

THE MYTHS OF DATA EXCLUSIVITY

by
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This Article contributes to an ongoing academic and public policy dialogue over whether and on what terms U.S. law should provide “data exclusivity” for new medicines. Five years after a new drug has been approved on the basis of an extensive application that may have cost more than one billion dollars to generate, federal law permits submission of a much smaller application to market a duplicate version of the drug. This second application is a different type of application, and it may cost no more than a few million dollars to prepare. A similar sequence is true for biological medicines: 12 years after approval of an application that may have cost over one billion dollars to generate, the law permits approval of a smaller and less expensive application for a duplicate. Scholars, courts, and policymakers use the phrase “data exclusivity” to describe the period before the new pathway opens—a nod to the fact that applications of the second type rely on the research submitted by the first entrant. The primary “myth” of data exclusivity is that it is a benefit provided by the government for the benefit of first entrants. This Article breaks new ground by reframing data exclusivity instead as a period of time during which all firms are subject to the same rules governing market entry. It uses this insight as the foundation for an exploration of the complex web of legal, regulatory, and practical factors that may influence whether and on what terms firms enter the market with duplicates during and after that period. This Article provides the first systematic comparison of the new drug exclusivity and biological product exclusivity schemes in order to propose an approach that could prompt

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strategic decisions—both during and after that period—that will contribute to dynamic social welfare.

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Darth Vader: Calrissian. Take the princess and the Wookie to my ship.

Lando: You said they'd be left at the city under my supervision!

Darth Vader: I am altering the deal. Pray I don't alter it any further.¹

I. INTRODUCTION

Lando Calrissian made a deal with Darth Vader to prevent imperial forces from invading and occupying Cloud City. He would lead Han Solo and his party into a trap, allowing Han Solo to be taken prisoner, in exchange for protecting Princess Leia and Chewbacca. When the moment

¹ STAR WARS: EPISODE V—THE EMPIRE STRIKES BACK (Lucasfilm 1980).

comes, however, Darth Vader orders all three taken prisoner. Lando complains, and the response above essentially shifts the burden back to Lando: Be grateful no more was taken. Indeed, the subtext is a threat that, with further complaint, more might be taken. The scene gave birth years later to an Internet meme: *I am altering the x; pray I don't alter it any further*. It is commonly used to “troll” people who complain about unfavorable developments.² It is a strange cognitive distortion: the notion that a person should be accepting when something has been taken, or when harm has been inflicted—grateful, even, that more was not taken, more harm not inflicted. This Article suggests the same distortion has infected discussion of the U.S. drug regulatory scheme in both academic and policy circles.

The distortion arises in connection with the question whether and on what terms there should be “data exclusivity” for medicines. At issue are two types of medicine, approved by the U.S. Food and Drug Administration (FDA) under different statutes: non-biological and biological drugs. Lipitor (atorvastatin), for treatment of elevated cholesterol levels, among other things, is an example of the former; Epogen (erythropoietin alfa), an erythropoiesis-stimulating agent for various forms of anemia, is an example of the latter. Five years after a non-biological drug has been approved by the FDA on the basis of an extensive and expensive application, federal law permits submission of an unlimited number of much smaller and cheaper applications to market copies of the drug. These copies are known as “generic” drugs. A similar sequence is true for biological drugs: 12 years after approval of an extensive and expensive application for a new biologic, the law permits approval of an unlimited number of smaller and less expensive applications for close replicas of the biologic, known as “biosimilar” biologics.³ Scholars, courts, and policymakers use the phrase “data exclusivity” to describe the period before the second pathway opens—a nod to the fact that applications of the second type rely on the research submitted by the first market entrant.⁴

Those participating in the discussion of the merits of data exclusivity comprise not only legal and economic scholars, but also international and national policymakers, manufacturers, industry organizations, and patient groups. The discussion arises today primarily in three settings: *first*, ongoing adoption around the world of pathways for approval of biosimilar biological products;⁵ *second*, international treaty negotiations in

² See *I Am Altering the X*, KNOW YOUR MEME, <http://knowyourmeme.com/memes/i-am-altering-the-x>.

³ See *infra* Section II.A.

⁴ See *infra* notes 62–63 and accompanying text for discussion of the reliance. There is a dispute about the label “data exclusivity” for the law in question. See *infra* Section II.B for a discussion of the dispute.

⁵ The Europeans paved the way in 2003, followed by Japan (2009), Canada (2010), and the United States (2010), among others. See Peter Bogaert, Erika Lietzan

which the United States and Europe ask prospective treaty partners to commit to approaches to medicine approval and intellectual property that are modeled on U.S. and European law;⁶ and *third*, continued dialogue about the design of the U.S. system, prompted at least in part by lingering dissatisfaction with the length of the exclusivity term for biological drugs.⁷ The merits of data exclusivity are, in other words, the topic of intense current debate. This Article suggests a new way of looking at exclusivity, and it aims to immediately inform that debate.

The well-accepted narrative of data exclusivity is that it is provided by the government as an incentive to perform the research necessary to obtain the marketing authorization in question. Further, the narrative often states, exclusivity is analogous to a federal intellectual-property right,

& Laura Sim, *Biosimilar Regulation: Important Considerations and Global Developments*, PRAC. L. (Nov. 1, 2010), <http://us.practicallaw.com/3-500-9862>. Efforts are underway in other parts of the world to implement biosimilar pathways. See, e.g., *China Drafts First Biosimilar Guideline*, PHARMA & MEDTECH BUS. INTELL.: PINK SHEET DAILY, (Nov. 7, 2014), <https://www.pharmamedtechbi.com/publications/the-pink-sheet-daily/2014/11/7/china-drafts-first-biosimilar-guideline>.

⁶ See generally Brook K. Baker, *Ending Drug Registration Apartheid: Taming Data Exclusivity and Patent/Registration Linkage*, 34 AM. J.L. & MED. 303, 343 (2008) (arguing that a U.S. government/industry “tag-team has been relentless” in pressing data exclusivity terms in international trade agreements, with the result that “[d]eath by patent is being reinforced by death by registration”). Recently, the issue has arisen in connection with negotiation of the Trans-Pacific Partnership (TPP). In August 2011, for instance, Representative Waxman wrote to President Obama, to oppose inclusion of the U.S. biologics-exclusivity term in the text of the TPP, stating that 12 years of exclusivity would conflict with “stated Administration policy” reflected in budget proposals, and “that the exclusivity period for biologics [should] be reduced to 7 years.” See Letter from Rep. Henry Waxman et al. to President Barack Obama (Aug. 4, 2011) (on file with author). He was responding to a letter to the President authored by a group of more than three dozen members of Congress, urging precisely the opposite. See Letter from Rep. Ron Kind et al. to President Barack Obama (July 27, 2011) (on file with author) (“The U.S.-led biopharmaceutical industry would be disadvantaged if the U.S. does not ensure consistency with U.S. law as part of the TPP . . .”). These 2 letters and 11 others on the topic of biologics data exclusivity were obtained by a FOIA request by Knowledge Economy International, and are available online at <http://keionline.org/node/2069>. The Administration has continued to press for an approach generally consistent with U.S. law, but as of spring 2015 the issue remained controversial. See Derrick Gingery, *Biologics Exclusivity: GPhA Making Last Stand Against TPP*, PHARMA & MEDTECH BUS. INTELL.: PHARMASIA NEWS, (Jan. 8, 2015), <https://www.pharmamedtechbi.com/publications/pharmasia-news/2015/1/8/biologics-exclusivity-gpha-making-last-stand-against-tpp>; Len Bracken, *Coalition of Groups Presses Obama on TPP Provisions Concerning Medicine*, 32 INT’L TRADE REP. (BNA) 53 (Dec. 17, 2014).

⁷ President Obama includes a reduction in the data exclusivity term for biologics in his proposed budget every year. See, e.g., U.S. DEP’T OF HEALTH & HUMAN SERVS., FISCAL YEAR 2015 BUDGET IN BRIEF: STRENGTHENING HEALTH AND OPPORTUNITY FOR ALL AMERICANS 64 (2015), <http://www.hhs.gov/sites/default/files/budget/fy2015/fy-2015-budget-in-brief.pdf>.

providing a sort of monopoly in the marketplace, as well as protection from price competition, meaning competition from lower-priced replicas that reached the market less expensively. The essence of the narrative is that something *beneficial* has been *given* to the first entrant, the pioneer.

Section II of this Article reframes data exclusivity not as an affirmative government grant, but rather as a period of time during which every prospective market entrant faces the same regulatory barrier to market entry. In other words, any applicant may market the molecule in question (subject to patent considerations and business judgment), but all must file full applications with clinical data. The central myth of data exclusivity is that it is an affirmative grant to initial entrants from the government. Instead, “data exclusivity” is simply the phrase we use to describe the period of time *before* the law provides *subsequent* applicants a second, and substantially cheaper, shortcut to market. A variety of patent, regulatory, and business considerations may drive subsequent applicants toward, or away from, full applications for duplicates (as opposed to modified versions or even second-in-class products) in the years when all comers are subject to the same license requirements. But “data exclusivity” in itself does not preclude them from marketing competing products on the same terms as the first applicant.

Section III uses the insights of the previous Section as the foundation for exploring the question *whether*, and *on what terms*, society derives a net benefit from a period of time during which all applicants face the same barrier to market entry. As to *whether*, this Section concludes that there is a compelling public health need for a shortcut pathway for medicines given the resultant lowering of drug prices. But, reframing exclusivity as a period of time when all competitors face the same barrier to entry brings into greater focus the impact of approval shortcuts—and decisions about how those shortcuts are designed—on incentives to innovate. Accordingly, in order to answer the question *on what terms*, this Section explores three fundamental structural differences between the two U.S. data-exclusivity schemes (one for biological drugs and the other for non-biological drugs) that have been largely unexplored in the academic literature to date. As to each structural difference, it describes the impact each scheme’s approach could have on company incentives to bring forward new treatments for patients, both during and after the period when all entrants are subject to the same rules.

The goal of this Article is to orient scholars and policymakers to a new way of thinking about data exclusivity and to suggest an overall approach that will maximize dynamic social welfare—innovation for tomorrow’s patients, in addition to less expensive replicas for today’s patients. Section III, therefore, ultimately recommends taking design elements from each U.S. scheme and one from European data-exclusivity law that may mitigate a key weakness in both U.S. schemes. Section IV of the Article, the conclusion, discusses the possible impact of the overall proposed

exclusivity scheme—all pieces working together—on behaviors in the marketplace both during the period when all entrants are subject to the same rules and after this period ends and the shortcut becomes available.

II. REFRAMING DATA EXCLUSIVITY

The United States bifurcates its regulation of medicines. The FDA licenses most biological drugs under the Public Health Service Act (PHSA) and approves non-biological drugs under the Federal Food, Drug, and Cosmetic Act (FDCA).⁸ Although this statutory bifurcation is largely a result of historical accident,⁹ and the pathways to the market for pioneers are largely harmonized in practice, the statutes take significantly different approaches to abbreviated applications and data exclusivity.

A. *Pathways to Market*

1. *Non-Biological Drugs*

Under the FDCA, a new drug application (NDA) for a non-biological drug must contain full reports of the investigations performed to determine whether the drug is safe and effective for the conditions of use in its labeling.¹⁰ This requires “substantial evidence,” which is defined to include at least one adequate and well-controlled clinical investigation.¹¹ The traditional approach is to perform two Phase III (pivotal) clinical trials that prove effectiveness following earlier phase trials that explored safety and provided initial insight into effectiveness.¹² NDAs typically con-

⁸ See 42 U.S.C. § 262 (2012); Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 301–399f (2012). The text indicates that the FDA licenses “most” biologics under the PHSA because a handful of protein products currently approved under the FDCA meet the definition of “biological product.” Congress has directed that new drug applications for biologics currently licensed under the FDCA be converted to biologics license applications under the PHSA beginning in 2020. See Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(e)(2), 124 Stat. 119, 817 (2010) (codified at 42 U.S.C. § 262(e)(2)).

⁹ See Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 682–83 (2010).

¹⁰ FDCA, 21 U.S.C. § 355(a)–(b).

¹¹ *Id.* § 355(d). The statute originally referred to investigations (plural), but it was amended in 1997 to confirm that one trial is sufficient. See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 115(a), 111 Stat. 2296, 2313 (“If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.”).

¹² See 21 C.F.R. § 312.22 (2015); AVIK S.A. ROY, MANHATTAN INST. FOR POLICY RESEARCH, STIFLING NEW CURES: THE TRUE COST OF LENGTHY CLINICAL DRUG TRIALS 3 (Mar. 2012), http://www.manhattan-institute.org/pdf/fda_05.pdf.

tain data from dozens of analytical (laboratory) studies, preclinical (animal) studies, and clinical (human) trials.¹³ As a regulatory matter, it is also permissible to pay another company (that has done the research) for the right to reference some, or all, of the company's research, which then substitutes for some, or all, of one's own research. The result is still a full NDA.¹⁴

The Hatch–Waxman Amendments of 1984 created the statutory abbreviated new drug application (ANDA) pathway for generic drugs.¹⁵ An ANDA contains data demonstrating that the proposed generic drug is the same as, and bioequivalent to, a drug previously approved by the FDA as safe and effective.¹⁶ The previously approved drug is known as a “reference drug,” “reference product,” or “reference listed drug.” The proposed drug is the “same” as its reference product if it has the same active ingredient, route of administration, dosage form, and strength, although the FDA will permit deviations if no clinical data are necessary to establish the safety and effectiveness of the generic in question.¹⁷ Indeed, the FDA may not require clinical data in a generic application, apart from pharmacokinetic data needed to show bioequivalence.¹⁸

There is also a third category of drug application under the FDCA: the “505(b)(2) application,” named after the provision of the Act in which it appears. This application may rely on a previously approved application, but need not copy the previously approved product slavishly. In other words, the applicant may propose innovations (such as new indications, new routes of administration, or even changes to the active ingredient) and support those innovations with original clinical data.¹⁹ In addition to relying on a previously approved application, a 505(b)(2) application may rely on published literature describing adequate and well-controlled investigations, if the applicant lacks a right of reference to the underlying raw data.²⁰

¹³ Erika Lietzan, *A New Framework for Assessing Clinical Data Transparency Initiatives*, 18 MARQ. INTELL. PROP. L. REV. 33, 41 (2014). Depending on the molecule and therapeutic category, the clinical trials can range from surprisingly modest to enormous. For an example of the latter, consider two factor Xa inhibitors (a new class of anti-coagulants that act directly on Factor X in the coagulation cascade without using anti-thrombin as a mediator), Xarelto and Eliquis, that were studied in more than 130,000 patients prior to approval. See ROY, *supra* note 12, at 6.

¹⁴ FDA, GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2) (draft, Oct. 1999) [hereinafter 505(b)(2) GUIDANCE], <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm079345.pdf>.

¹⁵ Carver, Elikan & Lietzan, *supra* note 9, at 676–77; see Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch–Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355(j)).

¹⁶ FDCA, 21 U.S.C. § 355(j)(2)(A)(iv).

¹⁷ *Id.* § 355(j)(2)(C).

¹⁸ *Id.* § 355(j)(2)(A).

¹⁹ See 505(b)(2) GUIDANCE, *supra* note 14, at 4–5.

²⁰ *Id.*

The FDCA contains two exclusivity rules relating to the timing of ANDAs and 505(b)(2) applications: a five-year rule and a three-year rule, conventionally known as new chemical entity (NCE) exclusivity and new product (NP) exclusivity. In brief, an abbreviated application may be submitted five years after approval of a full application for a new chemical entity, and an abbreviated application may be approved three years after approval of other full applications.²¹ The five-year prohibition on submission shortens to four years if the generic applicant challenges a patent claiming the pioneer's drug or a method of using that drug.²²

A third set of timing rules—which are not data exclusivity rules—connect approval of these abbreviated applications to the pioneer's patent portfolio. Every NDA must identify the patents that claim the new drug in question or a method of using the drug.²³ A generic applicant must address each—stating either that: (a) it intends to wait until patent expiry before marketing its product; or (b) the patent in question is invalid or not infringed. The former is called a “paragraph III certification” and the latter a “paragraph IV” certification, after the provisions of the statute in which they appear.²⁴ If the generic applicant includes a paragraph III certification, FDA approval of the generic drug may not take effect until patent expiry.²⁵ If the generic applicant includes a paragraph IV certification, challenging a patent, FDA approval may take effect immediately, unless the NDA holder or patent owner files a patent infringement suit within 45 days.²⁶ In that scenario, FDA approval is stayed for 30 months.²⁷ Also, if the litigation begins during the fifth year after NCE approval, the stay is lengthened to toll FDA approval of the generic until seven-and-a-half years after NCE approval.²⁸ If the generic company prevails during the stay, the stay ends and FDA approves the generic drug. If the innovator prevails during or after the stay, the generic com-

²¹ See FDCA, 21 U.S.C. §§ 355(c)(3)(E)(ii)–(iv), (j)(5)(F)(ii)–(iv). The three-year rule applies so long as the application contained clinical data, other than bioavailability data, essential to its approval. The statute also contains provisions making these terms 2 and 10 years, rather than 3 and 5 years, for products approved between 1982 and 1984. *Id.* § 355(c)(3)(E)(i), (v); *id.* § 355(j)(5)(F)(i), (v). These are conceptually identical to the NP and NCE provisions. Provisions more recently added to the statute confirm that enantiomers and antibiotics are, in some instances, entitled to NCE exclusivity. *Id.* §§ 355(u) (enantiomers), (v) (antibiotics).

²² *Id.* §§ 355(c)(3)(E)(ii), (j)(5)(F)(ii).

²³ *Id.* § 355(b)(1). Specifically, this requirement applies to any patent that claims the drug or claims a method of using the drug “and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.” *Id.*

²⁴ *Id.* §§ 355(b)(2)(A)(iii), (iv).

²⁵ *Id.* § 355(c)(3)(B).

²⁶ *Id.* § 355(c)(3)(C).

²⁷ *Id.*

²⁸ *Id.* § 355(c)(3)(E)(ii).

pany must convert its paragraph IV certification to a paragraph III certification and FDA approval takes effect only after patent expiry.²⁹

As a practical matter, the five-year prohibition on submission of generic drug applications citing new chemical entities generally results in a guarantee of at least six to seven-and-a-half years before generic market entry. This is for two reasons. *First*, if there is no patent challenge, FDA review and approval of an application submitted after five years might take another year.³⁰ *Second*, as just noted, if a patent challenge results in patent litigation, the stay of FDA approval will generally preclude generic market entry until seven-and-a-half years.³¹

The FDA generic approval timing provisions tied to the pioneer's patent portfolio are known as "linkage." The linkage provisions are generally outside the scope of this Article. This Article focuses on the exclusivity rules, which, standing alone, contemplate either three years until generic drug approval or four/five years until generic application submission, depending on whether the innovative product is a new chemical entity.

2. *Biologic Drugs*

The FDA licenses biological drugs under the PHSA. This statute does not require proof of safety and effectiveness, but rather proof of safety, purity, and potency.³² Biological products are, however, also drugs, and since receiving jurisdiction in the 1970s, the FDA has required proof of safety and effectiveness. It has also applied the substantial-evidence standard for effectiveness, albeit more flexibly than for non-biological drugs.³³ The contents of biologics license applications (BLAs) are therefore roughly analogous to the contents of NDAs.

The Biologics Price Competition and Innovation Act of 2009 (BPCIA) created the abbreviated pathway to market for biological products.³⁴ An abbreviated application must show that the proposed product—known as a "biosimilar" rather than a "generic"—is highly similar to

²⁹ *Id.* § 505(c)(3)(C)(ii).

³⁰ The FDA's current performance goals anticipate the agency reviewing and acting on 90% of complete ANDAs within 10 months of submission. *See Generic Drug User Fee Act Program Performance Goals and Procedures* 5, FDA, <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

³¹ Recent amendments to patent law give third parties, like generic companies, an opportunity to challenge issued patents at the U.S. Patent and Trademark Office (PTO). *See* 35 U.S.C. § 311 (2012). It is possible that these new inter partes review procedures will shift patent disputes between innovators and generic companies to the PTO and out of the courts, which in turn may affect the average timing of generic entry.

³² *See* Public Health Service Act (PHSA), 42 U.S.C. § 262(a)(2)(C)(i)(I) (2012).

³³ *See* Procedures for Review of Safety, Effectiveness, and Labeling, 37 Fed. Reg. 16679 (Aug. 18, 1972) (to be codified at 21 C.F.R. pt. 273) (now pt. 601.25).

³⁴ *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002, 124 Stat. 119, 807–21 (2010) (codified at 42 U.S.C. § 262); *see also* Carver, Elikan & Lietzan, *supra* note 9, at 671.

its reference product and that there are no clinically meaningful differences between the two.³⁵ The law presumes that these applications will contain clinical data, although it grants the FDA authority to waive the requirement.³⁶ These clinical data derive from head-to-head comparative trials with the reference product that are designed to show similarity rather than safety and effectiveness.³⁷

The PHSA contains one data-exclusivity rule relating to the timing of biosimilar applications. A biosimilar application may be submitted four years after first licensure of the reference product and approved after 12 years.³⁸ The 4- and 12-year clocks start with first licensure, and the statute adds that certain FDA approvals are not first licensure. To begin with, when the FDA approves a supplement to an application (for instance, for a new use—also known as an “indication”), the approval in question is not a first licensure and does not trigger a new exclusivity clock.³⁹ More significantly, certain subsequent full applications do not count as first licensure. These are applications filed by the same sponsor or manufacturer (or its licensor, predecessor in interest, or other related entity) for: (1) “a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule or form, delivery system, or strength; or (2) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.”⁴⁰ Section III takes up interpretation of this provision, but in brief the idea is that certain follow-up applications from the same company or a related company will not be protected by a separate 12-year exclusivity period.

No provisions in the PHSA expressly tie the timing of FDA approval to patents that might be infringed by the biosimilar applicant. There is a scheme for patent litigation prior to biosimilar market entry, but it is different from the patent-litigation scheme in the FDCA for non-biological drugs, and no provision addresses the timing of FDA approval.⁴¹

³⁵ See PHSA, 42 U.S.C. § 262(i) (2).

³⁶ *Id.* § 262(k) (2) (A) (ii).

³⁷ See, e.g., FDA, GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT 7 (Apr. 2015), <http://www.fda.gov/ucm/groups/fdagov-public/documents/document/ucm291128.pdf> [hereinafter SCIENTIFIC CONSIDERATIONS GUIDANCE].

³⁸ 42 U.S.C. § 262(k) (7) (A)–(B).

³⁹ *Id.* § 262(k) (7) (C) (i).

⁴⁰ *Id.* § 262(k) (7) (C) (ii).

⁴¹ Since enactment of the statute, there has been a dispute over whether the premarket patent-litigation process in the PHSA—which involves an exchange of information beginning when the biosimilar applicant shares its marketing application with the innovator—is mandatory for biosimilar applicants. In July 2015, a three-judge panel of the Federal Circuit ruled that the process is not mandatory, and that when a biosimilar applicant fails to initiate the process, the innovator’s sole remedy is to sue for patent infringement under 35 U.S.C. § 271 (2012). See *Amgen Inc. v.*

3. *Old Drugs*

Complicating all of this is the theoretical possibility for non-biological drugs of generic market entry as an “old drug.” This is because the FDCA requires a premarket application only for a “new drug.” The definition of “new drug” has changed over time, but for about 40 years generic drugs reached the market as “old drugs” and even now most nonprescription drugs reach the market as “old drugs”—all without premarket applications.

From 1938 to 1962, a drug that was “generally recognized as safe” under the conditions described in its labeling could be marketed without submission of an NDA.⁴² In the years following enactment of the statute in 1938, once a pioneer brought a new drug to market via the NDA route, other companies brought copies (the equivalent of today’s generics) to market without submitting applications. Some did so on the strength of their own reasoning that the drugs in question were generally recognized as safe because other companies held effective NDAs for their versions.⁴³ Others did so on the strength of affirmative written opinions from the agency to that effect—known as “old drug opinions.”⁴⁴

Since 1962, the statutory rule has been different: no application is required if a drug is generally recognized as safe *and effective*, and if it has been marketed to a material extent or for a material time, under the conditions described in its labeling.⁴⁵ Following the 1962 amendments to the FDCA, the FDA withdrew all of the old drug opinions it had previously issued. Therefore, as a practical matter, a generic drug company wishing to market a generic drug faced a choice: (a) reach a decision internally that the drug was generally recognized as safe and effective because of another company’s NDA, and thus not subject to the NDA requirement; or (b) file a premarket application with the agency. In the late

Sandoz Inc., 794 F.3d 1347, 1357 (Fed. Cir. 2015). Request for a rehearing en banc was denied on October 16, 2015.

