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Regulatory Exclusivity Reform in the 115th Congress

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Summary

Regulatory exclusivities provide incentives for pharmaceutical innovation in the United States. Overseen by the Food and Drug Administration (FDA), regulatory exclusivities are alternatively known as marketing exclusivities, data exclusivities, or data protection. Each of the distinct regulatory exclusivities establishes a period of time during which the FDA affords an approved drug protection from competing applications for marketing approval.

Between them, the Federal Food, Drug, and Cosmetic Act, P.L. 75-717 (as amended), and the Public Health Service Act, P. L. 78-410 (as amended), require the FDA to enforce 16 different regulatory exclusivities. They include exclusivity terms of 12 years for biologics, 7 years for orphan drugs, 5 years for drugs that qualify as a new chemical entity (NCE), 3 years for certain clinical investigations, and 180 days for generic drug companies that challenge relevant patents under certain conditions. Other, more specialized regulatory exclusivities pertain to antibiotics, enantiomers, and qualifying infectious disease products.

Legislation introduced in the 115th Congress would modify the current system of regulatory exclusivities. One bill, the FDA Reauthorization Act of 2017, was signed into law on August 18, 2017, as P.L. 115-52. That legislation establishes a wholly new 180-day “competitive generic therapy” exclusivity period in order to address circumstances of “inadequate generic competition.”

Other legislation has been introduced but not enacted. The Improving Access to Affordable Prescription Drugs Act, introduced as both H.R. 1776 and S. 771, would modify the NCE exclusivity period to allow FDA to accept a generic drug application for the brand-name product after three years rather than five. However, the agency may not approve the generic application until five years have passed since the brand-name product’s approval date. This legislation would also limit the award of the three-year clinical investigation exclusivity to drugs that show significant clinical benefit over existing therapies manufactured by the applicant in the five-year period prior to the application.

H.R. 1776 and S. 771 would also reduce the regulatory exclusivity period for biologics from 12 to 7 years. The two bills would also call for the termination of a regulatory exclusivity if its proprietor engages in one of certain specified activities, including adulteration, misbranding, illegally marketing a drug, or making false statements to the FDA. In addition, the Abuse-Deterrent Opioids Plan for Tomorrow Act of 2017, H.R. 2025, would limit the scope of regulatory exclusivities with respect to so-called “505(b)(2) applications” that relate to abuse-resistant opioids.

Finally, the Orphan Products Extension Now Accelerating Cures and Treatments Act (OPEN ACT) of 2017, S. 1509, would require the FDA to extend by six months the exclusivity period for an approved drug or biological product when the product is additionally approved to prevent, diagnose, or treat a new indication that is a rare disease or condition. S. 1509 and another bill, S. 934, the FDA Reauthorization Act, would also clarify that the orphan drug exclusivity does not bar the FDA from approving a new, clinically superior drug with the same active ingredient that will be marketed for treatment of the same disease or condition. As well, the OPEN ACT would extend a “labelling carve out” to section 505(b)(2) applications with respect to pediatric uses.

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Introduction

Congress has established regulatory exclusivities to encourage different activities within the pharmaceutical and biotechnology industries. Regulatory exclusivities consist of a period of time during which the Food and Drug Administration (FDA) protects an approved drug from competition in the marketplace.¹ In combination, the Federal Food, Drug, and Cosmetic Act, P.L. 75-717 (as amended), and Public Health Service Act, P. L. 78-410 (as amended), require the FDA to enforce 16 different regulatory exclusivities:

- Twelve-Year Biologics Exclusivity,²
- Ten-Year Transitional Exclusivity,³
- Seven-Year Orphan Drug Exclusivity,⁴
- Five-Year New Chemical Entity Exclusivity,⁵
- Five-Year Enantiomer Exclusivity,⁶
- Five-Year Qualifying Infectious (QI) Disease Product Exclusivity,⁷
- Five-Year QI Act Antibiotic Exclusivity,⁸
- Four-Year Biologics Exclusivity,⁹
- Three-Year QI Act Antibiotic Exclusivity,¹⁰
- Three-Year Clinical Investigation Exclusivity for an Original NDA,¹¹
- Three-Year Clinical Investigation Exclusivity for a Supplemental NDA,¹²
- Two-Year Transitional Exclusivity,¹³
- One-Year Interchangeable Biologics Exclusivity,¹⁴
- Six-Month Pediatric Exclusivity,¹⁵
- 180-Day Generic Exclusivity,¹⁶ and
- 180-Day Competitive Generic Therapy Exclusivity.¹⁷

¹ See Yaniv Heled, “Regulatory Competitive Shelters,” *Ohio State Law Journal*, vol. 76 (2015), p. 299.

