the possibility that strategic behavior may be increasing over time, makes these latest years important to consider. Our final grouping included a total of 106 best-selling drugs from the ten years of 2005 to 2014, for which we analyzed the frequency of protection cliff extension behavior.