⁴² The statute at the time defined a “new drug” as any drug not “generally recognized” as “safe for use under the conditions prescribed, recommended, or suggested” in its labeling. 21 U.S.C. § 321(p)(1) (1958).

⁴³ Under the scheme in place from 1938 to 1962, the FDA did not approve applications. Instead, an NDA became “effective” unless the agency objected. 21 U.S.C. § 355(c) (1958).

⁴⁴ See PETER BARTON HUTT ET AL., *FOOD AND DRUG LAW: CASES AND MATERIALS*, 775–76 (4th ed. 2014); see also Carlen S. Magad, Comment, *Generic Drugs: Breaking the Definitional Barriers to FDA Regulations*, 76 *Nw. U. L. Rev.* 613, 617–18 (1981).

⁴⁵ Congress redefined “new drug” as any drug not generally recognized as “safe and effective” as described in the labeling, or any drug which “as a result of investigations” is so recognized but which has not otherwise “been used to a material extent or for a material time” under the conditions described in its labeling. See Drug Amendments of 1962, Pub. L. No. 87-781, § 10(a)(1), 76 Stat. 780, 781 (adding the “effective” language); Kenneth C. Baumgartner, *Getting a Grip on Material Time and Extent*, 49 *FOOD & DRUG L.J.* 433, 434 (1994) (discussing judicial interpretations of the “new drug” definition).

1960s, bowing to pressure to ease the burden on those who opted for premarket review, the agency developed, through rulemaking, an “abbreviated new drug application” (ANDA) pathway.⁴⁶ This application—like today’s ANDA—contained proof of sameness and bioequivalence but no proof of safety and effectiveness. It was available to anyone seeking to copy a pre-1962 product. And an ANDA was—and still is—a type of new-drug application.

The FDA also announced that it would take regulatory action against any generic drug marketed without an approved application, effectively saying that—contrary to the generic industry’s position on the matter—approval of an NDA did not render the underlying drug generally recognized as safe and effective.⁴⁷ In other words, it eliminated the “old drug” pathway for generics.⁴⁸ This meant that every generic company would need an approved application—either an NDA or an ANDA. The problem for the generic industry was that the ANDA regulation on the books permitted copies of only pre-1962 pioneer drugs.⁴⁹ The FDA attempted to fill the gap with a “paper NDA” pathway for copies of post-1962 drugs; this would have permitted generic applicants to submit published literature as proof of safety and effectiveness of their copies.⁵⁰ But innovators rarely placed enough information in published journal articles to make this a viable pathway for generic companies. Although the FDA considered extending the ANDA regulation to permit copies of post-1962 drugs and even drafted proposed regulations to that effect, the effort stalled due to concerns that the contents of post-1962 NDAs were trade secrets.⁵¹ The proposal was never published in the Federal Register. Enactment of

⁴⁶ See *New Drugs*, 34 Fed. Reg. 2673 (proposed Feb. 27, 1969); *New Drugs*, 35 Fed. Reg. 6574 (Apr. 24, 1970) (to be codified at 21 C.F.R. pt. 130).

⁴⁷ *Marketed New Drugs Without Approved New Drug Applications*, 41 Fed. Reg. 41,770–71 (Sept. 23, 1976).

⁴⁸ The Courts of Appeals divided on whether generic drugs were new drugs requiring applications. Compare *Premo Pharm. Labs., Inc. v. United States*, 629 F.2d 795, 805 (2d Cir. 1980) (holding that FDCA’s “new drug” definition applies to drug products, not just to active ingredients), with *United States v. Generix Drug Corp.*, 654 F.2d 1114, 1120 (5th Cir. Unit B 1981) (finding that FDA approval is not required for a drug containing the same active ingredient as a previously approved drug), *rev’d*, 460 U.S. 353 (1983). The Supreme Court effectively sided with the agency by concluding that the “generally recognized as safe and effective” inquiry focuses on the finished drug product rather than the active ingredient. *Generix Drug Corp.*, 460 U.S. at 457.

⁴⁹ See *Generic Pharm. Ass’n, Supplemental Comment Letter on Pfizer, Inc and Pharmacia Corp. Citizen Petition*, at 4 (Oct. 9, 2003), <http://www.fda.gov/ohrms/dockets/dailys/03/oct03/101403/01p-0323-c000006-vol2.pdf>.

⁵⁰ See *id.*

⁵¹ See *id.* at 5, 17; see also *Closing the Gaps in Hatch–Waxman: Assuring Greater Access to Affordable Pharmaceuticals: Hearing Before the S. Comm. on Health, Educ., Labor, & Pensions*, 107th Cong. 52 (2002) (statement of Gregory J. Glover, on behalf of Pharm. Research & Mfrs. of Am.).

the Hatch–Waxman generic-drug pathway in 1984—authorizing ANDAs for copies of any new drug—mooted the exercise.⁵²

Today, it is probably not possible as a practical matter for a generic drug company to argue, after time has passed, that a previously approved new chemical entity is no longer a new drug and that a generic copy therefore does not require an approved application. But it is theoretically possible as a legal matter for a drug to attain “old drug” status and be thereby exempt from premarket approval requirements.⁵³

B. *Exclusivity Narratives*

There are several ways to characterize the pathway provisions and timing rules described in the preceding Subsection. Before exploring those, it is worth noting a terminology problem: divergence regarding the phrases “data exclusivity” and “market exclusivity.” Some use “data exclusivity” to refer to statutory prohibitions on *submission* of abbreviated applications and “market exclusivity” to refer to statutory prohibitions on *approval* of abbreviated applications and by extension market entry. Others use “data exclusivity” to refer to statutory provisions relating to either approval or submission of *abbreviated applications*, on the theory that these applications rely on the data submitted in earlier applications. These writers reserve “market exclusivity” for schemes (such as orphan drug exclusivity, discussed later in this Article) that preclude submission or approval of *any application*, regardless of whether it relies on an innovator’s data. One terminology approach or the other must be adopted in order to move forward with a piece of writing.⁵⁴ This Article takes the latter approach. By “data exclusivity,” this Article thus refers to prohibitions on submission or approval of *abbreviated* applications, which implicitly or explicitly rely on previously submitted data. And by “market exclusivity,” it refers to prohibitions on submission or approval of any competing application, even if supported by a full complement of original data. Section I explains why this disagreement is not merely a vocabulary quarrel but has substantive implications.

⁵² See *infra* notes 15–18 and accompanying text.

⁵³ Further, most marketed nonprescription drugs are old drugs without approved NDAs. Regulations in 21 C.F.R. pt. 330 (2015), specify active ingredients, dosages, and labeling claims that render a nonprescription drug not new and not misbranded. Any person may comply with the relevant regulation—called a monograph—and avoid the NDA process altogether. See *generally* Over-the-Counter Drugs, 37 Fed. Reg. 85 (proposed Jan. 5, 1972) (to be codified at 21 C.F.R. pt. 130) (now at pt. 330).

⁵⁴ Professor Heled has taken a third approach: referring to both as “regulatory competitive shelters,” which avoids the dispute altogether. See Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299 (2015). The present Article focuses on a distinction between what it labels “data exclusivity” and what it labels “market exclusivity,” however, so it must adopt differing labels. See *infra* Section II.C (comparing NCE exclusivity and orphan exclusivity).

This Article suggests a new way of characterizing the *function* of data-exclusivity provisions. The conventional narrative indicates that data exclusivity is *affirmatively* provided by the state—the subtext being that the natural state of affairs is one *without* data exclusivity.⁵⁵ Many legal scholars and policy writers describe data exclusivity as comparable to intellectual property, as patent-like, or even as a sub-type of intellectual property.⁵⁶ The innovative industry also tends to characterize it as a type of intellectual property.⁵⁷ Both economic and legal scholars analogize to monopoly when describing market conditions during data exclusivity—the subtext

⁵⁵ E.g., *Twenty-First Century Cures: Examining the Role of Incentives in Advancing Treatments and Cures for Patients: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 113th Cong. 9, 86 (2014) (statement of Rep. Henry A. Waxman, Member, H. Comm. on Energy & Commerce) (asserting that, in the Hatch–Waxman Amendments, Congress “gave the brands 5 years of exclusivity” and in the BPCIA “we gave 12 years of exclusivity to biologics” (emphasis added)). Scholars, too, use the language of an affirmative grant from the government. E.g., CARLOS MARÍA CORREA, PROTECTION OF DATA SUBMITTED FOR THE REGISTRATION OF PHARMACEUTICALS: IMPLEMENTING THE STANDARDS OF THE TRIPS AGREEMENT (2002), http://www.who.int/medicines/areas/policy/protection_of_data.pdf (“data . . . are subject to a sui generis system of protection, based on a temporary right to the exclusive use of such data . . .”); Katherine N. Addison, *The Impact of the Biosimilars Provision of the Health Care Reform Bill on Innovation Investments*, 10 J. MARSHALL REV. INTELL. PROP. L. 553, 563 (2011) (“The BPCIA grants an exclusivity period . . .” (emphasis added)); *id.* at 565 (“Reference product sponsors are rewarded . . . with twelve years of [data] exclusivity.” (emphasis added)); Baker, *supra* note 6, at 307 (“In addition to securing data exclusivity and patent term extensions to compensate for regulatory delays via the Hatch–Waxman Act . . .” (emphasis added)); Rebecca S. Eisenberg, Lecture, *Patents, Product Exclusivity, and Information Dissemination: How Law Directs Biopharmaceutical Research and Development*, 72 FORDHAM L. REV. 477, 482–83 (2003) (stating that the FDA “confers formal exclusivity in product markets” and “reward[s] innovation by granting valuable exclusionary rights” (emphases added)). The present Author has herself used the term “grant” in many publications and presentations; it is the conventional narrative.

⁵⁶ E.g., Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 360 (2007) (“FDA-administered proprietary rights in regulatory data, awarded to encourage particular kinds of innovation”); *id.* at 361 (“patent-like protection under the auspices of the FDA”); Robert Alan Hess, *Excavating Treasure from the Amber of the Prior Art: Why the Public Benefit Doctrine Is Ill-Suited to the Pharmaceutical Sciences*, 66 FOOD & DRUG L.J. 105, 107 (2011) (“pseudo-patents”); Trudo Lemmens & Candice Telfer, *Access to Information and the Right to Health: The Human Rights Case for Clinical Trials Transparency*, 38 AM. J.L. & MED. 63, 84–85 (2012) (“patent-style protection”); John R. Thomas, *Toward a Theory of Regulatory Exclusivities*, in PATENT LAW IN GLOBAL PERSPECTIVE 345, 347 (Ruth L. Okediji & Margo A. Bagley eds., 2014) (“fairly described as the newest form of intellectual property”).

⁵⁷ See, e.g., PHARM. RESEARCH & MFRS. OF AM. (PhRMA), SPECIAL 301 SUBMISSION 2015, at 2–11 (2015), <http://www.phrma.org/sites/default/files/pdf/PhRMA-2015-Special-301-Rev.pdf> (discussing data exclusivity/protection as an intellectual-property right); *id.* at 8 (“IP rights, including patents, trademarks, and regulatory data protection.”).

again being that natural competition has been affirmatively blocked by the State.⁵⁸ The key to the conventional narrative is that exclusivity is artificial and provided, as a benefit, to pioneers.

But there is another way to understand what is going on. The government requires a license to market new drugs, which it will issue after reviewing the results of research to support the marketability of the drug. Anyone may apply for a license, and indeed—subject to any relevant patent protection one or another of the companies might enjoy as well as their business judgment about the value of the investment—multiple companies may file for licenses to market the same drug or drugs that are similar. That is to say, the *drug approval statutes*—the regulatory apparatuses—do not preclude two, or three or more applicants from seeking approval of the same thing on the same terms. From a regulatory perspective, all face the same scientific burden—preclinical and clinical research in a full application, showing the finished product is safe and effective.⁵⁹ The second and third applicant will have a reduced burden as a practical matter simply because approval of the first product—and the large volume of information released about the contents of the application—will eliminate much of the trial and error that the first applicant experienced.⁶⁰ They will know what to study and what not to study, they will

⁵⁸ E.g., LAURENCE J. KOTLIKOFF, *STIMULATING INNOVATION IN THE BIOLOGICS INDUSTRY: A BALANCED APPROACH TO MARKETING EXCLUSIVITY* 1 (Sept. 2008), http://www.kotlikoff.net/sites/default/files/Kotlikoff_Innovation_in_Biologics21.pdf (“monopoly”); Alfred B. Engelberg et al., *Balancing Innovation, Access, and Profits—Market Exclusivity for Biologics*, 361 *NEW ENG. J. MED.* 1917, 1918 (2009) (“boon”); Yaniv Heled, *Why Primary Patents Covering Biologics Should Be Unenforceable Against Generic Applicants Under the Biologics Price Competition and Innovation Act*, 21 *ANNALS HEALTH L.* 211, 218 (2012) (“monopolies”); Emily Marden, *Open Source Drug Development: A Path to More Accessible Drugs and Diagnostics?*, 11 *MINN. J.L. SCI. & TECH.* 217, 264 (2010) (“monopoly”); Vincent J. Roth, *Will Data Exclusivity Make Biologic Patents Passé?*, 29 *SANTA CLARA COMPUTER & HIGH TECH. L.J.* 249, 251, 303 (2013) (“measure of monopoly” and “form[] of intellectual property”); Sarah Sorscher, Note, *A Longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy*, 23 *HARV. J.L. & TECH.* 285, 289 (2009) (“expanding monopoly protection”).

⁵⁹ A finished product, also called a drug product or a finished drug product, is the final form of the drug for administration to patients—for example, a tablet or capsule that contains the active drug substance and often other ingredients. See 21 C.F.R. § 314.3 (2015).

⁶⁰ The contents of the application are summarized in the approved labeling, but they are also described in detail in the “action package” released by the FDA pursuant to § 505(l) of the FDCA. See 21 U.S.C. § 355(l) (2012). The action package includes a review memorandum (or several review memoranda) from each reviewing discipline at the agency—e.g., medical reviewers, clinical pharmacology reviewers, and statistical reviewers—as well as a summary memorandum explaining the agency’s decision. Additional information about the supporting clinical trials is typically available through the National Institutes of Health at www.clinicaltrials.gov, and often through peer-reviewed medical journals. See generally Lietzan, *supra* note 13 (discussing clinical

know how to design their trials, they will know what results to expect, and they can reverse engineer the first entrant's product to determine a suitable formulation, route of administration, dosage form, and strength. All of this will save these applicants *some* time and money, but the bulk of their expenses remain, deriving from the clinical trials that must still be performed to obtain a license.⁶¹

After a period of time, federal law permits other companies to obtain licenses for identical or highly similar medicines *without* the same amount of supporting research. The drug approval statutes remove the high evidentiary hurdle and substitute a different one, with a significantly lower investment requirement. A license to market is now available for the price of comparative analytical testing and perhaps modest comparative clinical testing. As a scientific matter, these follow-on applicants are able to obtain licenses because they rely on the research performed by the earlier applicant. That these are reliance-based applications should not be controversial. FDA has conceded that as a regulatory matter a follow-on applicant uses the first entrant's research, even if sometimes couching it as using the "fact" of the first entrant's approval.⁶² Many courts characterizing generic drug approval use the same language.⁶³ In brief, then,

data confidentiality and disclosure). The information publicly available does not include the raw data or the applicant's clinical study reports, but it contains a substantial amount of information that can guide subsequent applicants studying the same or a related molecule.

⁶¹ See ROY, *supra* note 12, at 2.

⁶² See Letter from Janet Woodcock, Dir., Ctr. for Drug Eval. & Research, to Katherine [sic] M. Sanzo et al. at 10 n.14 (Oct. 14, 2003), <http://www.fdalawyersblog.com/wp-content/uploads/sites/8/2015/07/Takings-CP-Response-505b2.pdf> ("[R]eliance on an FDA finding of safety and effectiveness for an NDA is certainly indirect reliance on the data submitted in the original NDA . . ."); see also CTR. FOR DRUG EVAL. & RESEARCH, FDA, A BRIEF BACKGROUND ON THE REGULATION OF GENERIC DRUGS (AKA OGD 101), at slide 8 (Aug. 7, 2014) (showing that a generic application must show bioequivalence with the innovator's drug in order to avoid submission of clinical studies); Letter from Steven K. Galson, Dir., Ctr. for Drug Eval. & Research, to Kathleen M. Sanzo et al. at 31 (May 30, 2006), <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> (noting that FDA's approval of the drug Omnitrope was based on the "finding of safety and effectiveness for Genotropin" which was, "in turn, based upon additional adequate and well-controlled studies" cited in the Genotropin application).

⁶³ See, e.g., Purepac Pharm. Co. v. Thompson, 354 F.3d 877, 879 (D.C. Cir. 2004) (describing ANDAs as applications "that 'piggyback' on the safety-and-effectiveness information that the brand-name manufacturers submitted in their NDAs"); Am. Bioscience, Inc. v. Thompson, 243 F.3d 579, 580 (D.C. Cir. 2001) (observing that ANDA applicants are "relying on the NDA filed by the original manufacturer"); Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1495 (D.C. Cir. 1996) (stating that a generic applicant "may rely upon research paid for by the manufacturer of the listed drug"); Zenith Labs., Inc. v. Abbott Labs., No. 96-1661, 1996 WL 33344963, at *1 (D.N.J. Aug. 7, 1996) (describing the ANDA process as allowing an applicant to "rely upon the pioneer company's tests."); Merck & Co. v. Kessler, 80 F.3d 1543, 1546 (Fed.

once data exclusivity expires, any applicant may justify market entry using the research paid for and submitted by the pioneer to justify its own entry to the market. This reframes data exclusivity as a period before the law gives the pioneer's competitors something not previously available to them—a faster and cheaper license, resulting from permission to rely on the pioneer's research.

The question of how much faster and cheaper is the subject of some dispute. The length of time to bring a new molecular entity from the research laboratory to patients in finished product form varies, but generally averages 10 to 12 years.⁶⁴ Researchers at Tufts University have estimated the average cost to a pharmaceutical company of developing a new drug, reaching the figure of \$1.04 billion in 2013 dollars for the 1983 to 1994 period and more recently reaching the figure of \$2.6 billion in 2013 dollars for the 1995 to 2007 period.⁶⁵ (This number reflects the cost of first approval for entirely new drugs, not the cost of subsequent innovation, like the development of new indications or formulations.) By way of comparison, the Federal Trade Commission (FTC) reported in 2009 that generic non-biological drug applications typically take three to five years to assemble, with a corresponding cost of one to five million dollars.⁶⁶

Cir. 1996) (describing the ANDA process as permitting a “generic producer of the fully tested drug to rely on the safety and efficacy data of a prior applicant”); *Am. Bioscience Inc. v. Thompson*, 141 F. Supp. 2d 88, 91 (D.D.C. 2001) (“In other words, the generic manufacturer is allowed to rely on the safety and effectiveness data submitted in the pioneer’s NDA.”), *rev’d*, 269 F.3d 1077 (D.C. Cir. 2001); *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 172 (D. Md. 1990) (explaining that ANDA applicants are “permitted . . . to rely on the safety and effectiveness data submitted by the ‘pioneer’ drug manufacturer with its NDA”); *Glaxo, Inc. v. Heckler*, 623 F. Supp. 69, 72 (E.D.N.C. 1985) (stating that ANDA applicants “may rely on existing data and information on file with the FDA in order to satisfy the safety and efficacy requirements of federal food and drug law”).

⁶⁴ See Press Release, Tufts Ctr. for the Study of Drug Dev., Cost to Develop and Win Marketing Approval for a New Drug is \$2.6 Billion (Nov. 18, 2014), http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Nearly 20 years ago, the FDA placed the timeline at eight and a half years. See CTR. FOR DRUG EVAL. & RESEARCH, FDA, FROM TEST TUBE TO PATIENT: IMPROVING HEALTH THROUGH HUMAN DRUGS 21 (Sept. 1999), <http://www.canceractionnow.org/FromTestTubeToPatient.pdf>.

⁶⁵ See Press Release, *supra* note 64; see also Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180 (2003). More than half of the total cost reflects out-of-pocket clinical testing costs, which have nearly doubled since the earlier window. The researchers attribute this to increased clinical trial complexity, larger trial sizes, and changes in clinical trial protocol design (including design changes to gather information about cost effectiveness and comparative effectiveness, which are increasingly required by payers and health technology assessment bodies). *Id.* at 177–81.

⁶⁶ FTC, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, at iii (June 2009), <https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade->

These numbers suggest generic applicants benefit from a 50% to 75% reduction in time required and a more than 500-fold reduction in cost.

The Tufts research draws criticism, in part because it relies on proprietary data.⁶⁷ But in 2006, an economist and research analyst at the FTC independently replicated the Tufts estimates, using a publicly available data set. They found considerable variation with costs varying from around \$500 million to more than \$2 billion, depending on the therapy and the company.⁶⁸ And there is good reason to assume variation in the length of research and development period as well, with some well-documented examples like Avastin (bevacizumab) for colorectal cancer substantially exceeding 12 years.⁶⁹ Without a doubt, there is a considerable amount of variation in the length of the research and development period as well. The FDA's requirements vary by drug class and indication; a cardiovascular drug may require a large number of trial subjects and mortality and morbidity endpoints that inherently entail longer trials, for instance, whereas a cancer drug may be approvable after phase II on the strength of surrogate endpoints which can be measured more quickly (such as tumor shrinkage or a short extension in lifespan).

Like generic drug applications under the FDCA, biosimilar applications under the PHSa should be faster and cheaper than pioneer applications. But because the scheme is so new, we have very little information

commission-report/p083901biologicsreport.pdf. This estimate is repeated in the academic literature. *See, e.g.*, Kristina M. Lybecker, *Essay: When Patents Aren't Enough: Why Biologics Necessitate Data Exclusivity Protection*, 40 WM. MITCHELL L. REV. 1427, 1436 (2014).

⁶⁷ *See, e.g.*, Donald W. Light & Rebecca N. Warburton, *Extraordinary Claims Require Extraordinary Evidence*, 24 J. HEALTH ECON. 1030, 1031–32 (2005); Donald W. Light & Rebecca Warburton, *Demythologizing the High Costs of Pharmaceutical Research*, 6 Biosocieties 34 (2011); *see also* Cynthia M. Ho, *Drugged Out: How Cognitive Bias Hurts Drug Innovation*, 51 SAN DIEGO L. REV. 419, 448–57 (2014) (arguing that cognitive biases pervade discussion of drug development costs, affecting the widely cited Tufts numbers and possibly affecting its critics as well).

⁶⁸ *See* Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really \$802 Million?*, 25 HEALTH AFFAIRS 420, 427 (2006). The authors also observe that: (a) drug development costs vary greatly even among the largest pharmaceutical firms; (b) some difference is attributable to differences in success rates and duration of testing necessary among the various therapeutic categories; (c) FDA regulatory policy itself can and does reduce development costs, as it has done with respect to HIV/AIDS drugs; and (d) “some of the estimated costs could be attributable to the strategic decisions of the drug firms themselves.” *Id.* at 424–47.

⁶⁹ *See, e.g.*, Henry Grabowski, *Data Exclusivity for New Biological Entities* 10 (Duke Univ. Dept. of Econ. Working Paper, 2007), <http://public.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf> (noting that approval of Avastin came 15 years after a Genentech scientist discovered the existence of vascular endothelial growth factor, a protein that helps grow blood vessels and can help cancers grow and spread). The phase III trial in metastatic colorectal cancer took three years. *Id.*

about the time and costs involved for these applications.⁷⁰ Before the statute was enacted but after its regulatory provisions had been finalized, the FTC estimated that biosimilars would take 8 to 10 years to develop, with a corresponding cost of \$100 to \$200 million.⁷¹ This suggests a modest reduction in the time involved but perhaps a 90% decrease in financial burden (taking the top-end figures for both, from \$2 billion to \$200 million). But the statutory requirements for biosimilar approval are more discretionary than the ANDA provisions and will inherently vary with the complexity of the reference product.⁷² Some companies have been turned away at early meetings with the agency due to deficiencies in their analytical data,⁷³ for instance, and one experienced biosimilar sponsor faced unexpected review issues that seem to have slowed approval and undoubtedly are increasing cost.⁷⁴ It may therefore be difficult to generate a meaningful “average” cost for biosimilars. Further, because the regulatory requirements will almost certainly lessen over time as the FDA gains experience with the scheme and as analytical methodology improves, as they have in Europe since its biosimilar pathway launched in 2006, average costs may decrease over time.⁷⁵

⁷⁰ Only one biosimilar had been approved at the time of drafting, although several more applications were pending. See Christopher J. Betti et al., *FDA Accepts First Biosimilar Application Filed Under Section 351(k) of the Public Health Service Act*, K&L GATES (July 28, 2014), <http://www.klgates.com/fda-accepts-first-biosimilar-application-filed-under-section-351k-of-the-public-health-services-act-07-28-2014/>.