² 42 U.S.C. §262(k)(7)(A).

³ 21 U.S.C. §355(j)(5)(F)(i).

⁴ 21 U.S.C. §360cc.

⁵ 21 U.S.C. §355(j)(5)(F)(ii).

⁶ 21 U.S.C. §355(u)(1).

⁷ 21 U.S.C. §355f.

⁸ 21 U.S.C. §355(v)(2)(A)(i)(II).

⁹ 42 U.S.C. §262(k)(7)(B).

¹⁰ 21 U.S.C. §355(v)(1)(A).

¹¹ 21 U.S.C. §355(j)(5)(F)(iii).

¹² 21 U.S.C. §355(j)(5)(F)(iv).

¹³ 21 U.S.C. §355(j)(5)(F)(v).

¹⁴ 42 U.S.C. §262(k)(6).

¹⁵ 21 U.S.C. §355a.

¹⁶ 21 U.S.C. §355(j)(B)(iv).

¹⁷ 21 U.S.C. §355(j)(5)(B)(v).

This report introduces the various regulatory exclusivities and then describes pertinent legislation in the 115th Congress addressing them.

Fundamentals of Regulatory Exclusivity

The U.S. government regulates the marketing of pharmaceuticals in the interest of public health. The developer of a new drug—known as its “sponsor”—must demonstrate that the product is safe and effective before it can be distributed to the public.¹⁸ This showing requires a sponsor to conduct both preclinical and clinical investigations of drugs that have not been previously tested.¹⁹ In deciding whether to issue marketing approval or not, the FDA evaluates the test data that the sponsor submits in a so-called New Drug Application (NDA).²⁰

The FDA maintains the test data incorporated into an NDA in confidence.²¹ In addition, because the required test data is usually quite costly to generate, sponsors of new pharmaceuticals ordinarily do not disclose them to the public. Otherwise the sponsor’s competitors could file their own NDAs using that test data, and thereby avoid the expenses of developing the information themselves.²²

Until 1984, federal law contained no separate provisions addressing lower-cost generic versions of brand-name drugs that the FDA had previously approved for marketing. The result was that a would-be generic drug manufacturer had to file its own NDA in order to market its drug. Some generic manufacturers could rely on published scientific literature demonstrating the safety and efficacy of the drug. Because these sorts of studies were not available for all drugs, however, not all generic firms could file these so-called “paper NDAs.”²³ Further, at times the FDA would request additional studies to address safety and efficacy questions that arose from experience with the drug following its initial approval. The result was that some generic manufacturers were forced to prove independently that their pharmaceuticals were safe and effective, even though their products were chemically identical to those of previously approved drugs.²⁴

Some commentators believed that the approval of a generic drug was a needlessly costly, redundant, and time-consuming process under this system. These observers noted that although patents on important drugs had expired, manufacturers were not moving to introduce generic equivalents for these products due to the level of resource expenditure required to obtain FDA marketing approval. As the introduction of generic drugs often causes prices to decrease, the interest of consumers was arguably not being served through these observed costs and delays.²⁵

¹⁸ 21 U.S.C. §355.

¹⁹ Development and Approval Process (Drugs), Food and Drug Administration, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>.

²⁰ 21 C.F.R. §314.50.

²¹ 21 C.F.R. §20.61.

²² See Mustafa Ünlü, “It Is Time: Why the FDA Should Start Disclosing Drug Trial Data,” 16 *Michigan Telecommunications and Technology Law Review* (2010), 511.

²³ See Colleen Kelly, “The Balance Between Innovation and Competition: The Hatch-Waxman Act, the 2003 Amendments, and Beyond,” 66 *Food and Drug Law Journal* (2011), 417.

²⁴ See D. Christopher Ohly and Sailesh K. Patel, “The Hatch-Waxman Act: Prescriptions for Innovative and Inexpensive Medicines,” 19 *University of Baltimore Intellectual Property Law Journal* (2011), 107.