⁷¹ See FTC, *supra* note 66, at 14; see also Henry Grabowski et al., *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 522 (2011) (noting that research and development for complex biosimilars might take eight years and range in cost from \$100 to \$150 million). Other estimates are higher. See, e.g., George Dranitsaris et al., *Biosimilars of Biological Drug Therapies: Regulatory, Clinical and Commercial Considerations*, 71 DRUGS 1527, 1533–34 (2011) (“Manufacturing and development costs for some of the first-generation approved biosimilars [have] been estimated to be [\$75] to [\$250] million. For more complex monoclonal antibodies, costs of up to [\$500] million have been projected.” (footnote omitted)).

⁷² The European Medicines Agency (EMA) has issued guidelines explaining the requirements for biosimilar medicine applications by product class. See *Scientific Guidelines on Biosimilar Medicines*, EUR. MEDS. AGENCY (2015), http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp.

⁷³ See *FDA’s Latest Biosimilar Guidance Lays Out Expectations for Sponsor Meetings*, FDA WEEK (April 5, 2013) (“[L]ast year an FDA biosimilar official said the agency was turning away some sponsors because they lacked the necessary analytical data . . .”).

⁷⁴ M. Nielsen Hobbs, *Celltrion’s Biosimilar User Fee Deadline Passes with Conspicuous Silence*, PHARMA & MEDTECH BUS. INTELL.: PINK SHEET DAILY, (June 9, 2015), <https://www.pharmamedtechbi.com/publications/the-pink-sheet-daily/2015/6/9/celltrions-biosimilar-user-fee-deadline-passes-with-conspicuous-silence>.

⁷⁵ See Henry Grabowski & Erika Lietzan, *FDA Regulation of Biosimilars*, in *FDA IN THE TWENTY-FIRST CENTURY: THE CHALLENGES OF REGULATING DRUGS AND NEW TECHNOLOGIES* 414, 428–29 (Holly Fernandez Lynch & I. Glenn Cohen eds., 2015).

The question of how much faster and cheaper a generic or biosimilar drug application might be, as compared to the reference-product application, is important when considering likely market behaviors in a re-designed exclusivity scheme,⁷⁶ but it does not matter to the basic point being made in this Section about data exclusivity. The point is that data exclusivity can be understood as a period of time during which regulatory barriers to market entry are symmetrical—in other words, all applicants seeking to market a particular molecule (or variations thereof) face the same regulatory burden of demonstrating safety and efficacy through a full preclinical and clinical research and development program, which the applicants perform, fund, or purchase.

C. *The Myth of Exclusivity*

When the narrative is recast, the central myth of exclusivity is exposed; it is not a grant of anything to anyone. Data exclusivity is the *absence* of an abbreviated pathway. It does not prevent subsequent entrants from doing exactly what the first entrant did—developing the product, testing it, submitting a full application, and launching the drug, subject to relevant patent and business considerations.⁷⁷ Contrasting *data* exclusivity with *market* exclusivity should make this clear.

Orphan-drug exclusivity is the main example in current U.S. law of market exclusivity. An orphan drug is intended to treat a rare disease or condition; the sponsor makes this showing by demonstrating that the disease affects fewer than 200,000 persons in this country or that the company does not expect to recover its costs of research and development when marketing the product.⁷⁸ If a drug has been designated as an orphan drug, then—upon approval—it is entitled to seven years of market exclusivity.⁷⁹ This means the FDA may not approve the same drug for the same condition for seven years, even if proposed in a full application supported by original research.⁸⁰ Orphan-drug exclusivity is an affirmatively granted right, in the sense that it prevents subsequent entrants from doing what they would ordinarily and otherwise be permitted to

⁷⁶ See *infra* Section III.

⁷⁷ See Elizabeth H. Dickinson, *FDA's Role in Making Exclusivity Determinations*, 54 FOOD & DRUG L.J. 195, 200 (1999) (“The five-year exclusivity provision does not prohibit FDA from accepting another full competitor NDA if the sponsor of the second application has done all the work itself.”). When she wrote this article, Ms. Dickinson was Associate Counsel for Drugs at FDA. She is now the agency’s Chief Counsel.

⁷⁸ See FDCA, 21 U.S.C. §§ 360bb(a)(1)–(2) (2012).

⁷⁹ *Id.* § 360cc(a).

⁸⁰ See *id.*; see also *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 23 (D.D.C. 1996) (noting that the Orphan Drug Act “precludes the grant of FDA approval to other manufacturers of the same drug intended for treatment of the same disease”).

do—study the molecule themselves and reach the market on the same terms as the first entrant.

Another example of market exclusivity is the 180-day exclusivity awarded to the first generic applicants to challenge a particular innovator's patent (as invalid or not infringed) in its ANDA.⁸¹ Like orphan exclusivity and unlike data exclusivity, it bars subsequent similarly situated applicants—other generic companies challenging the innovator's patents—from obtaining approval on the same terms for a fixed period of time. Subsequent applicants who similarly challenged the patent and whose products are otherwise approvable must wait. A third example is the exclusivity granted to the first biosimilar sponsor to demonstrate its biosimilar interchangeable with a particular reference product. For a period of time after FDA finds this product interchangeable, no other biosimilar product may be deemed interchangeable with the same reference product—even if the applicant has performed comparable research and made the same showing.⁸² It may be fair to call orphan exclusivity, 180-day exclusivity, and interchangeability exclusivity patent-like rights,⁸³ in the sense that they block others who would otherwise do the same thing, by virtue of an affirmative step taken by Congress (i.e., *as of now, others may not do what you did*). But one cannot fairly say the same of data exclusivity.⁸⁴ Data exclusivity does not prevent competitors from doing the same thing the pioneer did. And this is why the terminology dispute—*data* versus *market* exclusivity—matters. Using the phrase *market* exclusivity to describe a regulatory scheme in which competitors are in fact free to exploit the market using the same pathway for their competing products (including replicas) perpetuates the myth of exclusivity.

⁸¹ See 21 U.S.C., § 355(j) (5) (B) (iv). See generally David E. Korn, Erika Lietzan & Shaw W. Scott, *A New History and Discussion of 180-Day Exclusivity*, 64 FOOD & DRUG L.J. 335 (2009); Erika Lietzan & David E. Korn, *Issues in the Interpretation of 180-Day Exclusivity*, 62 FOOD & DRUG L.J. 49 (2007); Erika King Lietzan, *2004 Update: 180-Day Exclusivity Under the Hatch–Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, 59 FOOD & DRUG L.J. 459 (2004); Erika King Lietzan, *A Brief History of 180-Day Exclusivity Under the Hatch–Waxman Amendments to the Federal Food, Drug, and Cosmetic Act*, 59 FOOD & DRUG L.J. 287 (2004).

⁸² 42 U.S.C. § 262(k) (6) (2012). At the time this Article was written, no sponsor of a biosimilar had proven its product interchangeable, and thus no exclusivity had been awarded.

⁸³ See Rebecca S. Eisenberg, *Patents and Regulatory Exclusivity*, in THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 167, 184 (Patricia M. Danzon & Sean Nicholson eds., 2012) (“Market exclusivity under the Orphan Drug Act is similar to a patent on a particular use of a drug, enforced by FDA, with the drug narrowly defined to exclude ‘clinically superior’ formulations.”).

⁸⁴ See TREVOR M. COOK, THE PROTECTION OF REGULATORY DATA IN PHARMACEUTICAL AND OTHER SECTORS 4 (2000); Ian Dodds-Smith, *Data Protection and Abridged Applications for Marketing Authorisations in the Pharmaceutical Industry*, in PHARMACEUTICAL MEDICINE, BIOTECHNOLOGY AND EUROPEAN LAW 93, 100 (Richard Goldberg & Julian Lonbay eds., 2000).

It should not be assumed that this is a simple fiction—in other words that regulatory symmetry (subjecting all applicants to the same rules) is purely hypothetical, and in fact the pioneer always has a non-competitive marketplace entirely to itself. Indeed, there would be no need for orphan exclusivity—preventing the FDA from approving full applications for the same drug for seven years—if the threat of full applications for duplicates were not real. Whether second and third applicants do—or with a change in the length or nature of exclusivity would—seek approval for duplicates (or slight variations) on the basis of full applications is a complex question. The answer almost certainly depends on a variety of factors.

To begin with, in the non-biological drug world, second entrants do not often compete with *identical* products during the data exclusivity period. This can be attributed to patent protection in many cases, and in almost every case probably also to the fact that it is less expensive and more rational to wait the brief period (five years, or four with a patent challenge) until the shortcut pathway opens. There are, however, some examples; the FDA has approved multiple comparable-in-scope new drug applications for hyaluronidase, levothyroxine, recombinant somatropin, and norethindrone, for instance. Generating a full list of examples and understanding their stories would be helpful.⁸⁵ But in the end, we have a thin historical record to shed light on market behavior in the absence of a ready generic-drug pathway; as already noted, generic drugs have been legally possible and marketed since enactment of the FDCA in 1938, through the old drug pathway until the late 1970s and via ANDAs (albeit only for copies of pioneer products that reached the market before 1962) after that.⁸⁶ As for biological drugs, it is less clear that a 12-year exclusivity period will always make waiting for an abbreviated pathway the most rational choice for a second entrant hoping to market a replica.

But even if subsequent entrants shy away from duplicates due to patent protection (or the irrationality of preparing a full application a mere four years before abbreviated applications are permitted), the pioneer may face competitive pressures during the data-exclusivity period with respect to both price and product features. That is, patent protection on the pioneer's product may drive second entrants toward non-infringing variations or, indeed, competing products in the same drug class, which would presumably compete—to the benefit of patients and payers—on the basis of differentiating features as well as price. Vigorous competition

⁸⁵ At least some of these are probably idiosyncratic situations; for instance, it made sense to file NDAs for recombinant somatropin, because the FDA was not prepared to approve abbreviated applications as a scientific matter until 2006—and even then approved only a 505(b)(2) application that contained extensive data, rather than an ANDA. This was Omnitrope, discussed *supra* note 62 and *infra* note 149.

⁸⁶ See *supra* Section II.A.3.

within a new class of non-biological drugs recently approved to treat chronic Hepatitis C infection indicates that in the absence of pressure from a substitutable generic, prompt in-class competition from an innovator can place substantial pressure on first-entrant prices. These drugs represented a paradigm shift in treatment of HCV infection, blocking a protein needed by the virus to replicate.⁸⁷ Gilead Sciences obtained approval of Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) in December 2013 and October 2014, respectively. These drugs began with list prices of more than \$80,000 for 12 weeks of treatment. AbbVie obtained approval of its Viekira Pak (ombitasvir/paritaprevir/ritonavir) in December 2014, at which point purchasers of *each* began to extract significant discounts in exchange for exclusive contracts.⁸⁸

Review of innovation in the biological marketplace from 1986 (licensure of the first recombinant biological product) to 2010 (when abbreviated biologics applications were authorized by law) might offer additional examples and valuable insights on second-entrant behavior during the data-exclusivity term. This review would need to take into account the strategic impact of both the patent landscape and orphan exclusivity. The nature of the patent protection—a simple composition of matter patent, on the one hand, versus a foundational technology claim, on the other hand—presumably will affect the second-in-class strategies available to second entrants. And the FDA’s willingness to make exceptions to orphan exclusivity—by characterizing a second entrant’s proposed use as different even if it varies only slightly, for instance, or by characterizing the second entrant’s drug as different on account of claims of clinical superiority (for instance, fewer injection-site reactions)—will also affect strategies.

But there are interesting stories to explore. For instance, with only a full-application option on the table, two companies raced to clone the hormone erythropoietin for administration to patients with anemia; a patent ruling ultimately meant that only Amgen—and not Chugai—would market in the United States.⁸⁹ Genzyme and Transkaryotic Therapies also

⁸⁷ See Press Release, FDA, FDA Approves Sovaldi for Chronic Hepatitis C (Dec. 6, 2013), <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm377888.htm>.

⁸⁸ See, e.g., Caroline Humer, *UnitedHealth Backs Gilead’s Harvoni as Preferred Hepatitis C Treatment*, Reuters (Jan. 28, 2014), <http://www.reuters.com/article/unitedhealth-gilead-hepatitis-idUSL1NOV72GD20150128>; Samantha Liss, *Express Scripts to Drop Hepatitis Drug Sovaldi, Offer Competing Viekira Pak*, ST. LOUIS POST-DISPATCH (Dec. 21, 2014), http://www.stltoday.com/business/local/express-scripts-to-drop-hepatitis-c-drug-sovaldi-offer-competing/article_7363d48e-a79e-5bda-8198-3090c17876d5.html; Meg Tirrell, *Gilead Fights Back: CVS to Cover Its Hepatitis C Drugs Exclusively*, CNBC (Jan. 5, 2015), <http://www.cnbc.com/2015/01/05/gilead-inks-deal-with-cvs-to-cover-its-hepatitis-c-drugs-exclusively.html>.

⁸⁹ See Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA’s Uncertain Interpretation of the Orphan Drug Act*, 12 HARV. J.L. & TECH. 365, 388–89

raced to market with agalactosidase alpha products for Fabry's disease; Genzyme entered the market alone on account of orphan designation and receiving approval first, but *not* on account of patent protection.⁹⁰ These and other examples could be explored more deeply. It is possible that with a long enough delay before available shortcuts, second entrants will generate copies as well as second-in-class and third-in-class products (creating price and feature competition); and it is possible that crowded classes (or a brief delay before shortcuts open) will prompt industry to pursue new lines of research and development.

This competitive marketplace during data exclusivity contrasts with the marketplace after the second pathway opens. Once the shortcut pathway opens, generic drugs generally obtain their market share by operation of state law, rather than through active competition for freely choosing consumers. Specifically, the FDA awards every approved generic drug product a therapeutic equivalence rating, indicating the agency's judgment whether the generic can be substituted for the pioneer product. In the absence of a change to route of administration, dosage form, or strength, a generic drug receives an "A" rating—signaling that the two products can be expected to have the same clinical profile and the generic can therefore be substituted without the intervention of healthcare providers.⁹¹ Under state law, the generic drug is then generally substituted at the point of sale, even when a physician prescribes the pioneer drug.⁹² This has a profound impact on the pioneer's market share. A recent case study of six drugs that lost exclusivity between 2009 and 2013 found it took on average three months for generic penetration to reach 60%.⁹³ Further, even where substitution does not drive market share, it

(1999).

⁹⁰ See Andrew Pollack, *A Genzyme Drug Receives Qualified Support*, N.Y. TIMES (Jan. 14, 2003), <http://www.nytimes.com/2003/01/14/business/a-genzyme-drug-wins-qualified-support.html>; see also Claire Cassidy & James Love, *Timeline for Fabrazyme, Replagal*, KNOWLEDGE ECOLOGY INT'L (July 14, 2014), http://keionline.org/sites/default/files/Replagal_Fabrazyme_Timeline.pdf.

⁹¹ FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at vii (35th ed. 2015). This FDA list is commonly known as the *Orange Book*.

⁹² The laws of the states are written differently, with some permitting substitution at the pharmacist's discretion and others requiring substitution (though subject to physician override, the precise wording of which varies), and some referencing therapeutic equivalence determinations in the *Orange Book* and others not. See *infra* note 100.

⁹³ See Murray L. Aitken et al., *The Regulation of Prescription Drug Competition and Market Responses: Patterns in Prices and Sales Following Loss of Exclusivity* 1 (Nat'l Bureau of Econ. Research, Working Paper No. 19487, 2013) (finding that "compared with the 1980s and 1990s, the speed with which generics have gained market share . . . following [loss of exclusivity] has accelerated").

remains a myth that generic companies offer horizontal competition to innovators.⁹⁴

The biosimilar marketplace will operate differently in the near term because the cost of generating biosimilars will be more substantial and because biosimilars will not initially earn therapeutic equivalence ratings (called “interchangeability” determinations in the PHSA).⁹⁵ Competition between reference products and biosimilars will probably resemble traditional brand-to-brand competition at first, with biosimilar sponsors branding and promoting their medicines and initial savings being modest.⁹⁶ But this is likely to be a short-term to medium-term state of affairs. The FDA has suggested ways to reduce the clinical-testing burden on biosimilar applicants,⁹⁷ and analytical methodology may improve sufficiently over the next decade to reduce that burden even further. The agency has also begun considering what will be needed for interchangeability determinations,⁹⁸ some companies are conducting switching trials,⁹⁹ and state legislatures have begun amending their laws to accommodate biosimilar substitution.¹⁰⁰ Eventually the biosimilar marketplace may resemble the generic drug marketplace, in which case there will not be meaningful brand-to-brand-style price and feature competition after the

⁹⁴ Emily Michiko Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch–Waxman Act*, 22 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 245, 278 (2012) (arguing that generic manufacturers are not horizontal competitors to brand-name pharma for a variety of reasons, including that “private insurers and other third-party payers not only interrupt the chain between patient consumers and pharmaceutical manufacturers but also skew the demand for those pharmaceuticals”).

⁹⁵ See, e.g., FDA, GUIDANCE FOR INDUSTRY: BIOSIMILARS: ADDITIONAL QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009, at 7 (draft, May 2015), <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM273001.pdf> (“At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application given the statutory standard for interchangeability and the sequential nature of that assessment. FDA is continuing to consider the type of information sufficient to enable FDA to determine that a biological product is interchangeable with the reference product.”); see also Grabowski & Lietzan, *supra* note 75, at 428–29.

⁹⁶ See generally Grabowski & Lietzan, *supra* note 75.

⁹⁷ See, e.g., SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 37, at 7.

⁹⁸ See *Guidance Agenda: New & Revised Draft Guidances CDER Is Planning to Publish During Calendar Year 2015* (April 28, 2015), <http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm417290.pdf>.

⁹⁹ See *Study into Switching from Aranesp to Biosimilar Epoetin Alfa*, GENERICS & BIOSIMILARS INITIATIVE (July 11, 2014), <http://gabionline.net/Biosimilars/News/Study-into-switching-from-Aranesp-to-biosimilar-epoetin-alfa>; see also *Study of Haemodialysis Patients Switching from Aranesp to Biosimilar*, CLINICALTRIALS.GOV (June 3, 2015), <https://clinicaltrials.gov/ct2/show/NCT02191150>.

¹⁰⁰ See, e.g., DEL. CODE ANN. tit. 24, § 2549A (2015); FLA. STAT. ANN. § 465.0252 (West 2015); IND. CODE § 16-42-25-5 (2015); N.D. CENT. CODE § 19-02.1-14.3 (2015); UTAH CODE § 58-17b-605.5 (2015).

shortcut pathway opens, but instead non-competitive substitution by pharmacies and payers.

Further, at least in the biological drug marketplace, it is possible that even *after* the second pathway opens, some competitors will choose to file full applications rather than abbreviated applications. Specifically, both regulatory and intellectual property considerations could prompt sponsors to file full applications for their replicas of pioneer biological drugs. The PHSA requires a biosimilar biological product to be highly similar to its reference product, and it precludes clinically meaningful differences between the two.¹⁰¹ The biosimilar must also have the same route of administration, dosage form, and strength as its reference product, and its “conditions of use” must have been approved for the reference product.¹⁰² The statute thus presents a stark choice: file a biosimilar application striving to be as similar as possible to the reference product, or file a full application supported by a full complement of preclinical and clinical trials.

The tradeoff is complex, with advantages and disadvantages to each pathway. For instance, the FDA has decided that a biosimilar applicant may in many cases submit clinical data for only one indication and justify approval for all reference product indications—an advantageous process known as extrapolation.¹⁰³ In addition, as noted, the PHSA authorizes issuance of interchangeability determinations for biosimilars if certain showings are made, and this will eventually lead to substitution under state pharmacy law. The benefits of extrapolation and interchangeability for biosimilars may, for some companies, outweigh the disadvantage of being limited to the innovator’s indications and other conditions of use. For other companies, they may not, and whether they do may depend on the number of indications at issue (and their cost to prove as well as their value in the marketplace) and on the therapeutic class (including how crowded the class is).

Until recently, there had also been a question whether the pre-market patent litigation provisions of the PHSA would push companies to full applications instead of abbreviated applications because many interpreted these provisions as requiring the biosimilar applicant to provide a copy of its application to the innovator.¹⁰⁴ Although an initial court ruling

¹⁰¹ 42 U.S.C. § 262(i) (2012).

¹⁰² *Id.* § 262(k)(2)(A)(i)(III)–(V). The phrase “conditions of use” encompasses all circumstances described in approved labeling related to use of an approved product, e.g., indications, dosing regimens, dosing instructions, dose levels, strengths, frequency of administration, durations of use, routes of administration, dosage forms, monotherapy versus concomitant therapy, first-line versus second-line therapy, and so forth.

¹⁰³ SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 37, at 21.

¹⁰⁴ *E.g.*, FDA Says It Prefers, but Can’t Mandate, Firms Utilize Biosimilars Pathway, FDA WEEK (Dec. 17, 2010) (noting that several firms developing biosimilar-like products

indicates otherwise,¹⁰⁵ the dispute may not yet be fully resolved. If a company concludes that it prefers the full pathway, recasting the biosimilar application as a full application may be feasible, provided the submitted studies *standing alone* fully establish the safety and effectiveness of the proposed product. Indeed, soon after enactment of the BPCIA, the FDA approved a full application for Teva's filgrastim product, though the very same product had been authorized as a biosimilar in Europe on the basis of largely the same application.¹⁰⁶ This is an area that will need to be watched closely.

In brief, a variety of patent, regulatory, and business considerations may drive subsequent entrants toward, or away from, a full application for a "copy" (or instead a "tweaked" version, or even instead a second-in-class product) in the years following pioneer approval when all comers are subject to the same license requirements.¹⁰⁷ The decision in any par-

indicated they might not file their applications under the new pathway, citing "drawbacks" including the patent litigation provisions).

¹⁰⁵ See *Amgen, Inc. v. Sandoz, Inc.*, 794 F.3d 1347 (Fed. Cir. 2015).

¹⁰⁶ See Grabowski & Lietzan, *supra* note 75, at 427. The application had been submitted prior to enactment of the BPCIA, when only the full pathway was available but, as a practical matter, it could presumably have been withdrawn and resubmitted under the new pathway.

¹⁰⁷ There is an important additional question whether ethical considerations affect the decision to proceed with a full application. See, e.g., CORREA, *supra* note 55, at 5–6 ("If the regulatory body is not free, when assessing a file, to use all the knowledge available to it, including data from other files and published information, a great deal of *repetitive* toxicological and clinical investigation will be required, which will be wasteful and in the case of animal testing, ethically questionable."); Lemmens & Telfer, *supra* note 56, at 85 ("This will be particularly ethically problematic in the case of healthy subjects research and when patients are asked to participate in placebo-controlled trials."); Peter K. Yu, *The Political Economy of Data Protection*, 84 CHI.-KENT L. REV. 777, 784–85 (2010) (stating that "commentators have found the need for data exclusivity laws economically dubious" because "[i]t is also wasteful and highly undesirable to require duplicative testing in countries that have very limited economic resources" and because "[i]t is simply immoral to require the use of human subjects and animals to retest drugs that are considered bioequivalent to those that have already been approved for the market."). This issue is beyond the scope of this Article, but preliminary thoughts from a regulatory perspective follow.

First, one concern may be the use of a placebo arm or the randomization of some study subjects to a different treatment than the one under investigation. Use of the first approved product as the active control (and approval on the basis of non-inferiority) should mitigate most of this concern, although it does not alleviate concerns relating to testing procedures themselves (such as blood draws). A strong tradition of autonomy in this country with respect to personal healthcare decisions, combined with the emphasis we place on giving patients and consumers access to information (i.e., a less paternalistic model of the physician–patient relationship), may give informed consent a sufficiently mitigating role in this case. See generally Robert Temple & Susan S. Ellenberg, *Placebo-Controlled Trials and Active-Control Trials in the Evaluation of New Treatments Part 1: Ethical and Scientific Issues*, 133 ANNALS OF INTERNAL MED. 455 (2000). Dr. Temple is a senior medical official at the FDA, where

ticular case is complex and idiosyncratic, and in some cases, duplicates may well be marketed. The claim here is that from a regulatory perspective, subsequent entrants *may* file full applications for copies or near-copies. Data exclusivity does not speak to this; it is simply the phrase used to describe the period of time before a *second* pathway to market is available for their use before they can use the research generated by the pioneer to satisfy their own premarket burden.

Recasting data exclusivity in this fashion sheds light on why it is a mistake to refer to data exclusivity as a discrete element of either the Hatch–Waxman compromise or the BPCIA compromise. This is not to say that these statutes were not compromises. They were. In the years leading to enactment of the generic drug provisions of 1984, for instance, the innovator and generic industries had been seeking separate reforms. The innovative industry had grown frustrated with the delay in market entry stemming from the expanded premarket research and development requirements attributable to the 1962 drug amendments. Noting that the average effective patent life (actual time on the market with an unexpired patent to exploit) had dropped to 11 or 12 years,¹⁰⁸ they sought restoration of at least some of the patent term lost to regulatory requirements. The generic industry sought a mechanism for abbreviated approval of copies of new drugs approved after the 1962 amendments. The final legislation provided both. And because it codified an experimental-use exemption to patent infringement for companies preparing

he currently serves as (among other things) Deputy Center Director for Clinical Science within the Center for Drug Evaluation and Research (CDER).

Second, a new drug is never fully understood when approved, nor has it been proven safe and effective in any absolute sense. Approval means only that its benefits are thought to outweigh its risks, based on a premarket testing program involving carefully selected subjects in tightly controlled usage conditions. The risk–benefit profile of the drug clarifies over time, as the company continues controlled testing and as data from the real world accumulate. The relative paucity of data at first-entrant approval might well be sufficient to justify a system of study replication for some period of time. Arguably, until the molecule is so well understood that regulators are confident no meaningful new safety or efficacy information will emerge from controlled clinical testing—indeed perhaps until “old drug” status is achieved—continued safety and efficacy testing may contribute to social welfare.

This is, indeed, one theory behind the “monitoring” period which substitutes for data exclusivity in the Pacific Rim countries. Japan, for instance, requires a drug with a new active ingredient to be the subject of full applications for an eight-year monitoring period, in part so that the safety and effectiveness of the drug can be more fully elucidated. See JAPAN PHARM. MFRS. ASS’N, PHARMACEUTICAL ADMINISTRATION AND REGULATIONS IN JAPAN ch. 4, § 6 (2015), <http://www.jpma.or.jp/english/parj/pdf/2015.pdf>; see also INT’L FED’N OF PHARM. MFRS. & ASS’NS, DATA EXCLUSIVITY: ENCOURAGING DEVELOPMENT OF NEW MEDICINES 70 (July 2011).

¹⁰⁸ See Bruce N. Kuhlik, *The Assault on Pharmaceutical Intellectual Property*, 71 U. CHI. L. REV. 93, 96–97 (2004); James J. Wheaton, *Generic Competition and Pharmaceutical Innovation: The Drug Price Competition and Patent Term Restoration Act of 1984*, 35 CATH. U. L. REV. 433, 451–52 (1986).

applications,¹⁰⁹ the statute also included an artificial act of patent infringement—submission of an ANDA with the intent to market during the patent term—giving the innovator an opportunity to enforce its patent rights before generic market entry.¹¹⁰ The conventional narrative states that innovators also received the five-year exclusivity term. But this cannot be right. Instead, subsequent entrants received the right to compete on different (cheaper, less burdensome) terms after five years.

So, too, with the biosimilar statute. Negotiations leading to the enactment of the BPCIA were contentious, mainly around the data-exclusivity provisions.¹¹¹ There is no question that a compromise was struck. Congress created an abbreviated pathway for approval of biological products, which will reduce the cost of market entry to a fraction of the price paid by first entrants. While the biological drug industry had already received patent-term restoration in 1984 along with the non-biologics drug industry, and competitors already had the benefit of the investigational-use exemption, pioneers now obtained a mechanism for patent litigation prior to market entry of follow-on products.¹¹² Some describing the compromise have suggested that the innovative industry also received 12 years of exclusivity.¹¹³ Again, this cannot be right. The innovative industry received nothing, when the four lead senators agreed, in June 2007, to years of exclusivity.¹¹⁴ The *status quo ante* was symmetrical barriers to entry. Data exclusivity is not a “give” to the innovators when it represents the opening of a second pathway that benefits their competitors.

The analytical error is apparent also when one focuses on the “piggyback” aspect of the abbreviated pathways. When the Hatch–Waxman amendments were under consideration—putting aside the ineffectual paper NDA policy—innovators of new drugs approved after 1962 faced competition only from products approved through full applications. No one could file a cheaper, faster application to copy their drugs; no one could rely on their research to support a competing product. Thus, the decision to permit abbreviated applications five years after NCE approval ended what had been perpetual enjoyment of the exclusive right of pio-

¹⁰⁹ 35 U.S.C. § 271(e)(1) (2012).

¹¹⁰ See *supra* Section II.A.1.

¹¹¹ The author participated extensively in these negotiations and co-authored an exhaustive history of the process from 2002 to 2010. See Carver, Elikan & Lietzan, *supra* note 9.

¹¹² The structure of the scheme is different, with no public listing of relevant patents, no 180-day exclusivity for the first to challenge a patent, and no 30-month stay in the case of timely litigation. And again, as noted, whether this scheme is in fact mandatory is the subject of ongoing controversy. See *supra* note 41. One might ask whether any true compromise remains (i.e., whether the innovative industry received anything in 2010, after all) if the initial ruling of the Federal Circuit stands.

¹¹³ See *infra* note 116.

¹¹⁴ See Carver, Elikan & Lietzan, *supra* note 9, at 746.

neers to their own research. One could say that, in 1984, Congress shortened infinite data exclusivity to five years of data exclusivity. So, too, with the biologics statute. Prior to 2010, the PHSA did not authorize follow-on applications or reliance on innovator data. The decision to permit approval of abbreviated applications, relying on innovator data, 12 years after BLA approval, represented a truncation of what had been perpetual enjoyment of the exclusive right of BLA owners to their own research. Congress, in 2010, shortened infinite data exclusivity to 12 years of data exclusivity. Innovators may well have been relieved it was not shortened to seven (and this is the reason for the epigram to this Article), but their starting position had been infinite exclusive rights to their research data.

The myth can lead to analytical mistakes in other settings. For instance, Professor Epstein has made the argument that approval of biosimilar biological drugs constitutes an uncompensated taking of innovator property (trade secrets).¹¹⁵ One response has been that data exclusivity provides sufficient compensation.¹¹⁶ But this is illogical. The length of the period of time *before* a taking cannot logically be compensation *for* the taking. Nor is it logical to suggest that income from lawfully exploiting one's property is compensation for a subsequent taking of the property. Whatever the merit of Professor Epstein's position on the Fifth Amendment issue, which is beyond the scope of this Article, it cannot be correct analytically that the exclusivity term might constitute "compensation" for the taking that Professor Epstein finds.

III. REFRAMED DIALOGUE ABOUT EXCLUSIVITY: NET BENEFIT TO SOCIETY

Opponents of data exclusivity often seek the high ground by suggesting it is an artificial barrier to entry for the benefit of first applicants. But this is mythical thinking. This Article proposes an alternative way of thinking about data exclusivity—as the period of time before the law

¹¹⁵ Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L.J. 285 (2011). He argues that innovators with BLAs already approved in 2010 had no reasonable investment-backed expectation that their data would be used to support competitor products. *Id.* at 302–04. And he argues that, although innovators now have such an expectation, the unconstitutional-conditions doctrine precludes requiring them to relinquish Fifth Amendment rights in exchange for market entry. *Id.* at 313.

¹¹⁶ *E.g.*, Zuckerman Spaeder LLP, Comment Letter on Abbott Laboratories Citizen Petition, at 15–17 (Dec. 24, 2012), <http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0317-0007> (arguing that the statute "provides just compensation" in part because of the 12-year exclusivity provision); Michelle L. Butler, *Abbott Petitions FDA on Biosimilars; Argues Fifth Amendment Takings Clause*, FDA L. BLOG (May 17, 2012), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/05/abbott-petitions-fda-on-biosimilars-argues-fifth-amendment-takings-clause.html.

changes for the benefit of later applicants. Whether, and on what terms, subsequent entrants will offer marketplace competition to the first entrant during this time will depend on a variety of factors, some of which were explored in the last Section. The insight of Section II is that data exclusivity does not prevent subsequent entrants from marketing duplicates on the same terms as the first entrant; it is merely the *absence* of a pathway for marketing duplicates on different terms. Indeed, as pointed out, once the law changes for the benefit of subsequent applicants, those applicants do not compete in the usual sense of the term; generic drugs generally receive their market share by operation of law, and eventually biosimilars will do so as well.

The insights from Section II provide the foundation for the analysis that follows here in Section III. As noted, the goal of this Article is to contribute to an ongoing discussion of the merits of data exclusivity. This Section therefore takes up the ultimate question: *whether*, and *on what terms*, society derives a net benefit from a period of time during which all applicants face the same barrier to entry, followed by introduction of a shortcut reliance-based pathway that allows applicants to reach the market on cheaper and faster terms. After concluding that dynamic welfare considerations call for a period of time before subsequent entrants can reach the market more cheaply and quickly, this Section discusses the extent to which patent protection can—and cannot—provide that period of time. It then presents and assesses differing approaches to data exclusivity by exploring the fundamental structural differences between the PHSA and FDCA schemes. This Section demonstrates that exclusivity design choices themselves are likely to have a profound impact on whether, when, and on what terms subsequent entrants will compete with the first entrant.

A. Whether Society Derives a Net Benefit: Public Health and the Incentive to Innovate

1. Dynamic Public Welfare

There is a compelling public-health case for an abbreviated pathway that permits reliance on earlier performed research. Generic drugs are cheaper, and the healthcare finance system has a compelling interest in lower drug prices. Lower drug prices permit the purchase of additional healthcare goods and services (for the same patients or, in the case of a payer, for additional patients), the same healthcare goods and services for a longer period of time (for the same patients), or even needed non-healthcare goods and services.¹¹⁷ That consumer costs decline dramati-

¹¹⁷ According to the Centers for Medicare and Medicaid Services, in 2013 Medicare prescription drug expenditures reached \$74.647 billion. Medicaid expenditures reached \$21.173 billion, Children's Health Insurance Program expenditures reached \$1.415 billion, Department of Defense expenditures reached

ly is not disputed.¹¹⁸ The question of increasing overall utilization (i.e., whether utilization of the brand plus generic exceeds prior utilization of the brand alone)—and whether that utilization reflects treatment of previously untreated patients, as opposed to patients previously treated on another brand product—turns out to be more complicated. A pioneer might stop promotion of the branded product when generics reach the market, which in turn may reduce overall utilization of the molecule. At the same time, the generic product is much less expensive, and patients taking other branded products may switch, increasing overall utilization of the particular molecule and decreasing overall expenditures. The net effect of these differing pressures on overall utilization of the molecule may depend on the drug category.¹¹⁹

There is also, however, a compelling public-health case for delay in the availability of the abbreviated pathway. Few would quarrel with the proposition that society has a profound need for a continuing flow of new medicines for currently untreatable and poorly treated diseases like Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and many pediatric cancers, and also for chronic diseases that place significant socioeconomic stress on patients and families, for diseases of the developing world, and for common and disabling diseases of aging. In order to ensure that pioneers will do the research in question, for the benefit of follow-on applicants and patients, some delay is necessary before that research may be used by others.¹²⁰ Simply put, no company would pay \$2 billion for a license if its competitor could pay \$5 million immediately afterward—even if that competitor did *not* receive its market share by operation of law. In economic parlance, one might speak of trading dynamic efficiency (satisfying the need of future generations of patients for as-yet

\$4.803 billion, and Veterans Affairs expenditures reached \$2.697 billion. Private health insurers paid \$117.937 billion. *Table 19: National Health Expenditures by Type of Expenditure and Program: Calendar Year 2013*, CMS.GOV (Dec. 9, 2014), <http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsHistorical.html> (download "NHE Tables" ZIP file).

¹¹⁸ See, e.g., Ernst R. Berndt & Murray L. Aitken, *Brand Loyalty, Generic Entry and Price Competition in Pharmaceuticals in the Quarter Century After the 1984 Waxman-Hatch Legislation* 20 (Nat'l Bureau of Econ. Research, Working Paper No. 16431, 2010).

¹¹⁹ See Aitken et al., *supra* note 93, at 9–11 (noting the "conventional wisdom that total brand plus generic utilization of a molecule declines following patent expiration," but recounting contrary precedent where payers switched patients from Lipitor to generic versions of Zocor, increasing utilization of the latter molecule after patent expiry). The authors found that "expansion of total molecule sales (brand plus generic) following [loss of patent exclusivity] is an increasingly common phenomenon compared with prior observations." *Id.* at 2–3.

¹²⁰ See Memorandum in Support of Defendants Motion for Stay Pending Appeal, *Tummino v. Hamburg*, 936 F. Supp. 2d 162 (E.D.N.Y. 2013) (No. 12-CV-763 (ERK/VVP)) ("[E]xclusivity provides a critical incentive for drug development that advances FDA's goal of protecting and promoting public health.").

undiscovered and undeveloped drugs) for static efficiency (satisfying the need of the healthcare finance system for cheaper copies of today's drugs). Due respect for dynamic social welfare would ensure that pioneers conducting essential research do not face immediate competition from companies who omit the research and pay a fraction of the same price for market entry.

2. *The Market Failure Perspective*

The law of unfair competition, specifically misappropriation, suggests the same conclusion. The doctrine itself may not be a comfortable fit here, but its themes resonate when one considers approval of abbreviated applications. After all, a drug pioneer invests substantial time and money generating the information that, once submitted to and reviewed by the FDA, entitles it to enter the marketplace via the licensing process. When the shortcut opens, a second applicant may use that same information without payment to the pioneer to justify its own entry into the marketplace. It is not coincidence that Amgen recently characterized Sandoz's biosimilar application as amounting to conversion of Amgen's property when Sandoz failed to submit to premarket patent-litigation procedures that Amgen believed were statutorily mandated.¹²¹ In essence, the Amgen complaint suggests a reliance-based application that does not comply with the compromise legislation of 2010 constitutes nonconsensual use of its earlier research and gives rise to a cause of action sounding in tort.

The key unfair competition case similarly involves nonconsensual use of intangible business assets. In *International News Service v. Associated Press (INS)*, the defendant (INS) took news gathered by the plaintiff (AP) "as the result of organization and the expenditure of labor, skill, and money," and sold the news as its own.¹²² Thus, the defendant was "endeavoring to reap where it [had] not sown" and "appropriating to itself the harvest of those who have sown."¹²³ Here, too, a follow-on drug applicant market entrant reaps where it did not sow, relying instead on the work performed by a pioneer drug applicant. The case is not on all fours (except perhaps in the Sandoz example above) because of the whiff of impropriety on the part of INS, which is absent where a follow-on drug applicant complies with a scheme that Congress has laid out. Moreover, many scholars reject the idea that *INS* lays a foundation for a sweeping law of unfair competition with respect to information goods. But the

¹²¹ See *Amgen Inc. v. Sandoz Inc.*, No.14-cv-04741-RS, 2015 WL 1264756, at *8–9 (N.D. Cal. Mar. 19, 2015), *rev'd in part*, 794 F.3d 1347 (Fed. Cir. 2015). The Federal Circuit rejected the conversion theory, in part because it concluded the patent litigation procedures are not mandatory. See also *supra* note 41.

¹²² *Int'l News Serv. v. Assoc. Press*, 248 U.S. 215, 239–40 (1918).

¹²³ *Id.*; see also *Saratoga Vichy Spring Co. v. Lehman*, 625 F.2d 1037, 1044 (2d Cir. 1980) ("The essence of an unfair competition claim under New York law is that the defendant has misappropriated the labors and expenditures of another.").

case, even if read narrowly, suggests a basis for recovery that finds analogy in the drug setting.

The value of the news gathered by the Associated Press lay specifically in the lead time during which it held special value. Appropriation of the news deprived the AP of its lead-time advantage on the West Coast.¹²⁴ If permitted too soon, approval of generic drugs and biosimilar biologics could deprive the first entrant of otherwise inherent lead time. This inherent lead time stems from the investment necessary to develop a full application as the second or third innovator in the queue; if an abbreviated application is permitted before that time expires, it has eliminated some natural lead time. For instance, if a second company were to start the full pathway from scratch following approval of the first entrant's product, the first entrant's lead time could be two years—the time it may take to generate a full application from scratch.

This claim about natural lead time requires caveats. *First*, a second applicant's timeline may be shorter than the average timeline for new drug applicants because it can learn things from the public record once the first entrant's drug is approved.¹²⁵ This would truncate the first entrant's natural lead time a bit. *Second*, the second applicant could in theory start down the full pathway before the first entrant gained approval. Although it would not (at least initially) have the benefit of public information about the first application, it would still presumably receive approval earlier than had it started *after* the first entrant's approval. This would truncate the first entrant's natural lead time as well. All of that said, with an abbreviated pathway in the law, the data exclusivity term fixes a new lead time—five (to seven) years for non-biological new chemical entities and 12 years for first-licensed biological drugs. Particularly in the non-biological drug context, this may eliminate years of natural lead time—in many cases providing at least a rough analogy to *INS*. And, of course, permitting abbreviated applications immediately—without a data exclusivity term—would eliminate all natural lead time.

Somewhat like misappropriation, the follow-on applicant's reliance on the pioneer's work—if it occurred too soon—could lead to market failure. After all, the cost of developing the information in question is high, and the cost of relying on the information is low. A piggyback application would offer consumers a drug product that was identical or highly similar, and yet the follow-on applicant would be able to price more cheaply, not having incurred costs comparable to those incurred by the first entrant. Where given the choice, consumers would purchase (or payers would require the purchase of) the less expensive of the products. The result is market failure—essentially because the pioneer is not able

¹²⁴ See RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 38 cmt. c (Am. Law Inst. 1995).

¹²⁵ See *supra* note 60 and accompanying text.

to use or exploit the market *or* license its research to those who are able to do so.¹²⁶ In the non-biological drug context, the fact that the second entrant would receive market share by operation of law—specifically, the combination of FDA therapeutic equivalence ratings and mandatory substitution under state pharmacy law—rather than the rough and tumble of a competitive marketplace free of coercion may exacerbate the market failure.

Preventing market failure—ensuring that pioneers conducting expensive research do not face immediate competition from companies who use their research without their consent—may require a sufficient period of data exclusivity.

3. *The Utility of Patents*

The preceding Subsections suggest that society will derive a net benefit if pioneers who conduct expensive research to support the safety and effectiveness of new medicines do not face immediate competition from other companies marketing duplicates for a fraction of the effort. The question immediately arises, however, whether patent protection might provide adequate insulation from this competition. Several points need to be made in response.

First, the patentability inquiry does not inherently align with the public-health inquiry. Public health is not advanced only by medicines that also happen to satisfy the standard for patent protection—medicines as to which there is an invention that is novel and non-obvious. For instance, the fact that a person of ordinary skill in the scientific art in question might have reasoned his way to a particular molecular configuration for a particular disease given prior research in the space has no bearing on whether the public health would be advanced by development of the molecule in question into a medicine for patients. To give another example, an invention might be patent ineligible because the inventor published his discovery; again, though, that has no bearing on whether the public health would be advanced by development of the resultant medicine. The inquiries are fundamentally different, and, with the stakes so high, patentability should not stand as a proxy for public health benefit.

¹²⁶ Professor Gordon's work limiting the reap/sow principle for intellectual property through the law of restitution—with a new tort that she calls "malcompetitive copying"—includes a discussion rationalizing recovery in *INS* on roughly these grounds. See Wendy J. Gordon, *On Owning Information: Intellectual Property and the Restitutory Impulse*, 78 VA. L. REV. 149, 266–73 (1992). For discussions of Professor Gordon's approach, see also J.H. Reichman & Pamela Samuelson, *Intellectual Property Rights in Data?*, 50 VAND. L. REV. 51, 139–44 (1997), and Brian F. Fitzgerald & Leif Gamertsfelder, *Protecting Informational Products (Including Databases) Through Unjust Enrichment Law: An Australian Perspective*, 20 EUR. INTELL. PROP. REV. 244, 246 (1998).

Second, despite the vitality of patent protection for the biopharmaceutical sector,¹²⁷ some core doctrines of patent law are poorly suited to the scientific and regulatory realities faced by drug pioneers. To begin with, the U.S. patent term of 20 years from application does not align with the economic life cycle of a new drug, given the lengthy research and development period necessary to satisfy FDA approval requirements. Specifically, as Professor Eisenberg points out, various patent-law doctrines (such as the obviousness requirement) effectively force drug sponsors to file early patent applications, but these run the risk of failing utility and enablement challenges given the paucity of data and information early in their life cycles.¹²⁸ Earlier-filed patent applications also result in a shorter effective patent life, reducing the value of the patent.¹²⁹ Professor Roin notes that novelty and non-obviousness standards sometimes preclude socially valuable drugs from being patented at all and argues that this deters pioneers from moving forward with development.¹³⁰ And Professors Adelman and Holman have concluded that the U.S. Patent and Trademark Office (PTO) applies a heightened written-description requirement to biopharmaceutical patents, a practice that arguably was buttressed by the Federal Circuit in 2010.¹³¹ Recent Supreme Court cases

¹²⁷ See Rebecca S. Eisenberg, *The Shifting Functional Balance of Patents and Drug Regulation*, HEALTH AFF., Sept. 2001, at 119, 120 (noting that drugs provide “as clear a success story for patents in promoting investment in innovation as may be found in any industry”).

¹²⁸ See, e.g., Eisenberg, *supra* note 56, at 351–52 (pointing out that “patent law promotes early filing of patent applications . . . typically years before the first commercial marketing of a drug”); *id.* at 348 (noting that applications for “composition of matter” patents are filed before clinical testing of a molecule begins). Professor Eisenberg has also pointed out that, with increased patenting of inventions related to early-stage biomedical research, relevant patents may correspond less closely to product markets, shifting monopoly rents away from drug developers. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL’Y L. & ETHICS 717, 720–23 (2005).

¹²⁹ See *supra* text accompanying notes 108–109 for discussion of effective patent life prior to enactment of the Hatch–Waxman Amendments. See also Henry G. Grabowski & John M. Vernon, *Effective Patent Life in Pharmaceuticals*, 19 INT’L J. TECH. MGMT. 98, 110 (2000) (finding a mean effective patent life of 11.7 years for drugs approved from 1990 to 1995). Patent term restoration only partially addresses this problem because it restores only half a day for each day spent in clinical testing and restores none of the time prior to clinical trials. See 35 U.S.C. § 156(c) (2012).

¹³⁰ Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 569–70 (2009) (arguing ultimately for an extension in exclusivity in order to capture unpatentable drugs). *But see* Kevin Outterson, Comment, *Death from the Public Domain?*, 87 TEX. L. REV. SEE ALSO 45 (2009), <http://www.texasrev.com/wp-content/uploads/Outterson-87-TLRS-45.pdf> (challenging the major example offered by Professor Roin and offering alternative solutions to the free-rider problem including government funding of clinical trials).