²⁵ See Linda P. Nussbaum & John D. Radice, “Where Do We Go Now? The Hatch-Waxman Act Twenty-Five Years Later: Successes, Failures, and Prescriptions for the Future,” 41 *Rutgers Law Journal* (2009), 229.

In response to these concerns, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984,²⁶ more commonly known as the Hatch-Waxman Act. This legislation created a new type of application for marketing approval of a generic drug.²⁷ This application, termed an “Abbreviated New Drug Application” (ANDA), may be filed at the FDA.²⁸ An ANDA may be filed if the active ingredient of the generic drug is the bioequivalent of the approved drug. An ANDA allows a generic drug manufacturer to rely upon the safety and efficacy data of the original manufacturer. The availability of the ANDA mechanism often allows a generic manufacturer to avoid the costs and delays associated with filing a full-fledged NDA. ANDAs also allow a generic manufacturer, in many cases, to place its FDA-approved bioequivalent drug on the market as soon as any relevant patents expire.²⁹

The Hatch-Waxman Act also modified the FDA’s earlier “paper NDA” practice by establishing a “section 505(b)(2)” application. A section 505(b)(2) application is, in a sense, a hybrid application that falls somewhere between an ANDA and a full NDA. More technically, a section 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted....”³⁰ A section 505(b)(2) application differs from an ANDA in that it includes full reports of investigations of the safety and efficacy of the proposed product. However, a section 505(b)(2) NDA is distinct from an NDA in that the section 505(b)(2) application relies upon data that the applicant did not develop itself.

The Hatch-Waxman Act placed certain limits upon the ability of generic competitors to sell their own versions of brand-name drugs. These limitations—termed regulatory exclusivities—consist of a period of time during which a competitor’s ability to obtain FDA permission to sell a generic version of a previously approved brand-name drug is restricted.³¹ The federal food and drug laws establish several different sorts of regulatory exclusivities relating to new chemical entities, new clinical studies, orphan drugs, pediatric studies, generic drugs, antibiotics, qualified infectious disease products, enantiomers, and biologics. This report will describe each of these regulatory exclusivities below.

Data Exclusivity Versus Market Exclusivity

Regulatory exclusivities are not subject to a standard terminology. Some commentators employ terms such as “statutory exclusivity,” “data protection,” and “marketing exclusivity” synonymously with the term “regulatory exclusivity.”³² This report will instead follow the approach of a second group of writers who ascribe distinct meanings to these terms.³³ Under this

²⁶ P.L. 84-417, 98 Stat. 1585 (1984).

²⁷ CRS Report R44643, *The Hatch-Waxman Act: A Primer*, by John R. Thomas.

²⁸ 21 U.S.C. §355(j)(1).

²⁹ See Martin S. Masar III, “Effects of the Federal Circuit Judges on Hatch-Waxman Litigation,” 19 *DePaul Journal of Art, Technology and Intellectual Property Law* (2009), 315.

³⁰ 21 U.S.C. § 355(b)(2).

³¹ See Brian F. McMahon, “The Biologics Price Competition and Innovation Act of 2009: Legislative Imprudence, Patent Devaluation, and the False Start of a Multi-Billion Dollar Industry,” 100 *Kentucky Law Review* (2011-12), 635.

³² See John R. Thomas, *Pharmaceutical Patent Law* (Bureau of National Affairs, 2d ed. 2010) (noting these terminological distinctions).

³³ See, e.g., Maxwell R. Morgan, “Regulation of Innovation Under Follow-On Biologics Legislation: FDA Exclusivity as an Efficient Incentive Mechanism,” 11 *Columbia Science and Technology Law Review* (2010), 93.

latter approach, “regulatory exclusivity” is an umbrella term that refers to any FDA-administered proprietary right. Regulatory exclusivities may in turn be divided into two categories: (1) those that provide data exclusivity, alternatively known as data protection, and (2) those that provide marketing exclusivity.

The distinction between data and marketing exclusivity lies in the scope of protection that each proprietary right affords. Data exclusivity protects the safety and efficacy information—often termed the “data package”—submitted by the brand-name firm from use by generic firms. As a result, a generic firm may not rely upon that data in support of its own application for FDA marketing approval for a period of years. Data exclusivity does not prevent a generic firm from submitting its own data package. In contrast, a marketing exclusivity prevents a competing firm from obtaining FDA approval whether or not it has generated its own safety and efficacy data.³⁴

For many firms the distinction between a data exclusivity and marketing exclusivity may be more apparent than real. The expense of generating clinical data and other information needed to obtain marketing approval from the FDA is prohibitive for many firms.³⁵ The difference between data and marketing exclusivity is of greater importance to firms that can afford to generate their own data packages for submission to the FDA.