¹³¹ See generally David E. Adelman & Christopher M. Holman, *Misplaced Fears in the Legislative Battle over Affordable Biotech Drugs*, 50 IDEA—INTELL. PROP. L. REV. 565

on subject-matter eligibility, calling into question the availability of patents for products of nature, may also hit the biologics space hard.¹³² Whether it would be possible to fix patent law to address these problems is unclear; our international treaty obligations generally require patent law to remain technologically neutral.¹³³

To this analysis, one might add the fact that patents reward invention, while data exclusivity facilitates recoupment of investment in an entirely different process—not the invention process, but the subsequent testing necessary to bring the invention to patients.¹³⁴ The fundamental tradeoff of patent law is the provision of exclusive rights to make, use, or sell an invention for a fixed period of time, in exchange for an enabling public disclosure of the invention. But society has a profound need for the patented invention to be not only disclosed *but brought forward in safe*

(2010). In 2007, Professor Holman surveyed court cases and patent office decisions, finding no heightened written-description requirement for biotechnology-derived drugs. In a later piece, however, he and Professor Adelman noted subsequent legal developments that might change this conclusion—including revised PTO-written description guidelines that strengthen the written-description requirements for these inventions, under which PTO may in fact be “applying the written description requirement as a ‘super enablement’ standard.” *Id.* at 576–78. The key Federal Circuit case is *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010). In this case, the court confirmed en banc that the written-description requirement is separate from the enablement requirement, and it found that Ariad’s patent, which claimed methods comprising the single step of reducing Nuclear Factor Kappa B (NF-kB) activity in eukaryotic cells, lacked sufficient written description, at least in part because the specification failed to disclose *how* the claimed reduction is achieved (despite hypothesizing three classes of molecules that could be responsible for the claimed reduction). *Id.* at 1340. Although the court denied that the written description functions as a “super enablement standard,” it recognized the uncertainty of the relationship between structure and function in the biotechnology context and the resulting difference between “describing an invention and enabling one to make and use it.” *See id.* at 1352; *see also* Christopher M. Holman, *Maintaining Incentives for Healthcare Innovation: A Response to the FTC’s Report on Follow-On Biologics*, 11 MINN. J.L. SCI. & TECH. 755, 774–78 (2010) (explaining, even before *Ariad* was decided, that his 2007 findings did not support the FTC’s conclusion that effective patent protection is available for biologics).

Professor Holman has also noted unpredictability in patent law—specifically the proliferation of ambiguous doctrines and the judiciary’s tendency to resolve ambiguities late (and sometimes retroactively)—which he argues has a particularly harmful effect on biopharmaceutical innovation. Christopher M. Holman, *Unpredictability in Patent Law and Its Effect on Pharmaceutical Innovation*, 76 MO. L. REV. 645, 660–61 (2011). He suggests a longer period of data exclusivity for non-biological drugs, “along the lines of the twelve years provided for biological drugs.” *Id.* at 693.

¹³² *See* Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2111 (2013); Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1294 (2012).

¹³³ *See* Eisenberg, *supra* note 55, at 486.

¹³⁴ *Id.* at 487 (“[T]he FDA provides product exclusivity, while the patent system provides invention exclusivity.”).

and effective form to patients, which requires an additional and burdensome testing process that is not necessary for the patent itself. Some might argue that, because federal law erects a barrier to entry, there is no practical reason to incentivize companies to overcome the barrier; desire to commercialize the patented invention will provide sufficient incentive. But the utilitarian point is that, in the absence of any reasonable prospect of recouping one's investment, no rational actor would invest in the work necessary to reach the market in the first instance. This is why shortened effective patent life and weaknesses of patent law in this industry sector are so problematic.

In brief, important new medicines may not be patentable or have a meaningful, effective patent life. And there is empirical support for this. For instance, in 2004 Professor Junod reported that she had reviewed new drug approvals between 1998 and 2004, finding 22 with NCE data exclusivity and yet no listed patents, and a 23rd with exclusivity expiring after the listed patent.¹³⁵ In a prior article, this author listed a number of drugs approved with new chemical-entity exclusivity but no listed patents.¹³⁶ These included Lariam (mefloquine hydrochloride), a synthetic analog of quinine approved by the FDA in 1989 for the treatment of mild to moderate acute malaria; Clozaril (clozapine), approved in 1989 for the management of severely ill schizophrenic patients; Hexalen (altretamine), a chemotherapy agent approved in 1990 for treatment of refractory ovarian cancer; Leustatin (cladribine), approved in 1993 for the treatment of active hairy cell leukemia; and Trasylol (aprotinin bovine), approved in 1993 to reduce bleeding during complex surgeries. Each of these drugs was important enough to earn priority review at the FDA, a designation reserved for drugs that represent "significant improvements" over the standard of care at the time.¹³⁷

Other drugs approved between 1984 and 2010 with NCE exclusivity and no listed patents¹³⁸ include: Provocholine (methacholine chloride),

¹³⁵ Valerie Junod, *Drug Marketing Exclusivity Under United States and European Union Law*, 59 FOOD & DRUG L.J. 479, 487 (2004); see also Enrique Seoane & Rosa Rodriguez-Monguio, *Effective Patent Life of Antiretroviral Drugs in the U.S. 1987–2007* (iHEA 2007 6th World Congress: Explorations in Health Economics Paper 2007) (noting that of 532 new molecular entities—some of which may not have had new chemical entity exclusivity—during the study period, 105 did not have listed patents).

¹³⁶ See Lietzan, *supra* note 13, at 64 n.103.

¹³⁷ See *Priority Review*, FDA, <http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm>. Three (Hexalem, Leustatin, and Trasylol) also had orphan-drug exclusivity, which was probably also a factor in the sponsor's investment decision.

¹³⁸ At this time, the electronic *Orange Book* shows only *unexpired* patents and exclusivity. Consequently, a search performed in a particular month of 2015 is reliable only with respect to drugs approved since the corresponding month in 2010. Exclusivity assignments and patent listings for drugs approved between 1984 and 2010 must currently be determined through review of historic copies of the *Orange Book* from 1985 to present, which are on file with the author. The FDA may upload

approved in 1986 for the diagnosis of bronchial airway hyper-reactivity in subjects who do not have clinically apparent asthma; Levatol (penbutolol sulfate), approved in 1987 for the treatment of mild to moderate arterial hypertension but since discontinued; Anafranil (clomipramine hydrochloride), approved in 1989 to treat obsessive-compulsive disorder; Optipranolol (metipranolol hydrochloride), approved in 1989 for treatment of open-angle glaucoma and other causes of high pressure inside the eye; Flumadine (rimantadine hydrochloride), approved in 1993 to prevent or treat influenza type-A infections; Revex (nalmefene hydrochloride), approved in 1995 to partially reverse the effects of narcotics but since discontinued; Proamatine (midodrine hydrochloride), approved in 1996 for treatment of orthostatic hypotension but since discontinued; Nilandron (nilutamide), approved in 1999 for use in treating prostate cancer in men who have/had undergone surgical castration; Normiflo (ardeparin sodium), approved in 1997 to prevent blood clot formation following certain types of surgery but since discontinued; Corlopam (fenoldopam mesylate), approved in 1997 for short-term management of hypertension in pediatric patients and for short-term management of severe hypertension in adults when rapid but quickly reversible emergency reduction of blood pressure is clinically indicated in an inpatient setting; Infasurf (calfactant), approved in 1998 for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS and for the treatment (“rescue”) of premature infants who develop RDS; Celexa (citalopram hydrobromide), approved in 2000 for the treatment of depression; Curosurf (poractant alfa), approved in 1999 for the treatment of RDS in premature infants; Innohep (tinzaparin sodium), approved in 2000 for the treatment of acute symptomatic deep vein thrombosis with or without pulmonary embolism when administered with warfarin sodium; Elestat (epinastine hydrochloride), approved in 2003 for the prevention of itching associated with allergic conjunctivitis; and Sanctura (trospium chloride), approved in 2004 for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency but since discontinued. Several of these drugs—Provocholine, Anafranil, and Flumadine—received priority review.¹³⁹

This author more recently also reviewed the electronic *Orange Book* database to identify products approved in the years 2011 through 2014 with NCE exclusivity and either no listed patents or listed patents expiring before the NCE exclusivity. This yielded the conclusion that of the 105 new chemical entities approved by the FDA in the four years in question, 11 either lacked listed patents or had listed patents expiring before the exclusivity expired. These included Potiga (ezogabine), approved in

historical information in 2016.

¹³⁹ Proamatine also held orphan-drug exclusivity.

June 2011 for use in treatment of seizures associated with epilepsy in adults; Firazyr (icatibant), approved in 2011 for the treatment of acute attacks of a rare condition called hereditary angioedema (HAE) in people ages 18 years and older; Ferriprox (deferiprone), approved in 2011 to treat patients with iron overload due to blood transfusions in patients with thalassemia—a genetic blood disorder that causes anemia—who had an inadequate response to prior chelation therapy; Choline C 11, a positron emission tomography imaging agent approved in 2012 to help detect recurrent prostate cancer; Dotarem (gadoterate meglumine), a contrast agent approved in March 2013 for use with MRI in brain, spine, and associated tissues in adult and pediatric patients; and Impavido (miltefosine), approved in March 2014 for treatment of (bacterial) leishmaniasis.¹⁴⁰

It is reasonable to *hypothesize* that in these cases the incentive to generate the research in question may have been provided by the duration of the statutory period before generics could be approved rather than by the prospect of patent protection. One limitation to this conclusion is that the *Orange Book* does not list patents that claim methods of manufacture, and some of these companies may have relied on—or be relying on—the protection afforded by such patents. Further, some companies in the 2011-to-2014 set currently holding data exclusivity may yet obtain listable patents. Further still, FDA can be slow to publish patents in the *Orange Book* even when those patents were timely submitted by the NDA holder. The *Orange Book* could still reflect patent listings for some of the drugs approved at the end of the review window. Finally, in some cases it is possible the size of the market in question would support only one entrant; in other words, the pioneer may also be relying on the relative unattractiveness of the market in question to its competitors.¹⁴¹

In terms of exploring the extent to which data exclusivity—rather than patents—provides the necessary incentive for research and development, it may also be worth noting that several products in the 2011-to-2014 set show listed patents that expire within a few months of data exclusivity. These include Zioptan (tafluprost), approved in February 2012 for reducing elevated intraocular pressure in patients with glaucoma; the listed patent expires in December 2017, roughly 10 months after the NCE exclusivity. Another example is Datscan (ioflupane), a priority review imaging drug approved in January 2011 to assist in evaluation of

¹⁴⁰ Firazyr had a listed patent expiring in July 2015, but its data exclusivity is slated to expire in August 2016. Firazyr, Ferriprox, and Impavido also hold orphan exclusivity. Firazyr earned priority review.

¹⁴¹ One final limitation is that the author did not check every historical *Orange Book* to determine whether the applicant listed a patent a few years after approval and then (for whatever reason) subsequently delisted it. Thus, the list of examples from 1984 to 2010 comprise drugs that received NCE exclusivity and that—at approval and again one year later—had no patents listed.

suspected Parkinsonian syndromes; the listed patent expires one month after data exclusivity. It is harder to know what to make of these examples, but these companies presumably did not know the precise timing of their drug approvals when they conducted clinical trials, and it is possible they, and similar sponsors, were uncertain until the end whether they would have any patent life that extended past data exclusivity.

Third, the need to enforce patents against follow-on applicants creates uncertainty, reducing its effectiveness as an incentive. To be fair, some regulatory provisions reduce the patent enforcement uncertainty for non-biological drug pioneers. But, it is important not to overstate the effect of these provisions. First, as already noted, the FDCA provides a 30-month stay of generic-drug approval while patent litigation unfolds. Some view this as tantamount to a preliminary injunction, without any showing of probable success on the merits.¹⁴² But, the stay is limited to 30 months. Once the stay expires, FDA approval is automatic (assuming the generic drug is otherwise approvable) and permits the generic company to market at risk. The generic company will not be precluded from the market as a regulatory matter unless and until the innovator prevails in the patent litigation.¹⁴³ Further, the PHSA provides no stay of biosimilar approval during patent litigation, instead permitting immediate market entry by biosimilar sponsors. And, there is no statutory preclusion of biosimilar market entry if the innovator prevails in the patent litigation, leaving the possibility of a reasonable royalty scenario rather than an injunction of biosimilar marketing.¹⁴⁴

Second, the FDCA reduces uncertainty by delaying the availability of a shortcut until patent expiry in the event the generic applicant declines to challenge a particular listed patent.¹⁴⁵ But, the pioneer will not know until the generic applicant submits its application that the generic has declined to challenge its patent.¹⁴⁶ And there is no such arrangement in the

¹⁴² *E.g.*, Eisenberg, *supra* note 55, at 483–84.

¹⁴³ Once the innovator prevails, the generic applicant must amend its paragraph IV certification to a paragraph III certification. 21 C.F.R. § 314.94(a)(12)(viii)(A) (2015); *see also supra* notes 24–29 and accompanying text. Consequently, the FDA may not approve the generic application until the patent expires. *See* FDCA, 21 U.S.C. § 355(c)(3)(C)(ii) & (j)(5)(B)(ii)(2012); 21 C.F.R. § 314.107(b)(3)(B)(iii)(2015). This is separate from any injunction that the court might issue in the patent litigation.

¹⁴⁴ The scheme requires an injunction of market entry—unlike the FDCA, it does not preclude FDA approval—if the innovator prevails prior to expiry of the 12-year exclusivity term. But this subsection considers the role of patents in the absence of data exclusivity.

¹⁴⁵ FDCA, § 355(c)(3)(C)(ii) & (j)(5)(B)(ii).

¹⁴⁶ Further, the pioneer will know this only if the generic challenges another patent (which entitles it to notice of the filing), and it will know this only by process of elimination. For instance, if the pioneer has listed two patents and receives notice of a paragraph IV certification with respect to only one patent, then the generic applicant has chosen not to challenge the other patent. There are only two

biologics statute, only privately communicated promises not to launch.¹⁴⁷ Ultimately, under both schemes, in order to preclude follow-on market entry, the pioneer must persuade the follow-on applicant, or establish in court, that the patent is valid, infringed, and enforceable. By way of contrast, exclusivity need not be asserted against a follow-on applicant. As a feature of the drug regulatory approval scheme, it automatically dictates the pathways to market available at any particular time. Although exclusivity is not entirely unassailable, an investor can generally plan around exclusivity expiry more confidently than it can plan around patent expiry.¹⁴⁸

Third, the regulatory standards applicable to follow-on applicants no longer align with composition of matter patents. While the ANDA pathway requires a generic drug to have the same active ingredient as its reference product, the agency's view—hinted in the 1990s and confirmed in 2006—that section 505(b)(2) permits follow-on applicants to propose merely similar active ingredients means that FDA will now approve follow-on companies that have designed around core-substance patents.¹⁴⁹

possibilities: the generic applicant has included a paragraph III certification indicating it will wait until patent expiry, or (if the patent covers a method of using the drug) the generic is carving out—not seeking approval for—the use in question.

¹⁴⁷ See PHSA, 42 U.S.C. § 262(l)(3)(B)(ii)(II) (2012).

¹⁴⁸ That said, exclusivity is not impermeable. *First*, it can be challenged both administratively and judicially. For instance, Sandoz successfully challenged administratively the exclusivity award to Wyeth for Torisel (temsirolimus) on the ground that temsirolimus was an ester of sirolimus, previously approved under the name Rapamune. See Letter to Kurt Karst, Counsel for Sandoz, from Keith O. Webber, Deputy Director, Office of Pharmaceutical Science, CDER (May 29, 2012), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022088Orig1s000Admincorres_Part%202.pdf. The award of exclusivity to Vyvanse (lisdexamfetamine dimesylate) was challenged administratively and then appealed judicially. See *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 762 (D.C. Cir. 2010). *Second*, in close cases under the FDCA, an innovator may be called upon to justify NCE status during the approval process, and it may not learn the agency's ruling until months after approval. *Third*, FDA has taken a hostile approach in the biologics setting, essentially requiring BLA applicants to submit extensive briefing documents to justify exclusivity and failing to inform BLA holders of their status until many months after approval. See, e.g., FDA, GUIDANCE FOR INDUSTRY: REFERENCE PRODUCT EXCLUSIVITY FOR BIOLOGICAL PRODUCTS FILED UNDER SECTION 351(A) OF THE PHS ACT 7–8 (drft. Aug. 2014), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf>. All of this noted, the uncertainty of exclusivity pales in comparison to the inherent uncertainty of, and need to enforce, patent protection.

¹⁴⁹ 21 C.F.R. § 314.54 (2015) (describing contents of a 505(b)(2) application); 505(b)(2) GUIDANCE, *supra* note 14, at 5 (permitting use of the provision for “a change in an active ingredient”). See generally Letter from Steven K. Galson, *supra* note 62, at 32 (explaining the FDA's assertion of legal authority to approve the 505(b)(2) application for Omnitrope in response to a citizen petition accompanying approval of Omnitrope, which was “highly similar” to the petitioner's reference product Genotropin).

Further, nothing in the agency's writings suggests it would refuse a dissimilar active ingredient, provided the 505(b)(2) applicant submitted sufficient bridging data to justify whatever reliance on the first entrant's research it desired. And yet, these companies file abbreviated applications; they rely on the pioneer's research. Data exclusivity—not patent protection—stands between the pioneer and these follow-on competitors. The biosimilar scheme continued this regulatory approach by scientific necessity (because biosimilars are necessarily highly similar to, rather than the same as, their reference products),¹⁵⁰ and may permit approval of abbreviated applications for products that are sufficiently dissimilar to avoid composition-of-matter patents.¹⁵¹ This will depend in part on how FDA applies the statutory standard for biosimilar approval and bears watching closely. In these cases, too, data exclusivity may be critical to motivate prospective first entrants; patents may not do the job.

Recent legislative proposals would provide the choice of either data exclusivity or patent protection—that is to say, they would allow innovators to select a longer period of data exclusivity in exchange for relinquishing patent-infringement claims against the sponsors of follow-on products.¹⁵² Although these proposals perpetuate the myth that data exclusivity is an affirmative federal benefit comparable to a patent, they do allow innovators to mitigate shortcomings in patent protection on a case-by-case basis with an additional period of time before abbreviated applications may be submitted (or approved, as the case may be).¹⁵³

¹⁵⁰ See, e.g., *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Gov't. Reform*, 110th Cong. 23 (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Med. Officer, Food & Drug Admin.) [hereinafter Woodcock] (noting a “general recognition that the idea of *sameness*, as the term is used in the generic drug approval process . . . will not usually be appropriate for . . . biological products”).

¹⁵¹ Bruce S. Manheim, Jr. et al., *Follow-On Biologics: Ensuring Continuing Innovation in the Biotechnology Industry*, 25 HEALTH AFF. 394, 397 (2006) (explaining the potential to work around patents given the similarity standard).

¹⁵² Variations of this proposal have been introduced repeatedly over the last several years, typically in freestanding bills and labeled as either the “Dormant Therapies Act” or the “MODDERN Cures Act.” As of this writing, inclusion of the language was under consideration for a larger omnibus bill, the 21st Century Cures Act, although it has not appeared in every discussion draft. See Kurt R. Karst, *House Energy & Commerce Committee Releases 21 [sic] Century Cures Act Discussion Draft; The Nearly 400-Page Bill Includes More Proposals than You Can Shake a Stick at!*, FDA L. BLOG (Jan. 28, 2015), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2015/01/house-energy-commerce-committee-releases-21-century-cures-act-discussion-draft-the-nearly-400-page-b.html.

¹⁵³ See also Yaniv Heled, *Why Primary Patents Covering Biologics Should Be Unenforceable Against Generic Applicants Under the Biologics Price Competition and Innovation Act*, 21 ANNALS HEALTH L. 211, 216–17 (2012) (arguing that allowing concurrent patent protection and data exclusivity is a waste of resources); Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419, 423–24 (2012) (arguing that the

B. On What Terms Society Derives a Net Benefit: Ensuring the Incentives Work

The preceding Subsection addressed *whether* society derives a net benefit from a period of time during which all applicants face the same barrier to entry, followed by introduction of a shortcut pathway that allows applicants to reach the market on cheaper and faster terms, relying on the pioneer's labor. This Subsection considers the remainder of the question: *on what terms* society derives this net benefit. It works from and assesses the key differences in approach toward exclusivity taken in non-biological drug and biological drug schemes.

The differences are as follows. *First*, the schemes take fundamentally different approaches to pioneer research supporting application approval. The FDCA protects research the first time, and only the first time, it is performed by someone to support approval of a particular active ingredient. The PHSA protects research every time a new company performs it to support its own first application for the product. This Article refers to the approach for non-biological drugs as the "active ingredient" approach although, as will be seen below, the FDA has narrowed it administratively to something called the "active moiety." This Article refers to the approach for biological drugs as the "product" or "product-by-product" approach. *Second*, the schemes take different approaches to subsequent research performed by pioneers with respect to their already approved active ingredients, although neither provides any meaningful incentive for this research. And *third*, the schemes take different approaches to innovation by follow-on applicants—in other words, to applications that are partly abbreviated (relying on earlier research without consent) and partly new. The FDCA permits this work; the PHSA does not. These foundational structural differences between the schemes are explained and weighed below.

1. Initial Research for Approval

By far the most significant difference between the non-biologic and biologic drug schemes is the basic approach to research performed by

exclusivity afforded to biologics is superior to patent protection and should replace primary patent protections once FDA has approved the pioneer). If the reframing of exclusivity in this article is correct—and exclusivity is not an affirmative grant from the state—mandatory substitution of exclusivity for patent protection would arguably be tantamount to eliminating patent protection. This would raise issues beyond the scope of this article. The federal legislative proposals discussed in Karst, *supra* note 152, have been voluntary.

It might be fruitful to also consider giving innovators the option to select waiver of patent linkage—the rules that prohibit FDA approval of a follow-on application until 30 months of litigation have completed or patent expiry, if the patent is valid and infringed—in exchange for a longer period of data exclusivity. This too would perpetuate the myth that data exclusivity is an affirmative federal benefit comparable to a patent, but would similarly allow innovators to mitigate shortcomings in patent protection on a case-by-case basis.

pioneers, i.e., to the safety and effectiveness data submitted to support a full NDA or BLA. The FDCA provides a single five-year waiting period for the abbreviated pathway, which dates from the first approval of the active ingredient, no matter who sponsored the application. The PHSA provides a 12-year period before abbreviated applications for each pioneer company's first application—in other words, every time a full-blown application for the biologic is submitted by a new pioneer. This difference, which has not been explored in academic scholarship to date, leads to inconsistent results.

a. Differing Approaches

Explaining the FDCA approach for non-biological drugs requires a detour into the statutory and regulatory language. The statutory five-year exclusivity provision delays abbreviated applications that propose to copy a drug “no active ingredient (including any ester or salt of the active ingredient) of which” has previously been approved.¹⁵⁴ The agency limits this exclusivity to what it labeled, in 1989, “new chemical entities” or NCEs. The FDA's regulations in turn define that phrase to mean drug products that do not contain any previously approved “active moiety,” which the agency defines as the molecule responsible for the physiological or pharmacological action of the drug.¹⁵⁵ In the FDA's view, the active moiety is different from active ingredient, which simply means the substance prior to its introduction to the body.¹⁵⁶

The FDA protects not only the initially approved product, but also any subsequent product containing the same active moiety proposed by the same company. In other words, if a company obtains approval of a new chemical entity and has exclusivity expiring on December 31, 2020, any subsequent application from that company for the same active moiety (for instance, an application for a new route of administration, or an application for a combination product) will also be protected from generics until December 31, 2020. This is known as “umbrella” exclusivity. The agency explained that if exclusivity applied only to the initial product, “an innovator's exclusivity could lose its value as soon as FDA approved a second full new drug application for a version of the drug, be-

¹⁵⁴ FDCA, 21 U.S.C. § 355(c)(3)(E)(ii) & (j)(5)(F)(ii) (2012).

¹⁵⁵ 21 C.F.R. § 314.108(a) (2015).

¹⁵⁶ *See* Abbott Labs. v. Young, 920 F.2d 984, 988 (D.C. Cir. 1990) (rejecting the FDA's construction of “active ingredient including any salt or ester” to mean any product that results in the same active moiety). The FDA based the “new chemical entity” concept on its pre-existing classification scheme for applications; one type was a “new molecular entity” application, and the agency concluded that Congress was aware of this scheme and had generally meant to emulate it, thus avoiding “significant periods of exclusivity” for “minor variations of previously approved chemical compounds.” Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,897–98 (proposed July 10, 1989) (to be codified at 21 C.F.R. pts. 10, 310, 314, 320).

cause an ANDA could be approved by reference to the second approved version of the drug, which would not be covered by exclusivity.”¹⁵⁷ This would be a “narrow” approach to exclusivity, and it would “seriously undermine its value, reducing the incentives for research and innovation in the pharmaceutical industry.”¹⁵⁸ The “broader” approach selected instead by FDA was to protect the active moiety itself, even if it appeared in “another approved version of the innovator’s drug.”¹⁵⁹

Congress structured biological-product exclusivity very differently. The PHSA delays abbreviated applications that propose to copy specific reference products. In other words, exclusivity attaches to finished products, which are inherently specific to individual pioneers, not to underlying active ingredients. And the schemes are therefore inconsistent. An example will demonstrate this. If two separate companies obtain approval of innovative NDAs for a new drug, only the first to gain approval receives five-year exclusivity. The second company is not entitled to five-year exclusivity, because the active moiety has been previously approved.¹⁶⁰ But if two separate companies obtain approval of innovative BLAs for a new biologic, each is protected by its own 12-year term. The PHSA does not permit FDA to deny exclusivity to the second company simply because the first company has obtained approval of a similar or even highly similar molecule, active ingredient, or active moiety.

The active ingredient approach for non-biological drugs probably reflects the ANDA provision’s historical roots in the “old drug” concept, discussed in Section II. As noted, for 40 years old drug status—specifically, the notion that once a particular ingredient had been the subject of an application, generic drugs could be marketed without their own applications—was the primary mechanism for generic drugs to reach the market. The product approach in the PHSA had no particular historical roots. And the legislative negotiations leading to enactment of

¹⁵⁷ *Id.* at 28,897.

¹⁵⁸ *Id.*

¹⁵⁹ *Id.* Early writings from the FDA suggested that the agency would protect the active moiety even if it appeared in *another company’s* finished drug product—for instance a product manufactured under a patent license or even a competitor’s copy. *See id.* Doing so would, after all, be consistent with the purpose of exclusivity and with the rationale for the umbrella. If Company *A* obtained an NCE approval for an unpatented drug in 2014, and Company *B* (which was developing the molecule at the same time) was able to obtain approval in 2015 (because exclusivity blocks only abbreviated applications, not full applications), failure to protect Product *B* under the Product *A* term expiring in 2019 would effectively eliminate Product *A*’s exclusivity as well. Under FDA’s initial proposal, where a first entrant received NCE and a second received three-year new-product exclusivity for the same active moiety, a third entrant could not file an ANDA citing the second application until the first applicant’s NCE exclusivity expired. The umbrella would protect the second entrant’s application.

¹⁶⁰ It may receive three-year new product exclusivity, discussed *infra* subsection III.B.2.

the biosimilar statute did not focus on the decision to adopt a product-by-product approach to exclusivity rather than the active ingredient approach in existing law.¹⁶¹ But the use of a product approach for biologics makes sense in light of the fact that two biological products generally cannot be shown identical to each other.¹⁶² In other words, if two innovators independently synthesize and study the non-biological drug fluoxetine (originally marketed as Prozac), it is easy for FDA to conclude that the second has developed the same active ingredient (and moiety) as the first. But if two innovators independently manufacture and develop the biological drug trastuzumab (marketed as Herceptin), it is possible that there will be clinically meaningful differences between the two that cannot be ruled out with analytical testing. Indeed, that is the very premise of the BPCIA: even where a second applicant deliberately tries to copy trastuzumab as closely as it can, some research will need to be performed to determine whether there might still be clinically meaningful differences.¹⁶³ FDA's inability today to conclude that two biological products have the same active ingredient makes the active ingredient approach to data exclusivity unworkable.

b. Assessing the Options

The primary problem with the active-ingredient approach in the FDCA is the uncertainty it creates. It has forced FDA into highly detailed and complex regulations, policies, and decisions that are admittedly inconsistent, disputed in administrative petitions and before courts, and reversed legislatively. Some of the problem can be traced to ambiguity in the statutory language itself, which could perhaps be remedied with more artful drafting.¹⁶⁴ FDA's implementing regulation adds specificity and detail,¹⁶⁵ but even still does not cover every possibility. Counsel still

¹⁶¹ See *supra* note 111 and accompanying text.

¹⁶² See Woodcock, *supra* note 150, at 23.

¹⁶³ See generally PHSA, 42 U.S.C. § 262(k) (2012); SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 37.

¹⁶⁴ See, e.g., *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765 (D.C. Cir. 2010) (finding ambiguity as to whether the phrase "active ingredient" requires the FDA to look at the molecule that reaches the site of drug action or at the form of the molecule that enters the body); *Abbott Labs. v. Young*, 920 F.2d 984, 987–88 (D.C. Cir. 1990) (noting ambiguity as to whether exclusivity is precluded only if the first drug is a salt of the second, or precluded also if the second is a salt of the first).

¹⁶⁵ The final regulation looks for prior approval of the molecule—excluding "appended portions of the molecule that cause the drug to be an ester, salt . . . or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule"—responsible for the action of the drug substance. 21 C.F.R. § 314.108(a) (2015). FDA reasons that the addition of a chelate, clathrate, or other noncovalent derivative "generally does not affect the active moiety of a drug product." Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50338, 50358 (Oct. 3, 1994). In contrast, the regulation permits five-year exclusivity for derivatives of previously approved active moieties when those derivatives contain

struggle to provide definitive answers when new scientific possibilities emerge. For example, just a few years ago, litigation erupted over a particular nuance not covered explicitly by the regulation—exclusivity for a prodrug containing a covalent non-ester bond.¹⁶⁶ Some decisions from FDA have prompted congressional intervention, including a now-defunct approach to enantiomers¹⁶⁷ and a still-evolving approach to fixed-dose combinations.¹⁶⁸

The inquiry into absolute novelty of the active moiety has also proven impossible with more complex and poorly understood molecules or mixtures of molecules. The FDA generally deems a product to contain an NCE when it is unable to determine the product's active moiety with specificity—in essence, defaulting to the more manageable (PHSA-style) approach of awarding exclusivity on a product-by-product basis. For instance, each approved hyaluronidase product has received NCE exclusivity, as has each pancrelipase product, largely because FDA was unable to discern the precise active moiety in it and in the prior products.¹⁶⁹ That

non-ester covalent bonds. In FDA's view, drug derivatives with non-ester covalent bonds are different and "deserving" of five-year exclusivity. *Actavis Elizabeth*, 625 F.3d at 765. Indeed, "even minor covalent structural changes are capable of producing not only major changes in the activity of a drug but changes that are not readily predicted." *Id.* at 765–66 (quoting the FDA's response to a 1989 petition).

¹⁶⁶ A prodrug is biologically inactive and must be metabolized in the body to produce the active drug. *See Actavis Elizabeth*, 625 F.3d at 763 (affirming agency's decision to permit exclusivity for any prodrug that is not an ester, salt, or other type of non-covalent derivative).

¹⁶⁷ FDA historically refused to grant exclusivity to enantiomers of previously approved racemates but not to single racemates of previously approved enantiomers. Congress acted in 2007, though FDA had been reassessing the issue since the 1990s. *See Food and Drug Administration Amendments Act of 2007*, Pub. L. No. 110-85, sec. 1113, 121 Stat. 823, 976–77; Dickinson, *supra* note 77, at 200.

¹⁶⁸ FDA historically required both ingredients to constitute new chemical entities. In response to a series of citizen petitions, FDA recently issued guidance stating that "new chemical entity" includes fixed-dose combination drugs that contain previously approved chemical entities, so long as one of the drug substances in combination meets the definition of new chemical entity. *See FDA, GUIDANCE FOR INDUSTRY: NEW CHEMICAL ENTITY EXCLUSIVITY DETERMINATIONS FOR CERTAIN FIXED-COMBINATION DRUG PRODUCTS 1, 6* (Oct. 2014), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf>. Pending federal legislation would go further, stating that "new chemical entity" includes any fixed-dose combination drug if the particular combination has not previously been approved and the application is supported by clinical data other than bioavailability data. *Combination Drug Development Incentive Act of 2015*, H.R. 406, 114th Cong. § 3 (2015).

¹⁶⁹ *See* Letter from Janet Woodcock, Dir., Ctr. for Drug Eval. & Research, to Robert A. Dormer at 9–10 (Feb. 21, 2014) (on file with author). Hyaluronidase is used to increase the absorption of other injected medicines. Pancrelipase is used to improve digestion of food in patients who do not have enough pancreatic enzymes—for instance, because of cystic fibrosis or a blockage between the pancreas and intestine. Uncertainty also prompted the agency to permit NCE status for Condylox

said, some of the agency's decisions when faced with uncertainty simply cannot be explained, and the agency has not even tried to resolve what it openly admits are "contradictions" in its decision-making.¹⁷⁰

Moreover, more than 30 years after enactment of the scheme, and more than 20 years after FDA finalized its exclusivity regulation, the basic approach of the regulation remains vulnerable. In May 2015, in a case relating to yet another nuance left unaddressed by FDA's regulation—involving a complex undifferentiated fish oil mixture, one consistently present molecule of which had been approved previously—a federal district court found the agency's denial of exclusivity conflicted with the statute's plain meaning, was not reasoned, and was in fact unreasonable.¹⁷¹ Among the problems cited by the court were FDA's basic approach of construing "active ingredient" in the exclusivity provision (but not elsewhere in the statute) as "active moiety" and the fact that the agency's approach creates uncertainty for innovators.¹⁷²

As a practical matter, and in contrast with the active ingredient approach, the product approach need not force the regulator into distracting and potentially unworkable efforts to pre-specify rules about—or otherwise parse—molecular distinctions. That is, after all, why FDA has essentially resorted to a product approach when faced with non-biological drugs as to which it cannot parse molecular distinctions. Experience with medical-device approval is supportive; the scheme provides six years of data protection for premarket-approval applications on a

(podofilox, or podophyllotoxin), approved in 1993 for treatment of warts. The agency was unable to determine whether any of the 13 previously marketed podophyllum-resin products included podophyllotoxin as an active ingredient. *Id.* at 10–11.

¹⁷⁰ *See id.* at 14–15. The FDA had awarded Infasurf five-year NCE exclusivity "despite having determined that Infasurf has the same active moiety as a previously approved drug, Survanta, under a definition of active moiety that is identical to that in the NCE context." *Id.* at 15. The letter noted that "there does not appear to be a record documenting the reasons for the decision" and that "there does not appear to have been an attempt to meaningfully distinguish" the NCE decision from the context in which the other decision was made. *Id.* A similar incident occurred with Curosurf, also awarded NCE status, and the letter stated that the "records for these determinations are sparse" and it is "not clear" whether the FDA has "attempted to resolve or address" the "contradiction" in question. *Id.*

¹⁷¹ *See* *Amarin Pharms. Ir. Ltd. v. FDA*, No. 14-cv-00324, 2015 WL 3407061, at *18 (D.D.C. May 28, 2015) ("Whether the problems with the FDA's decision are characterized as failures under *Chevron* step one, step two, or the APA's requirement of reasoned decision-making, the Agency's decision must be set aside."), *appeal docketed*, No. 15-5214 (D.C. Cir. July 30, 2015).

¹⁷² *See id.* ("The Agency makes no attempt to explain how its approach furthers Congress's purposes or is otherwise a reasonable policy choice, especially in light of the clear interest in providing notice to potential innovators of the exclusivity to which they might eventually be entitled.").

product-by-product basis, without any need to compare device types.¹⁷³ There have not been any meaningful disputes over interpretation or application of the provision.¹⁷⁴

The product approach may also encourage research that amplifies our understanding of already approved medicines, but in a nuanced way that allows market pressures to eventually point away from research that merely corroborates. By way of contrast, the active-ingredient approach is hard to square with an approach to public policy that values additional controlled testing of relatively new moieties. Specifically, the fact that exclusivity under the PHSA attaches to the product may provide an incentive for companies to be the second or third to develop and market an innovative biological molecule—the second or third to market filgrastim or trastuzumab, for instance. While the first innovator may face a biosimilar 12 years after its market entry, the second innovator will not face a biosimilar until 12 years after its own market entry. So long as biosimilars are not deemed interchangeable and are marketed more like branded competitors, and so long as the number of biosimilars for any particular biological product remains as low as currently expected, the second innovator may face the prospect of being only one of a few (the first entrant, the second entrant, and any biosimilars of the first entrant) in the marketplace.

Depending on the demand for and pricing of those particular products, this arrangement may still be sufficiently attractive to warrant second-place innovation. And because two innovative versions of the same biological molecule are unlikely to be clinically identical, patients may benefit from the additional option in the marketplace. If this approach were taken in the non-biological drug setting, and depending on the length of the first entrant's data-exclusivity period, it might lead to second-place innovation early in the data-exclusivity period, but is less likely to do so later given the prospect of (later) multiple substitutable generic copies of the first entrant. This would have the benefit of encouraging confirmatory research early in the molecule's lifespan and allowing market disincentives to dissuade this testing later.

¹⁷³ See FDCA, 21 U.S.C. § 360j(h)(4)(A) (2012) (“Any information contained in an application for premarket approval . . . shall be available, 6 years after the application has been approved by the Secretary, for use by the Secretary in . . . approving another device . . .”).

¹⁷⁴ The device provision has been used repeatedly and seemingly without controversy. *E.g.*, Reclassification of Stair-Climbing Wheelchairs, 79 Fed. Reg. 20,779 (Apr. 14, 2014) (to be codified at 21 C.F.R. pt. 890); Reclassification of the Intervertebral Body Fusion Device, 72 Fed. Reg. 32,170 (June 12, 2007) (to be codified at 21 C.F.R. pt. 888); Reclassification of the Extracorporeal Shock Wave Lithotripter, 65 Fed. Reg. 48,609 (Aug. 9, 2000) (to be codified at 21 C.F.R. pt. 876). The FDA received only one comment on the draft guidance implementing the provision, which it has not bothered to upload for public access.

2. *Subsequent Research by Pioneers*

The non-biological and biological drug schemes differ also in their treatment of subsequent research by pioneers once new molecular entities have been approved. This “incremental innovation” includes the development and testing of new conditions of use—indications, dosing regimens, dosing instructions, dose levels, strengths, frequency of administration, durations of use, routes of administration, dosage forms, and so forth. It also includes variations to the underlying active ingredient that do not rise to the level of a new molecular entity.

Sometimes this new research is the subject of a “supplement” to an approved application—a supplemental NDA or supplemental BLA—and sometimes it is the subject of a separate application—a new NDA or new BLA. FDA is the ultimate arbiter with respect to whether a supplement or full application will be required in any particular case, but typically a new indication appears in a supplement whereas a new route of administration or dosage form results in a separate application.¹⁷⁵ Examples of molecular variations—which always result in a new application—might include development of a different salt form of the active ingredient of a non-biological drug, or pegylation (addition of polyethylene-glycol polymer chains) in the case of a biological drug.

Ultimately, neither scheme provides a meaningful incentive for first entrants to conduct follow-up research, though the problem is particularly acute with respect to new indications and other new labeling information.

a. Differing Approaches

Incremental innovations for non-biological drugs (approved under the FDCA) are protected by three-year exclusivity.¹⁷⁶ As noted in Section II, if a pioneer’s drug is not a new chemical entity but the application contains clinical data essential to its approval, then an abbreviated application may not be approved until three years after the pioneer application. The three-year period applies to both full NDAs and also supplements. In other words, if a pioneer submits an NDA for a new route of administration for its previously approved drug, or an NDA for a molecular change that does not result in a new chemical entity, the new NDA will receive three years of exclusivity. And if the pioneer submits a sup-

¹⁷⁵ Some of the policies the agency follows can be found in FDA, GUIDANCE FOR INDUSTRY: SUBMITTING SEPARATE MARKETING APPLICATIONS AND CLINICAL DATA FOR PURPOSES OF ASSESSING USER FEES (Dec. 2004), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079320.pdf>

¹⁷⁶ In the case of a molecular variation, it is also possible the innovation would result in a new chemical entity entitled to five years of data exclusivity. But in the case of a new condition of use for an already approved active ingredient, the sponsor will receive three-year exclusivity or nothing at all. Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,899 (proposed July 10, 1989) (to be codified at 21 C.F.R. pts. 10, 310, 314, 320).

plement to its original NDA for a new indication, the supplement will receive three years of exclusivity.

As a practical matter, three-year exclusivity provides little incentive for innovators to continue studying their approved non-biological drugs. To begin with, three-year exclusivity is undermined by the FDA's narrow interpretation of when it applies. The FDA takes the position that only a "considerable" investment in clinical testing will result in protection¹⁷⁷ and will grant exclusivity only if there is documentation that the agency agreed that the studies performed to support the new condition of use were "essential" to its approval.¹⁷⁸ The protection is also undermined by the FDA's view that three-year exclusivity protects only the new condition of use in question. This means that if the condition of use is informational (like a new indication or dosing regimen) rather than functional (like a new dosage form or route of administration), three-year exclusivity functions only as a labeling restriction. Exclusivity means the generic applicant cannot include *that protected information* in its labeling.¹⁷⁹

Even when the FDA agrees that new information in the labeling of an already approved new drug is protected by three-year exclusivity, that information as a general rule is not worth very much. Although generic drugs must generally bear the same labeling as their reference drugs, a

¹⁷⁷ According to the FDA, "Congress intended to reward with 3 years of exclusivity only those investigations that require a considerable investment of time and money." *Id.* (citing statements of both Senator Hatch, 130 Cong. Rec. 23,764 (1984), and Representative Waxman, 130 Cong. Rec. at 24,425). Concluding that Congress intended to reward "only those who have made a substantial investment in new clinical studies," FDA has also interpreted the provision to deny exclusivity in the case of collection and submission of literature studies, as well as "buying the results of tests already done and submitting them to FDA." *Id.* at 28,900.

¹⁷⁸ The statutory language requires "clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the [applicant]." FDCA, 21 U.S.C. § 355(c)(3)(E)(iii)-(iv), (j)(5)(F)(iii)-(iv) (2012). The FDA defines "essential to approval" to mean that "there are no other data available that could support approval of the application." 21 C.F.R. § 314.108(a) (2015). FDA's insistence on unambiguous documentation to that effect can result in an exclusivity denial even where a company performs clinical research believing in good faith that the research was needed. *See Upjohn Co. v. Kessler*, 938 F. Supp. 439, 440-43 (W.D. Mich. 1996) (denying preliminary injunction challenging the FDA's denial of exclusivity for a supplemental application for nonprescription status of Rogaine and finding no likelihood of success on the merits, despite the sponsor's inclusion of a clinical study that had been described in meetings with FDA after agency officials specifically raised the need to address certain risks in the application).

¹⁷⁹ FDA currently construes three-year exclusivity to protect the *condition of use* that was the subject of the clinical study, rather than the *data* from the study per se. This can have significant consequences when follow-on applicants use the hybrid pathway of section 505(b)(2). *See supra* Section II.A.1. But even when so construed, the protection remains nothing more than a labeling restriction in the case of informational conditions of use and is therefore limited as discussed in the text.

variety of statutory and regulatory exceptions usually work together to permit approval of a generic drug where the applicant has omitted information protected by three-year exclusivity or patent.¹⁸⁰ Moreover, as noted in Section II.C, a generic drug is usually deemed therapeutically equivalent (“A rated”) by the FDA.¹⁸¹ This is true even if the generic drug labeling carves out protected information.¹⁸² Further, an A-rated generic drug will generally be substituted for its reference product under state law regardless of the intended use; prescriptions usually do not specify, and pharmacists usually do not inquire about, the purpose of the prescription, let alone check to see whether the generic labeling includes the use in question. Even if the generic applicant omits new-use information from its labeling because of three-year exclusivity, its generic drug will likely be dispensed for that use. In this case, the exclusivity is worth nothing.

¹⁸⁰ The same-labeling provision explicitly permits labeling differences due to permitted deviations in a generic drug’s route of administration, dosage form, strength, or active ingredient (in a combination product), or due to the fact that the generic and reference drug are produced or distributed by different manufacturers. *See* FDCA, 21 U.S.C. § 355(j)(2)(A)(v). The patent-certification provision implicitly permits the generic company also to carve out indications because it refers to not seeking approval for indications claimed by unexpired method of use patents. *Id.* § 355(j)(2)(A)(viii). The FDA’s regulations prohibit a generic company from carving out protected information if doing so renders the generic less safe and effective than the pioneer product for the remaining non-protected conditions of use. 21 C.F.R. § 314.127(a)(7) (2015). The agency has liberally permitted omission of information protected by intellectual property under this standard. *See* Kurt R. Karst, *Decisions, Decisions, Decisions! Our Updated Labeling Carve-Out Citizen Petition Scorecard*, FDA L. BLOG (May 16, 2012), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2012/05/decisions-decisions-decisions-our-updated-labeling-carve-out-citizen-petition-scorecard.html.

In addition, the agency will not attach three-year exclusivity to labeling changes if “protection of the public health” requires that generic labeling to reflect the changes. Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions, 59 Fed. Reg. 50,338, 50,356 (Oct. 3, 1994) (to be codified at 21 C.F.R. pt. 314). This includes certain new risk information. Further, FDA will not accept arguments that new safety information must be included as a matter of public health and yet may not be included as a matter of exclusivity. *See* AstraZeneca Pharms. LP v. FDA, 872 F. Supp. 2d 60, 85–86 (D.D.C. 2012). And the D.C. Circuit has rejected arguments that a generic product may not be approved until all new-indication exclusivity has expired. *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

¹⁸¹ This will not be the case where the generic applicant deviates with respect to route of administration, dosage form, strength, or single active ingredient (in a combination product).

¹⁸² *See, e.g.*, Letter from Janet Woodcock, Dir., Ctr. for Drug Eval. & Research, to Marcy Madonald et al. at 13 (June 11, 2002), <http://www.fda.gov/ohrms/dockets/dailys/03/Aug03/080103/03p-0321-c000003-03-Tab-02-vol1.pdf> (“FDA has consistently maintained that the omission of information protected by exclusivity will not be a basis for altering a therapeutic equivalence rating.” (citing 59 Fed. Reg. at 50,357)); *see also* FDA, *supra* note 91, at 2.

To be sure, pioneers may derive a benefit from three-year exclusivity tied to new product features (e.g., a new route of administration) and to molecular variations (i.e., a new active ingredient that does not meet FDA's standard for NCE exclusivity). The primary question for the pioneer, in these cases, is marketability, i.e., whether the new route of administration or molecular variation will provide enough clinical benefit to support premium pricing for a branded product once the generic of the older versions is available.¹⁸³ This should press the pioneer toward features of value in the clinic. Moreover, new indications and other informational conditions of use with three-year exclusivity can be protected from generic penetration as a practical matter if they happen to be linked to a product feature that itself has exclusivity or patent protection.¹⁸⁴ But even with the possibility of three-year protection for new

¹⁸³ The question whether the withdrawal of one product in connection with the introduction of a newer and different product can, in some cases, raise antitrust concerns is beyond the scope of this article. The Second Circuit recently ruled that Actavis could *not* withdraw an immediate-release version of its drug from the market, in favor of marketing only a newer (and patent-protected) extended release version, until a full month after generics had entered the market with their immediate-release products. *New York ex rel. Schneiderman v. Actavis PLC*, 787 F.3d 638, 650–51 (2d Cir. 2015). The court reasoned that withdrawal of the innovator's immediate-release product prior to generic entry would effect a "hard switch"—forcing patients to use the newer extended-release product—precluding them from evaluating the merits of, and choosing between, a generic immediate-release product and the more expensive branded extended-release product. *See id.* at 655 ("Had Defendants allowed Namenda IR to remain available until generic entry, doctors and Alzheimer's patients could have decided whether the benefits of switching to once-daily Namenda XR would outweigh the benefits of adhering to twice-daily therapy using less-expensive generic IR (or perhaps lower-priced Namenda IR)."). The court was influenced by the fact that the generic IR products would not be substitutable for the pioneer's ER product, which it felt would preclude their achieving meaningful market penetration. But the court did not reject the basic point—relevant where a pioneer introduces new product features when faced with generic competition for older versions of its product—that the market can determine product superiority so long as the free choice of consumers is preserved. *See Berkey Photo, Inc. v. Eastman Kodak Co.*, 603 F.2d 263, 287 (2d Cir. 1979). It remains to be seen whether any other court of appeals will agree with the Second Circuit. The point here is just that exclusivity tied to new product features may provide an incentive to develop those features, so long as generic drugs with the older features simply compete on the basis of actual clinical value.

¹⁸⁴ Presumably if treatment of a new disease requires a new route of administration, the generic drug (with the older features) would not be appropriate for use. If a drug is approved in capsule form for one disease and as an injectable for another disease, for instance, physicians are unlikely to prescribe the capsule for the second condition. They may lawfully do so, but they are unlikely to do so. And pharmacists will not dispense the capsule generic when they receive a prescription for the branded injectable, because FDA will not list the two as therapeutically equivalent.

product features, the worthlessness of three-year exclusivity for new indications is a significant weakness.