New Chemical Entities

The Hatch-Waxman Act established a five-year data exclusivity that is available to drugs that qualify as a new chemical entity (NCE). The purpose of this “NCE exclusivity” is to encourage the development of innovative drug products that include an entirely new active ingredient (commonly termed the “active moiety”), in contrast to “me-too” drugs that incorporate chemical variants of previously known compounds.³⁶ NCE exclusivity prevents a subsequent generic applicant from relying upon the data submitted by the innovative drug company during a five-year period. As a result, generic firms are precluded from relying upon this data for five years from the date of the marketing approval of the NDA for that active moiety.³⁷

A drug is judged to be an NCE if the FDA has not previously approved that drug’s active ingredient.³⁸ During that five-year period of NCE exclusivity, the FDA may not accept a generic drug company’s application to market a drug product containing the same active moiety protected under the NCE exclusivity. This prohibition holds even if these applications are directed toward a different use, dosage form, or ester or salt of the active ingredient.

As noted, NCE exclusivity acts as data exclusivity. It therefore does not preclude the FDA from accepting an application submitted by an entity that has performed all the required preclinical and clinical studies itself.³⁹

The Hatch-Waxman Act allows the five-year term of NCE exclusivity to be decreased to four years under one circumstance. If the NDA holder owns or licenses patents that the generic

³⁴ See McMahon, *supra*.

³⁵ See Rebecca S. Eisenberg, “The Role of the FDA in Innovation Policy,” 13 *Michigan Telecommunications and Technology Law Review* (2007), 345.

³⁶ See 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 Law Journal* (2011), 105.

³⁷ 21 U.S.C. §355(j)(5)(F)(ii).

³⁸ 21 C.F.R. §314.108(a).

³⁹ See Timothy A. Cook, “Pharmaceutical Patent Litigation Settlements: Balancing Patient & Antitrust Policy Through Institutional Choice,” 17 *Michigan Telecommunications and Technology Law Review* (2011), 417.

applicant believes are invalid or not infringed, then the generic applicant is allowed to file its application one year early—upon the expiration of four, rather than five years from the date the NDA was approved.⁴⁰

The practical effect of this arrangement is to restrict a potential generic manufacturer from bringing a product to market for the NCE exclusivity—either four or five years—plus the length of the FDA review of the generic application. If, for example, the FDA requires two years to approve a particular generic application, the real-world impact of the NCE exclusivity has been seven years of protection.⁴¹ In this respect NCE exclusivity operates differently from other forms of FDA-administered exclusivities. Other exclusivities generally prevent the FDA from approving applications, rather than accepting them in the first instance.

Clinical Investigations

In order to encourage improvements upon drugs that are already in use, the Hatch-Waxman Act also provided for a three-year clinical investigation exclusivity period. Clinical investigation exclusivity may be awarded with respect to an NDA that contains reports of new clinical studies conducted by the sponsor that are essential to FDA approval of that application. The FDA has granted clinical investigation exclusivity for such changes as new dosage forms, new indications, or a switch from prescription to over-the-counter status for the drug.⁴²

The Hatch-Waxman Act imposes four requirements that an investigation must fulfill in order to qualify for clinical investigation exclusivity.⁴³ First, the study must be new, in that it could not have been previously used for another FDA drug approval proceeding. Second, the study must be a clinical study on humans, as compared to a preclinical or other sort of study. Third, the study must have been “conducted or sponsored” by the applicant.

Finally, the study must be “essential to the approval” of the application. The FDA has defined the term “essential to approval” as meaning “that there are no other data available that could support approval of the application.” A study that provides useful background information, but is not essential to approving the change in the drug, does not provide sufficient basis for an FDA award of clinical investigation exclusivity.⁴⁴

As with NCE exclusivity, clinical investigation exclusivity acts as data exclusivity.⁴⁵ It therefore does not preclude the FDA from approving a full NDA. If the sponsor of a subsequent NDA has performed all the required preclinical and clinical studies itself, the FDA may approve the NDA without regard to the new clinical trial exclusivity.