Federal law provides even less incentive for innovators to continue studying their approved biological drugs. To begin with, there is no exclusivity for incremental improvements approved via supplements—nothing analogous to three-year exclusivity in the FDCA. Thus, now that abbreviated applications are approvable 12 years after first licensure of a pioneer's biologic, it is unclear how often pioneers will study new indications. It may be worthwhile to study new indications early in the 12-year term, if those indications are anticipated to substantially increase sales of the product during the remaining term. But as the number of remaining years of exclusivity drops, the value of studying new indications may drop, and the declining incentive will be particularly acute for any indications that require large, expensive, or long trials, as well as indications with relatively small patient populations. Patent protection will not fill the gap. Even if a biosimilar applicant omits the new indication from its labeling, avoiding liability for patent infringement, its product may be prescribed and used off-label, and pioneers are understandably unlikely to bring infringement cases against the physicians and patients involved.¹⁸⁵ All of this suggests that pioneers may now, after enactment of the BPCIA in 2010, have less incentive to study new indications once their biological drugs are approved. The rate and nature of incremental innovation—especially with respect to new indications—by biological drug pioneers would be worth watching closely in the years ahead.

The product approach to exclusivity in the PHSA could have—in theory—incentivized any incremental innovation that would be the subject of an entirely new application rather than a supplement. Put simply: under a pure product approach, every approved BLA would be associated with its own 12-year period without biosimilar competition. Thus, if a new indication or route of administration resulted in a separate application, a biosimilar applicant could use the shortcut pathway to copy the first product (with *its* indication or route of administration), but it could not use the shortcut pathway to copy the second product (with the *new* indication or route of administration). This would be functionally the same as three-year exclusivity under the FDCA (though much longer). Again, healthcare professionals could lawfully prescribe the biosimilar of the first pioneer product for the uses of the second pioneer product. This means that the unavailability of the shortcut to biosimilar companies would have been more or less valuable to the pioneer depending on whether the incremental innovation was purely informational (less valuable) or tangible *and* tied to patent protection (more valuable). But the

¹⁸⁵ As in the non-biological drug context, a new biological drug indication tied to a new product feature (like route of administration) with patent protection would receive indirect protection, for so long as biosimilar companies were unable to adopt the patented new feature.

product approach standing alone could have provided something functionally approximating three-year exclusivity under the FDCA.

All of this is moot, though, because the “first licensure” provision of the statute precludes this result. It explicitly prohibits a separate 12-year period for a full application from the same company proposing a new indication, route of administration, dosing schedule, dosage form, delivery system, or strength.¹⁸⁶ Moreover, it precludes a 12-year exclusivity period for a separate application from the same company proposing a structurally different biological product unless a clinical difference results from the structural changes. This creates substantial uncertainty for pioneers, because it may be impossible to predict the clinical significance of molecular modifications before investing the time and money in clinical trials and because it may be difficult to prove causation (i.e., that the structural change causes a clinical difference) given how poorly we understand the mechanism of action of some biological products. And—again—the statute contains no equivalent to the three-year exclusivity term under the FDCA, which is available for molecular variations that do not rise to the level of an NCE. A biological sponsor—if its new molecule fails this structural change/clinical difference test—has nothing to fall back on.

The first licensure provision of the PHSA reflects mistrust of innovators and the marketplace. During the legislative process, concerns were raised that pioneers would make minor changes to their products, obtain new approvals protected for 12 years, and frustrate effective biosimilar market penetration—a process called “evergreening” by some.¹⁸⁷ These concerns could have been put to rest by the observation that under a product approach to exclusivity, a 12-year protection period would attach only to the new biological product, leaving the old biological product free to copy. But some believed the innovative industry would use aggressive marketing to shift consumers to the newer product, leaving biosimilars of the older product to a smaller market. If the newer product were clinically different or better, however, it is not clear this result would be unwarranted; one might say this is precisely the work we *want* exclusivity to do. After all, therapeutic alternatives and drug improvements benefit society *but require research*. And a pioneer will perform the research only if it expects a period of time during which no abbreviated applications will be approved *and if* during that time it expects product sales.

Consumers must, therefore, be able to shift to the new product, if they are persuaded of its benefit. Their shifting effectuates the data exclusivity. Opponents of data exclusivity may have been concerned that the new products would not be clinically different or better, but rational purchasers should not shift patients to a newer more expensive molecule that offers no meaningful clinical benefit, when less expensive copies of

¹⁸⁶ See 42 U.S.C. § 262(k)(7)(C)(ii) (2012).

¹⁸⁷ See Carver, Elikan & Lietzan, *supra* note 9, at 764.

the initial molecule are available.¹⁸⁸ This may be particularly true in the biologics marketplace where payers may have more, and individual patients perhaps less, control over therapy choice. Recent economic research has confirmed that insurance firms and pharmacy benefit managers will correct when innovators introduce improvements that do not provide adequate clinical benefit.¹⁸⁹

Protecting new products for 12 years, while permitting copies of older products, would thus have used market-based incentives to focus subsequent research by pioneers on meaningful therapeutic alternatives or improvements. Concern about the gullibility of purchasers prevailed, however, and various categories of subsequent research were called out as per se insufficiently innovative to justify a new 12-year period. As a result, FDA will need to borrow umbrella exclusivity from the FDCA to give some hope that companies will perform new research during the initial 12-year term, something that would not otherwise have been necessary.¹⁹⁰ And there may be no incremental research as the 12 years wind down, let alone after they expire. Thus, the first licensure provision may well shut down whole categories of subsequent research by pioneers, to the detriment of tomorrow's patients—a potentially significant dynamic-efficiency loss.

The first licensure provision will also force the agency into a variety of complex decisions that a pure product approach would not have required. These include difficult decisions about corporate relationships—specifically, determining whether a subsequent pioneer is a “licensor, predecessor in interest, or other related entity” of the initial pioneer for purposes of denying exclusivity.¹⁹¹ The agency will also need to make de-

¹⁸⁸ The fact that Sloan-Kettering declined in 2013 to provide newly approved Zaltrap (aflibercept) to colorectal-cancer patients, despite a statistically significant improvement in overall survival, preferring instead the older Avastin (bevacizumab) at half the price, suggests a market skeptical of improvements with steep price tags. See Sally Pipes, Opinion, *For Cancer Treatments, a Rationing Trap*, WASH. EXAMINER (Jan. 9, 2013), <http://washingtonexaminer.com/article/2518040>.

¹⁸⁹ See Henry Grabowski & Joseph DiMasi, *Biosimilars, Data Exclusivity, and the Incentives for Innovation: A Critique of Kotlikoff's White Paper 5* (Duke Univ. Dept. of Econ. Working Paper No. 2009-02, 2009).

¹⁹⁰ Umbrella exclusivity from the first approval would protect supplements and new applications denied a separate term. Any other approach would effectively eliminate the first product's exclusivity. The agency's reasoning in 1989 is squarely on point. See *supra* text accompanying note 157. The FDA has given no indication that it intends to take a different approach in the PHSA setting.

¹⁹¹ See 42 U.S.C. § 262(k)(7)(C)(ii) (2012). Like the five-year exclusivity provision in the FDCA, this language is not free from ambiguity, particularly because one would ordinarily expect the subsequent applicant to be the *licensee* rather than the *licensor*, and the *successor* rather than the *predecessor*. The FDA's draft guidance document implementing this language perpetuates the confusion. The agency begins by following the plain language of the statute. FDA, GUIDANCE FOR INDUSTRY: REFERENCE PRODUCT EXCLUSIVITY FOR BIOLOGICAL PRODUCTS FILED UNDER SECTION

cisions about qualifying and disqualifying modifications to the structure of the biological product, and it will need to address the question of how an applicant can establish that structural modifications “result” in clinical differences. All of this will take place in regulation, guidance, policies, and individual decisions that will be perforce inconsistent, challenged, and politicized. It is hard to escape the conclusion that the first licensure provision could be just as messy, in the end, as the NCE-exclusivity provision has been.

b. Assessing the Options

Society benefits from encouraging continuing research with approved drugs, whether the research appears in a supplement or a separate application. The latter is easy to handle. A product-by-product approach to exclusivity can by its very structure reward the kinds of innovation that appear in separate applications (such as new dosage forms and new routes of administration, in most cases), and elimination of the first licensure provision would help to ensure that it does. There is one significant caveat: the risk of market share erosion through a competitor’s use of a partially abbreviated application for a “hybrid” product. Here, the competing applicant relies on the data that are no longer protected by exclusivity and then supplements with its own research. Hybrids applications, permitted by the FDA for non-biologics under the FDCA but not authorized for biologics under the PHSA, are discussed in the next Subsection. But with this caveat in place, product-by-product exclusivity for new medicines seems a good solution to ensuring the kind of research FDA requires in a full application.

A product-by-product approach to exclusivity, however, leaves *unaddressed* the kind of innovation that FDA is likely to require in a supplement rather than a new application, especially new indications. As noted, the FDCA approach of protecting only the new condition of use is problematic for innovation policy, given labeling carve-outs and automatic substitution; its adoption in the PHSA setting would be problematic despite the lack of automatic substitution in that setting, because of off-label prescribing. During the BPCIA negotiations, Congress considered a variety of drafts that provided exclusivity for subsequent research by pioneers. Most of the bills, discussion drafts, and markup amendments that addressed the issue followed the European approach rather than the FDCA approach.¹⁹² The Europeans add an extra year of exclusivity to the

351(a) OF THE PHS ACT 4–5 (drft. Aug. 2014), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf>. Later in the same document, the agency reverses the plain language, instructing (second) applicants to identify the previously licensed products for which a licensor or predecessor in interest was the (first) license holder. *Id.* at 8.

¹⁹² *E.g.*, Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2(a)(2) (2007) (extension of 14-year exclusivity period if FDA approved a supplement for a new indication for the reference product during the

base term if a significant new indication is approved before the end of the first eight years.¹⁹³ They require proof of significant clinical benefit, language that was echoed in many of the proposals under consideration in the United States.¹⁹⁴ Because this approach defers *all* copies of the pioneer product—rather than just preventing follow-on applicants from using protected language in their labeling—it mitigates the impact of off-label prescribing and dispensing. It can, therefore, provide a meaningful incentive to innovators. Why these proposals failed in the United States is hard to explain, although the evergreening issue overwhelmed most discussions relating to exclusivity, and a sense that the base exclusivity term was already long enough may have been a factor.¹⁹⁵ In a redesigned scheme that achieves dynamic efficiency, though, U.S. policymakers might want to not only include the European approach but extend it to all conditions of use that appear in supplements rather than separate applications, or at the very least all informational conditions of use, and either retain the “significant clinical benefit” requirement or use the FDCA concept of requiring clinical data essential to the new condition’s approval.

A modest extension of the base exclusivity term as a reward for innovations in supplements would seem to strike the right balance—better

first 12 years after licensure and if the new indication provided a significant clinical benefit); Affordable Biologics for Consumers Act, S. 1505, 110th Cong. § 2(a)(2) (2007) (same); Pathway for Biosimilars Act, H.R. 5629, 110th Cong. § 101(a)(2) (2008) (providing that if, within the first eight years after licensure of the reference product, the FDA approved a supplement for a new indication constituting “a significant improvement, compared to marketed products, in the treatment, diagnosis, or prevention of disease,” the data-exclusivity period would be extended by two years). The last of these—H.R. 5629—evolved into the final House-enacted language, albeit without the exclusivity extension. Discussion drafts of S. 1695, which would evolve into the final Senate-enacted language, also included an exclusivity extension period for new research. *See* Carver, Elikan & Lietzan, *supra* note 9, at 753–54 (noting that a discussion draft provided an extension of the applicable base period if within a certain period of time the reference product was approved for a new condition of use based on new clinical investigations essential to its approval and showing a “significant clinical benefit” in comparison with existing therapies); *see also id.* at 792–95 (discussing five proposed amendments, each taking a different approach to exclusivity, that were filed in the Senate HELP Committee’s markup of the bill).

¹⁹³ *See* Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, art. 10, 2001 O.J. (L 311) 67, *as amended by* Directive 2002/98/EC, 2003 (L 33) 30, *by* Directive 2004/24/EC, 2004 O.J. (L 136) 85, *and by* Directive 2004/27/EC, 2004 O.J. (L 136) 34. Separately, one year of data exclusivity is available to protect a new use supported by “significant pre-clinical or clinical studies” even where the base exclusivity has expired. *Id.* art. 10.5; *see also* Regulation (EC) 726/2004, art. 14, 2004 O.J. (L 136) 1 (governing data exclusivity).

¹⁹⁴ *See supra* note 192.

¹⁹⁵ *See* Carver, Elikan & Lietzan, *supra* note 9, at 791–92.

than either the PHSA approach (no incentive) or the FDCA approach (sometimes meaningless incentive).¹⁹⁶ Only one or a few extensions should be permitted, though, as it is hard to escape the view that if all follow-up innovation were to extend the initial exclusivity on the entire product, rational innovators would stack follow-up innovations in virtual perpetuity. That said, the clear disadvantage to the extension approach is that it provides no reward for new research after the base exclusivity term (as extended) expires. It might be fruitful to study the research life cycle of drugs and biological products in the current armamentarium to determine when, on average, most of the important new uses were discovered or developed, although the usefulness of this information may be diminished by the fact that the timing in some cases could have been a function of strategic choice as much as scientific necessity. In any case, policymakers may need to set the length of the initial exclusivity and extension long enough to capture the ordinary innovation life cycle for most new moieties and resign themselves to the fact that (absent more creative incentives) for-profit research is unlikely to take the molecule further after the exclusivity expires.

3. *Innovation by Follow-On Applicants*

Traditional regulatory provisions—non-exclusivity provisions in either statute—can play a significant role encouraging or discouraging research and development by industry. In other words, some provisions that are viewed as more traditional health-and-safety measures also implement, whether intentionally or incidentally, innovation policy.¹⁹⁷ One deserves attention here because it can directly undermine the incentive to perform additional research that would otherwise follow from data exclusivity.

a. *Differing Approaches*

The provision in question is section 505(b)(2) of the FDCA.¹⁹⁸ A little history may be helpful here. As noted earlier, prior to 1984, despite an ANDA regulation for generic copies of pre-1962 pioneer products, there

¹⁹⁶ See Heled, *supra* note 58, at 220 (making a similar proposal). Another solution would be to adopt both approaches, as Senator Gregg initially proposed in 2007. His bill would have extended base exclusivity two years for a new indication providing a significant clinical benefit, and it would have separately provided three-year exclusivity covering a new indication any time after approval for a new indication not meeting the significant clinical benefit standard, if supported by clinical data essential to its approval. See Affordable Biologics for Consumers Act, S. 1505, 110th Cong. § 2(a)(2) (2007).

¹⁹⁷ Professor Eisenberg has made this point before, largely focusing on clinical-trial requirements, drug-importation rules, and rules relating to manufacturer speech about unapproved uses. See Eisenberg, *supra* note 55, at 485; see also Eisenberg, *supra* note 56, at 373 (exploring FDA regulation of clinical trials from the perspective of innovation policy); Eisenberg, *supra* note 127, at 122–23.

¹⁹⁸ 21 U.S.C. § 355(b)(2).

was no pathway for generic copies of pioneer products approved *after* 1962.¹⁹⁹ The FDA attempted to fill the gap with a “paper NDA” policy. This policy theoretically permitted generic applicants to submit published literature as proof of the safety and effectiveness of their generic copies. But it was not workable in practice.

Congress then stepped in with the Hatch–Waxman Amendments, adding section 505(j) and the more curiously worded section 505(b)(2).²⁰⁰ Section 505(j) largely codified the agency’s ANDA regulation, but made it applicable to all pioneer drugs, no matter when approved. The innovative industry *then* argued for years that section 505(b)(2) codified the agency’s paper NDA policy. In other words, the argument went, section 505(b)(2) authorizes a follow-on applicant to rely on published literature describing studies that establish the safety and effectiveness of the drug in question where it lacks permission to reference the underlying raw data—but, the argument continued, the provision does *not* authorize reliance on the contents of a previously approved NDA. Thus, one may cite journal articles describing studies of one’s reference product *but one may not* make up the “difference” (whatever is missing for “full” approval) by referring to the approved reference product application.²⁰¹

The FDA rejected the “paper NDA” reading.²⁰² As noted in Section II, the agency instead permits abbreviated applications under section 505(b)(2) that rely on the contents of a previously approved application. Accordingly, 505(b)(2) applications can be characterized as “hybrid” applications—something of a cross between an ANDA and an NDA. They may rely on a first entrant’s research (like an ANDA does), but vary the product in some fashion and support the change with new research (like a pioneer NDA does).²⁰³ Consequently, a follow-on applicant might use this provision if it wanted to propose a condition of use that had not been sought by the pioneer. It might also use the provision if it wanted to vary the molecule in some fashion, for instance changing the salt. In

¹⁹⁹ See *supra* Subsection II.A.3.

²⁰⁰ Section 505(b)(2) refers to applications submitted under section 505(b)(1)—i.e., full new-drug applications—that nevertheless rely on investigations not performed by the applicant and to which the applicant does not have a right of reference. But it does not independently *authorize* the submission of applications, in the way that 505(b)(1) and 505(j) do. (Both begin with “[a]ny person may file”) Without further explanation, section 505(b)(2) indicates that *these* applications are subject to the Hatch–Waxman litigation provisions (including patent certifications and 30-month stays).

²⁰¹ For instance, Genentech made this argument in a citizen petition that FDA denied in 2006 when it approved the first 505(b)(2) application for a follow-on biotechnology product. See *generally* Letter from Steven K. Galson, *supra* note 62, at 4–7, 36–52.

²⁰² *Id.* at 40.

²⁰³ See 21 C.F.R. § 314.54 (2015).

short, then, under the FDCA a generic drug company may propose a perfect copy under section 505(j), or it may use the pioneer's research and propose something different under section 505(b)(2).

Congress considered, but did not enact, similar language for biologics.²⁰⁴ The statute does *not* authorize biosimilar applicants to rely on a pioneer's data and yet seek approval of something different. This precludes follow-on applicants from seeking approval of what some call "bio-betters"—new versions of the molecule, additional labeling for new indications, and improved routes of administration.²⁰⁵ Indeed, a biosimilar applicant may not rely on the pioneer's data and simply propose changes to avoid patent protection, such as alternative routes of administration or dosage forms. If a biosimilar applicant wants to rely on the pioneer's data, it must propose a biosimilar biological product. The result, as noted earlier, is a stark choice with complex trade-offs: seek approval of a biosimilar (meeting the similarity standard) or file a full application. There is no statutory option to seek partially abbreviated approval of a modified product.²⁰⁶

b. Assessing the Options

Depending on how it is drafted and interpreted, a hybrid pathway like section 505(b)(2) can undermine the incentive effect of data exclusivity as follows: Suppose a pioneer developed a second-generation version of its product—perhaps a pegylated version of its biological product²⁰⁷—and obtained approval of a separate application. In a scheme with product-by-product exclusivity, the new application would have its own exclusivity term, preventing abbreviated applications for pegylated prod-

²⁰⁴ See Access to Life-Saving Medicine Act, H.R. 6257, 109th Cong. (2006).

²⁰⁵ Of course, the pioneer may seek approval of a bio-better, whether through a supplement or a new application. This incremental innovation is the subject of the previous Section, II.

²⁰⁶ See *supra* Section II.C for a discussion of the trade-offs. There is a theoretical possibility that the FDA will permit innovative supplements—under section 351(a) of the PHSA—to biosimilar applications filed and approved under section 351(k) of the PHSA. When initially interpreting section 505(b)(2) of the FDCA in the late 1980s, the agency stated that it was possible for an ANDA applicant (under 505(j) of the statute and forbidden to vary its product) to file a subsequent supplement under section 505(b) (the pioneer provision) for variations it sought to market. See Letter from Paul Parkman, Dir., Ctr. For Biologics Evaluation & Research (Apr. 10, 1987). It is unclear whether the FDA had (or since, has) ever approved such a supplement—the point of the letter was to interpret section 505(b)(2) as a substitute mechanism so that generic applicants could seek the variation immediately without following the described two-step ANDA-then-supplement process.

²⁰⁷ Pegylation—the attaching of polyethylene glycol polymer chains to a molecule—can enhance solubility, prolong circulatory time, and reduce immunogenicity/antigenicity. See generally Xingwang Zhang et al., *Effects of Pharmaceutical PEGylation on Drug Metabolism and Its Clinical Concerns*, 10 EXPERT OP. ON DRUG METABOLISM & TOXICOLOGY 1691 (2014).

ucts. But if the scheme also permitted hybrid applications citing *one* product without regard to exclusivity held by *other* products, a follow-on applicant might obtain approval of its own pegylated product during that exclusivity term, simply by citing the first product when *its* exclusivity expired and submitting original research to support pegylation. In other words, it could obtain approval of a pegylated product more quickly and more cheaply than an innovator—it could use a shortcut to market—during the period when the pegylated product was theoretically the subject of data exclusivity. The availability of a hybrid application pathway to circumvent data exclusivity in this fashion would presumably deter pioneers from subsequent research that would result in new applications.

By way of contrast, if the scheme did not permit hybrid applications, or if it took into account exclusivity held by separate products, this would not happen.²⁰⁸ Under a product-by-product approach, companies seeking to market copies of the second-generation product would file full applications on the same regulatory terms for 12 years, though they could market copies of the first-generation product in the meantime. Using the example in the preceding paragraph, until piggybacking applications were permitted for the pegylated version, the only pegylated version on the market would be the pioneer's product (or a true competitor product: another pioneer version supported by a full application). This would ensure a robust incentive for the pioneer to develop the pegylated version. At the same time, there would be biosimilar copies of the non-pegylated version in the marketplace, once its earlier exclusivity period expired. If the pegylated version was not meaningfully different from the earlier non-pegylated version, presumably most of the market would shift to the copies of the first-generation product, creating a market-based incentive for first entrants to focus on clinically meaningful improvements to their products.

There is of course a significant public health argument in favor of the hybrid pathway. If an innovator has no plans to develop its molecule further, society benefits from a regulatory scheme that permits others to do so while enjoying use of the first entrant's research. The question is whether it is possible to permit *this* use while preventing uses that will deter the innovator from proceeding where it *does* want to—i.e., preventing

²⁰⁸ FDA currently takes the position that three-year exclusivity under the FDCA blocks approval of a 505(b)(2) application regardless of whether the application relies on the specific product that holds the exclusivity, at least where the applicant seeks the conditions of approval tied to the exclusivity. The agency thus declined to approve a 505(b)(2) application filed by Veloxis for Envarsus XR (tacrolimus), on the ground that the application sought approval for a dosage form protected by three-year exclusivity. The product with three-year exclusivity is Astagraf XL, however, which was *not* the reference product cited by Veloxis. Veloxis had cited Prograf. Veloxis challenged FDA's decision, and while this article was being drafted, a federal district court ruled in FDA's favor. *Veloxis Pharms. Inc. v. FDA*, No. 14-2126 (RBW), 2015 WL 3750672, at *7–8 (D.D.C. June 12, 2015).

use of the hybrid pathway to obtain approval of a first-generation hybrid that exactly duplicates (or nearly duplicates) a protected second-generation product. Drafting this in a way that maximized dynamic efficiency would be complex and require thoughtful attention to questions such as the right outcome where both applicants start studying the same innovation at the same time (each unaware of the other), and the right outcome where the pioneer obtains approval of the innovation in question shortly before the unsuspecting hybrid applicant submits its application. It is also very easy to imagine disputes—either during statutory drafting or during implementation—over whether a particular hybrid product is similar enough to the second-generation product that it should fall within the prohibition. A clean approach to the issue for a product-based scheme, with some precedent in U.S. law, might be to preclude hybrid applications citing a product without exclusivity, if the pioneer holds approval of another product with exclusivity that *could be* its reference product.²⁰⁹ But even this would generate interpretive challenges. In brief, an approach that attempted to reserve an area for follow-on applicants to innovate where pioneers have abandoned research could reinstate the problems of moiety exclusivity and first licensure exceptions that a pure product approach otherwise avoids.

If one were inclined to err on the side of maintaining incentives for first entrants, perhaps on the theory that on average their incremental innovation is more likely to be successful and clinically valuable than that of follow-on applicants who lack familiarity with the molecule—a theory that may benefit from empirical support—one would omit the hybrid pathway altogether. Current law does, after all, permit the would-be hybrid applicant to purchase a right of reference to the original data and continue research using its own resources. The resulting products would presumably be less expensive than if the applicant had performed the

²⁰⁹ Congress took a similar approach in a different context in the uncodified provisions of the BPICA. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(e)(2), 124 Stat. 119, 804 (2010) (authorizing applications for certain protein products under either the FDCA or the PHSA until 2020 but indicating that an application “may not be submitted” under the FDCA if there is a product under the PHSA that “could be a reference product”). Another possible precedent appears in recent regulations proposed by the FDA to implement the 2003 amendments to the Hatch–Waxman Amendments. Here, the agency has suggested that applications under section 505(b)(2) should select the most appropriate reference product. *See, e.g.*, Abbreviated New Drug Applications and 505(b)(2) Applications, 80 Fed. Reg. 6802, 6804–05 (proposed Feb. 6, 2015) (to be codified at 21 C.F.R. pts. 314, 320) (“We are proposing to require a 505(b)(2) applicant to identify a pharmaceutically equivalent product, if already approved, as a listed drug relied upon, and comply with applicable regulatory requirements. This is intended to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory patent certification obligations that would have applied if the proposed product was not ineligible for approval in an ANDA.”).

original research itself, particularly if the innovator has no further interest in pursuing the molecule (and consequently devalues the right of reference during negotiations for a license), and this may be all that policymakers can hope for in a scheme that adequately fosters innovation.²¹⁰

4. *Length of the Term*

With these basic structural questions addressed, it is possible to turn finally to the question of the length of the base exclusivity term. Current law provides a variety of data exclusivity terms for research-based licensing applications: 10 years for pesticides, 6 years for medical devices, 5 years for new drugs and new animal drugs, and 12 years for biological products. As a general rule, these term lengths were not supported during the legislative process by robust empirical work relating to innovation.²¹¹ In the late 1970s, as part of a reform effort unrelated to the later

²¹⁰ One interesting compromise is suggested—indirectly—in a 1997 article authored by Professors Reichman and Samuelson. Reichman & Samuelson, *supra* note 126, at 145–51. One might allow second entrants to propose “value-adding” follow-on products—here, innovative copies—so long as “adequate compensation” is paid under an automatic licensing scheme that would eventually sunset, much like the data compensation provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In essence, one would *require* the innovator to sell the right of reference.

²¹¹ The 10-year scheme for pesticides dates to the 1978 amendments to FIFRA. Although legislators considered terms ranging from 5 years to 15 years and spoke in general terms about innovation concerns, there does not appear to be any empirical support for the term chosen. *See, e.g.*, S. Rep. No. 95-334, at 6 (1977) (noting discussion of 12 to 15 years); *Federal Insecticide, Fungicide, and Rodenticide Act: Hearings Before the H. Comm. on Agric.*, 95th Cong. 227 (1977) (statement of Jack D. Early, President, Nat'l Agric. Chems. Ass'n) (same); S. 1678, 95th Cong. (1977) (enacted) (proposing seven years); H.R. 8954, 95th Cong. (1977) (proposing 10 years).

The legislative history of the medical-device-exclusivity provision does not explain the selection of six years. *See* FDA, GUIDANCE FOR INDUSTRY AND FOR FDA REVIEWERS: GUIDANCE ON SECTION 216 OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997, at 5 (Aug. 9, 2000), <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073709.pdf> (pointing out the lack of legislative history); *see also* S. Rep. No. 105-43, at 80–81 (1997).

The five-year and three-year terms for new drugs and new animal drugs also had no meaningful empirical support at the time. *See* Gerald J. Mossinghoff, *Overview of the Hatch–Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 191–92 (1999) (characterizing the terms as “arbitrary”). Mossinghoff was the President of the Pharmaceutical Manufacturers Association during legislative negotiations for Hatch–Waxman. *See also* Stuart M. Pape, *Market Exclusivity Under the Drug Price Competition and Patent Term Restoration Act of 1984—The Five Clauses*, 40 FOOD, DRUG, COSMETIC L.J. 310, 311 (1985) (“The absence of meaningful legislative history is not surprising, given that four of the five clauses were added to the legislation at the ‘eleventh hour’ after extended negotiations in August and September 1984 among the brand-name pharmaceutical companies, the generics and the principal Congressional sponsors of the legislation . . .”). The five- and three-year terms for animal drugs enacted four years later were simply modeled on the Hatch–Waxman provisions. S. Rep. No. 99-448, at 2 (1986) (noting that the Generic

Hatch–Waxman Amendments, Congress considered a seven-year term for new drugs, but the legislative history does not explain the choice of seven.²¹²

The exception is the 12-year term for biological products. There is a fair amount of legislative history for the biologics-exclusivity provision, including robust empirical support for the term and extended debate among participating economists. Terms of varying length were offered during the legislative process, ranging from the zero-years gauntlet thrown down by Representative Waxman in the fall of 2006 to the 14 years proposed by Senator Gregg and Representative Inslee in early 2007.²¹³ The key Senators selected 12 years on June 22, 2007.²¹⁴ This 12-year period finds two explanations in the legislative history. *First*, in the spring of 2007, Duke Economics Professor Henry Grabowski released a working paper concluding that biotechnology companies typically recover their investments in innovative products between 12.9 and 16.2 years after product approval.²¹⁵ He suggested that policymakers align data exclusivity “with the time necessary for the representative new biologic entity to earn a positive risk adjusted return” on its large up-front investment in research and development.²¹⁶ *Second*, beginning in 2007, some argued

Animal Drug and Patent Term Restoration Act of 1988 was “modeled after” the Hatch-Waxman Amendments and that its “purpose [was] to extend to veterinary drugs and biologicals the generic competition and restored patent life afforded human pharmaceuticals . . .”). See also Heled, *supra* note 54, at 330, 336, 348 (discussing the history of the ten-year pesticide exclusivity term, seven-year orphan drug exclusivity term, and six-year medical-device-data exclusivity term).

²¹² Senator Kennedy’s Drug Regulation Reform Act of 1979 would have abolished the distinction between new drugs and old drugs and would have required all prescription drugs to reach the market via approved applications. See Drug Regulation Reform Act of 1979, S. 1075, 96th Cong. (1979). Seven years after approval of a new drug application, abbreviated new drug applications would have been permitted. See also S. Rep. No. 96-321, at 42 (1979) (describing rationale for proposal but not explaining the selection of seven years).

²¹³ See Access to Life-Saving Medicine Act, H.R. 6257, 109th Cong. (2006) (Waxman); Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. (Inslee); Affordable Biologics for Consumers Act, S. 1505, 110th Cong. (2007) (Gregg). The zero-year term was probably intended to signal that the burden had been placed on the innovative industry to justify data exclusivity, consistent with the prevailing narrative that data exclusivity is an affirmative enactment for the benefit of first entrants. See SCIENTIFIC CONSIDERATIONS GUIDANCE, *supra* note 37, at 7.

²¹⁴ See Carver, Elikan & Lietzan, *supra* note 9, at 746.

²¹⁵ See Grabowski, *supra* note 69, at 26. This analysis worked from pre-approval research and development costs for biotechnology companies of \$1.24 billion to \$1.33 billion in 2005 dollars, which had been published by Professor Grabowski and Professor DiMasi (of Tufts University) earlier in the year. See *id.* at 22 (citing Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL AND DECISION ECON. 469 (2007)).

²¹⁶ *Id.* at 30.

that exclusivity for biological drugs should be roughly comparable to patent protection for non-biological drugs—either 14 years (because patent-term restoration is capped at 14 years)²¹⁷ or at least 12 years (on the theory that this might be a rough estimate of effective patent life in practice).²¹⁸ This argument was grounded in concerns that biological patents might not provide adequate incentive for pioneers, discussed in Section II above.

The discussion continued after the decision was made in June 2007. Professor Grabowski published his conclusion in June 2008 in *Nature Reviews*.²¹⁹ The FTC convened a roundtable in November 2008, at which the economic support for the data-exclusivity term was discussed.²²⁰ Alex Brill—an economist with Matrix Global Advisors—did not contest the basic economic framework put forward by Professor Grabowski, specifically the latter’s focus on the break-even point.²²¹ But he reached a different conclusion. Mainly, there is a dispute over the research-and-development costs for new drugs and biologics, which necessarily feeds into disagreement over the location of the break-even point. The two disagree over the cost of capital and over expected margins; others, including Professor Vernon at University of North Carolina, agree with Professor Grabowski.²²² In his remarks, Brill focused also on the fact that biolog-

²¹⁷ See Carver, Elikan & Lietzan, *supra* note 9, at 726–27 (describing the argument by the Biotechnology Industry Organization for 14-year period); see also Stephen A. Stack, Jr., *Afterword: Some Further Observations on the “Pharmaceutical Wars,”* 71 ANTITRUST L.J. 705, 708 (2003) (suggesting 14 years because of the patent-term restoration cap).

²¹⁸ See Carver, Elikan & Lietzan, *supra* note 9, at 796–98 (describing arguments for a 12-year period by Representative Eshoo, by Jeffrey Kushan on behalf of the Biotechnology Industry Organization, and by Jack Lasersohn on behalf of the National Venture Capital Association).

²¹⁹ Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479 (2008).

²²⁰ See FTC, Transcript, FTC Roundtable on Follow-on Biologic Drugs: Framework for Competition and Continued Innovation (Nov. 21, 2008) [hereinafter FTC Transcript], https://www.ftc.gov/sites/default/files/documents/publicevents/emerging_health_care_competition_and_consumer_issues/081121biologictranscript.pdf.

²²¹ *Id.* at 107 (“[T]he framework that Professor Grabowski has laid out is a framework that he refers to and that I refer to in my work as break-even analysis, which is asking the key question, which is the investment question, I think—I agree this is about investment—of recouping the costs, recouping the R&D costs . . . recouping the cost of capital as well and a whole associated number of costs that go into the risky development of . . . bringing to market new drugs.”); see also ALEX M. BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE 4 (Nov. 2008), http://www.matrixglobaladvisors.com/storage/mga-studies/Brill_Exclusivity_in_Biogenics.pdf.

²²² See Henry Grabowski et al., *Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques* (Duke Univ. Dept. of Econ. Working Paper No. 2008-10, 2008); see also FTC Transcript, *supra* note 220, at 118 (statement of Henry

biological drug pioneers are expected to retain some market share after biosimilar market entry, meaning that they will continue to recover research and development costs after data exclusivity expires. He ultimately concluded that the break-even date would not change substantially if data exclusivity were seven years instead of 12 years.²²³ But Professor Grabowski had similarly pointed out that innovators might retain market share. In the end, the participating economists agreed on the framework but used different input values (e.g., cost of capital) and therefore reached different conclusions. Professor Grabowski and colleagues published an updated analysis and response to Brill at the end of the year, concluding that limiting data exclusivity to fewer than 12–16 years would result in failure of a representative portfolio of biologics to break even within an extended period (after biosimilar entry).²²⁴

A separate debate, unrelated to the calculation of break-even points, erupted with Laurence Kotlikoff, a professor of economics at Boston University. Professor Kotlikoff criticized the 12-year term under discussion for the BPCIA—which he called “monopoly protection”—on the ground that competition stimulates innovation and that data exclusivity

Grabowski) (pointing out that Brill focused on a handful of large successful companies); John A. Vernon & Joseph H. Golec, A Response to the Brill Analysis for Proper Data Exclusivity Periods for Innovator Biologics (Mar. 31, 2009), <http://ssrn.com/abstract=1371020> (pointing out that Brill had ignored the most current research findings on the cost of capital for biotechnology research and development).

²²³ See FTC Transcript, *supra* note 220, at 116. In the legal literature, Professors Adelman and Holman made a similar point in 2010 that the difference between seven and 12 years of exclusivity for biological drugs would not materially affect aggregate prescription-drug expenditures. Adelman & Holman, *supra* note 131, at 589. They reached this conclusion by pointing out projections that each innovative biologic could have as few as three biosimilar competitors, leading to average price drops of only 20%. This, in turn, would have a “minor” effect on prescription drug expenditures, they argued, given that biotechnology products generate only 14% of all revenue for pharmaceuticals. *Id.* at 584.

²²⁴ Grabowski et al., *supra* note 222, at 2; see also Henry Grabowski et al., *Data Exclusivity for Biologics*, 10 NATURE REV. DRUG DISCOVERY 15, 15 (2011) (finding that—after revising their model in light of the FTC discussion and allowing the innovator to retain substantial market share after biosimilar entry—even if innovators were able to retain half the market with modest price decrease at biosimilar entry, the break-even point would not occur until at least 12 years for the average drug entity). At the end of 2010, Professor Vernon and others published a short paper working from Professor Grabowski’s model but concluding that his upper estimate of 16.2 years was “slightly low.” They cited a series of papers showing that pharmaceutical firm research and development spending is highly sensitive to financial returns and risk. They suggest that prior research underestimated the risk affecting the cost of capital and, adjusting the model, conclude that the appropriate length of data exclusivity for biologics should be closer to 17 years. John A. Vernon et al., *Exploration of Potential Economics of Follow-On Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55, 71 (2010).

can lead to less, rather than more, innovation over time.²²⁵ Working largely from work on the “socially optimal length” for patents, he argued that data-exclusivity terms “constitute uncontested grants of monopoly rights by government fiat” that would “substantially extend the duration of monopoly protection” and “thereby[] . . . delay the arrival of low-cost generic alternatives” as well as “exclude other innovators” from building on prior knowledge.²²⁶

Kotlikoff’s work repeated the myth of exclusivity. While it might be fair to call patents monopoly-like, that is not a fair characterization of data exclusivity.²²⁷ Professors Grabowski and Joseph DiMasi thus responded that data exclusivity does not provide a monopoly or protection from competitors with therapeutic alternatives.²²⁸ In fact, they pointed out, innovators face dynamic competition from other innovators and vigorously introduce therapeutic alternatives and advances—which would be deterred in a world with rapid entry of biosimilars.²²⁹ They pointed out that market forces, especially insurance firms and pharmacy-benefit managers, will correct when innovators introduce improvements that do not provide adequate clinical benefit.²³⁰ Unlike Alex Brill, Professor Kotlikoff did not offer economic analysis to support any particular length of exclusivity. This disagreement is thus largely over the nature of competition in the biologics industry, and the legal and regulatory research presented in *this* Article tends to align with the economic conclusions of Professor Grabowski and colleagues.²³¹

All of this invites the question: What should be done with respect to the term of exclusivity for non-biological drugs? Professor Grabowski’s June 2008 paper suggested that his conclusion supporting 12 years for biological drugs carries over to non-biological drugs. He presented a comparative analysis for new chemical entities under the FDCA with data previously collected for these cohorts and found break-even points of 16 years for the 1980s NCE cohort and 15 years for the 1990s cohort.²³² To this research one might add a recent paper in *Health Affairs* presenting a fresh analysis of returns on new drug research and development, includ-

²²⁵ See KOTLIKOFF, *supra* note 58, at 1.

²²⁶ *Id.* at 16.

²²⁷ See *supra* Section II.C.

²²⁸ See Grabowski & DiMasi, *supra* note 189, at 3–4.

²²⁹ See also *supra* Section II.

²³⁰ Grabowski & DiMasi, *supra* note 189, at 5.

²³¹ See also Henry Grabowski et al., *Data Exclusivity Periods and Next Generation Improvements to Innovator Biologics: Key Issues 1–7* (Duke Univ. Dept. of Econ. Working Paper No. 2009-05, 2009) (making many of the same points about the nature of competition in the biologics industry, turning to the question of incentives for pioneers to develop second-generation molecules, and concluding that products resulting in separate full BLAs should *not* receive a different, shorter exclusivity period).

²³² See Grabowski, *supra* note 219, at 484.

ing the 2000s cohort.²³³ This study found a significant drop in returns. Although the paper omitted a break-even analysis, unless the cost of capital has shrunk over time, break-even times for the average new-drug introduction may now exceed expected market life.²³⁴

Another empirical approach to the question is offered by Professor Dana Goldman at the University of Southern California. He projects that a 12-year term in the FDCA, instead of the five-year term, would result in 228 extra drug approvals between 2020 and 2060.²³⁵ He also calculates that people turning 55 in 2060 could expect an increase in life expectancy (as a result of new drugs) of 1.44 years with 12 years of exclusivity, as compared to 1.30 years under the status quo of five years. Finally, he concludes that the financial benefit of this additional longevity exceeds its cost, but notes the difference appears to be modest before 2060.²³⁶ This research is important because it may be the first to quantify the social-welfare benefit from a longer exclusivity term. It has limitations, however, because of inherent uncertainty about future changes in drug regulations as well as future scientific and medical progress. In any case, as the authors note, there has not been much appetite for lengthening data exclusivity for non-biological drugs, particularly when the net social benefits are more than five decades out.

IV. CONCLUSION

Section II of this Article offers an important insight about data exclusivity for drugs. The overall approach can be reframed as one in which there is one pathway to market for any who wish to market a particular new drug, subject to patent considerations and business judgment. After a period of time, the rules change to permit cheaper and faster licenses to market the drug, relying on another company's earlier submitted research. The myth of data exclusivity, exposed by this reframing, is that it is an affirmative grant to first entrants from the government. In 1984, pioneers with non-biological drugs approved after 1962 *lost* something: their right to perpetual exclusive use of their research became a right to only five years of exclusive use. And in 2010, pioneers with licensed biological drugs *lost* something: their perpetual exclusive right was shortened to 12 years. This reframing identifies the primary beneficiary of the

²³³ See Ernst R. Berndt et al., *Decline in Economic Returns from New Drugs Raises Questions About Sustaining Innovations*, 34 HEALTH AFF. 245, 250–51 (2015).

²³⁴ For similar reasons, in 2007 the National Academies recommended at least doubling the five-year term for new chemical entities. See NAT'L ACAD. OF SCI., NAT'L ACAD. OF ENG'G & INST. OF MED., *RIISING ABOVE THE GATHERING STORM: ENERGIZING AND EMPLOYING AMERICA FOR A BRIGHTER ECONOMIC FUTURE* 190 (2007).

²³⁵ See Dana P. Goldman et al., *The Benefits from Giving Makers of Conventional 'Small Molecule' Drugs Longer Exclusivity Over Clinical Trial Data*, 30 HEALTH AFF. 84, 87 (2011).

²³⁶ *Id.* at 87–89.

choice made by policymakers as follow-on applicants, rather than pioneers.

With this reframing in place, Section III of this Article turns to the question whether and on what terms society derives a net benefit from a period of time during which all applicants face the same barrier to market entry. The insights of the third Section are as follows.

First, it is possible that without a shortcut pathway to market, second entrants might introduce duplicates of a drug after the patent expired (or if there was no patent). More likely, though, given the cost of preparing a full application (even with a head start from public information), they would seek to be second-in-class in order to differentiate themselves in the market. But, society would not achieve the significant cost savings that are possible through undifferentiated copies that rely on the first entrant's labor, and at least with respect to medicines, society has a compelling need for those cost savings. If abbreviated applications were permitted immediately, however, innovators would not innovate except in complete alignment with patent protection and subject to the considerable uncertainty and shortcomings of patent protection in this industry sector. The net result would be cheaper duplicates of medicines in the current armamentarium, but less research into better cures or cures for currently untreatable diseases. For dynamic welfare reasons, and to prevent market failure, some sort of delay in the shortcut pathway is warranted.

Second, there are good reasons to adopt a product-by-product approach to abbreviated applications (the PHSA approach) rather than focusing on the novelty of the active ingredient (the FDCA approach). The product approach (standing alone, without a first licensure provision) does not force the agency into meticulous and possibly inconsistent distinctions or efforts to predict possible distinctions ahead of the science. It should therefore reduce administrative disputes and litigation, and their corollary for innovators, uncertainty. It may also encourage differentiating innovation. There are also good reasons to adopt the European approach to incremental innovation—one or a few modest extensions of the base exclusivity term for significant new conditions of use—and to require that follow-on applicants limit themselves to true copies (and not file hybrid applications).

This conclusion offers preliminary thoughts on how the choices discussed in Section III might play out in practice.

Consider, first, the FDCA model, where automatically substitutable generics may be proposed after five years. Even if the first entrant does not hold a patent that will block identical products, a second entrant is unlikely to seek approval of a copy via a full application, unless it was quite far along the research and development pathway at the time of first-entrant approval. The shortness of the first entrant's exclusivity term and the substitutability of its generics provide the second entrant with good

reason not to proceed with an innovative product. This is because the second entrant would face a market flooded with generic copies of its primary competitor only a few years after its own approval. Conceivably, the second entrant could change research strategy and differentiate itself in the marketplace, opting for a not-quite-identical product (perhaps a different route of administration and formulation) subject to a full application. It would receive three years of exclusivity, which would protect it from generic applications and probably also—under current FDA policy—from 505(b)(2) applications citing the first entrant and proposing variations that copied its differentiating innovation. But unless its differentiation was highly meaningful in the clinic, it would lose substantial market share to generics of the first entrant. If the first entrant *did* hold a patent that might block identical products, a second entrant would need to choose between filing an abbreviated application (as early as year four) challenging the patent, on the one hand, and innovating around the patents and filing a full application for a variation, on the other hand. The latter strategy would be rational *only* if the modifications in its product would be sufficiently valuable in the clinic to justify physician selection and premium (brand) pricing for several years *after* substitutable generics of the pioneer product became available.

And consider the PHSA model, which permits approval of biosimilars after 12 years but does not currently entail automatic therapeutic-equivalence ratings. If the first entrant does not have a patent that may block the second entrant, the latter might indeed seek approval of a duplicative product via a full application—particularly if it had started research and development at or around the same time as the first entrant. Where exclusivity attaches to each product, the second company's incentive to prepare a full application may increase, and in the absence of automatic substitution, its incentive may increase further, as it may not lose market share precipitously to copies of the first entrant. (This will depend a bit on payer policies). And if the second entrant can differentiate its product, so as to market on the basis of product features as well as price, it may choose to do so. A second entrant might not, however, start a duplicate from scratch after the first entrant's product is licensed, given the time necessary for the full research-and-development process (even with the head start from public information). Once therapeutic-equivalence designations become relatively automatic, second entrants who were well underway when the first entrant obtained approval might continue with identical products that could obtain approval *early* in the 12-year period, but the value of an undifferentiated market entry will drop drastically as one moves further into the 12-year period. This is particularly true if there are likely to be multiple copies of the first entrant.

In brief, as long as first-entrant data exclusivity expires before the second entrant research-and-development ramp ends—e.g., as long as data exclusivity is 5 or 12 years and research and development take 10 to

12 years—we will rarely see second entrants file full applications for duplicates, even where there is no patent protection. The primary exceptions might be where the regulatory requirements for abbreviated applications are uncertain (for example, in the case of a complex or poorly understood product, where an ANDA seems impossible and a 505(b)(2) with clinical data seems necessary); where automatic substitution of products approved via abbreviated application is less likely (for instance, because the follow-on product will require a 505(b)(2) application or because the drug has a narrow therapeutic index); or where the second entrant began research and development well before approval of the first entrant. We might see (and have seen) second entrants filing full applications for duplicates in those situations, and we might also see them do so if data exclusivity were substantially longer than the research-and-development ramp (assuming patents were also not an issue). On the whole, an abbreviated pathway should in itself steer second-entrant pioneers towards differentiated products, and a shorter data-exclusivity term may do so more than a longer data-exclusivity term.

This Article suggests adoption of a base exclusivity term for all drugs close to, or perhaps exceeding, the 12 years currently in place for biological drugs—with a modest base extension for incremental improvements, exclusivity on a product basis, and limitation of abbreviated applications to actual replicas (no hybrids). It also assumes automatic therapeutic-equivalence ratings. In this model, where patents are not in play, we might see undifferentiated second entrants at the very beginning of the data-exclusivity period, provided the companies had started research during the first entrant's own premarket period. We might also see them where there is uncertainty about the viability of an abbreviated pathway for scientific reasons. In general, however, we should see second entrants opting for meaningfully differentiated products or (more likely, especially where patents are in play) second-in-class positions, and we should see both (but especially the former) tapering off towards the end of the data-exclusivity period, on account of the threat of less expensive and substitutable copies of the first entrant. Their products will provide price and feature competition.

A similar analysis could be brought to bear with respect to other research-based licensure schemes. There, too, data exclusivity is not awarded by the government; it is the absence of a cheaper, faster, reliance-based pathway for competitors. It is thus not a monopoly (or analogous to patent), nor does it block competition from others on the same terms. Permitting abbreviated licensure applications immediately (or too soon) may result in market failure, and permitting them on the wrong terms may harm innovation incentives to the detriment of not only innovators but also follow-on applicants and consumers. Understanding the terms on which innovation will proceed, with an abbreviated pathway in place, requires understanding the larger regulatory structure and the nature of

competition in the marketplace in question. All of this is informed by a corrected understanding of what data exclusivity is, and what it is not.