In contrast to NCE exclusivity, clinical investigation exclusivity does not prevent the FDA from accepting a generic application with respect to the drug. If the clinical investigation exclusivity continues to bar the issuance of marketing approval at the close of FDA review, the FDA will

⁴⁰ See C. Scott Hemphill & Mark A. Lemley, “Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act,” 77 *Antitrust Law Journal* (2011), 947.

⁴¹ See Joyce Wing Yan Tam, “Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation,” 98 *Georgetown Law Journal* (2010), 535.

⁴² See Elizabeth H. Dickinson, “FDA’s Role in Making Exclusivity Determinations,” 54 *Food and Drug Law Journal* (1999), 195.

⁴³ 21 U.S.C. §355(j)(5)(F)(iii)-(iv).

⁴⁴ *Ibid.*

⁴⁵ See Anna B. Laakmann, “Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs,” 62 *Alabama Law Review* (2011), 305.

issue a tentative approval for the generic product that will become effective once the clinical investigation exclusivity has run its course.⁴⁶

In addition, clinical investigation exclusivity only applies to the “conditions of approval”—that is to say, the use of the product that was supported by the clinical investigation. If, for example, the new studies support a new indication or dosage form of the previously approved ingredient, then the three-year exclusivity applies only to that particular use or dosage form. The FDA is not barred from approving generic drugs for other indications or dosage forms.⁴⁷

A drug product may be subject both to NCE exclusivity and clinical investigation exclusivity during the life of that product. Commonly, a new drug will initially enjoy a five-year NCE exclusivity. Later in the life of that product, the sponsor of the drug may perform additional clinical trials to qualify the drug for additional three-year data exclusivities that apply only to those new, specific uses.⁴⁸

Orphan Drugs

In 1982, Congress enacted the Orphan Drug Act⁴⁹ in order to encourage firms to develop pharmaceuticals to treat rare diseases and conditions. Such drugs are called “orphan drugs” because firms may lack the financial incentives to sponsor products to treat small patient populations. The Orphan Drug Act provides several incentives, including FDA protocol assistance, tax breaks, and a clinical trial grants program.⁵⁰

The most commercially significant of all of these benefits is a seven-year term of marketing exclusivity.⁵¹ This period commences from the date the FDA issues marketing approval on the drug. The original version of the Orphan Drug Act extended marketing exclusivity only to drugs that were not patented. However, Congress amended the statute in 1985 to provide for regulatory exclusivity for both patented and unpatented products.⁵²

Because it acts as a marketing exclusivity, orphan drug exclusivity blocks competitors from obtaining FDA approval whether or not they have generated their own data. However, orphan drug regulatory exclusivity applies only to the indication for which the drug is approved. As a result, the FDA could approve a second application of the same drug for a different use. The FDA cannot approve the same drug made by another manufacturer for the same use, however, unless the original sponsor approves or the original sponsor is unable to provide sufficient quantities of the drug to the market.⁵³

As originally enacted, the Orphan Drug Act defined an orphan drug as one for which there was no “reasonable expectation that the cost of developing ... will be recovered from sales in the United

⁴⁶ See Dickinson, *supra*.

⁴⁷ See Rebecca S. Eisenberg, “The Problem of New Uses,” 5 *Yale Journal of Health Policy, Law and Ethics* (2005), 717.

⁴⁸ See Brook K. Baker, “Ending Drug Registration Apartheid: Taming Data Exclusivity and Patent/Registration Linkage,” 34 *American Journal of Law and Medicine* (2008), 303.

⁴⁹ P.L. 97-414, 96 Stat. 2049 (1982).

⁵⁰ See David Duffield Rohde, “The Orphan Drug Act: An Engine of Innovation? At What Cost?,” 55 *Food and Drug Law Journal* (2000), 125.

⁵¹ 21 U.S.C. §360cc.

⁵² Orphan Drug Amendments of 1985, P.L. 99-91.

⁵³ 21 U.S.C. §360cc(b).

States of such drug.”⁵⁴ In 1984, Congress changed the definition to its present form.⁵⁵ Currently, in order to qualify for orphan drug status, the drug must treat a rare disease or condition (1) affecting less than 200,000 people in the United States, or (2) affecting more than 200,000 people in the United States, but for which there is no reasonable expectation that the sales of the drug would recover the costs.⁵⁶ The effect of this change was to allow drug sponsors to avoid making a showing of unprofitability if the target population consisted of fewer than 200,000 persons.

Biologics

The Biologics Price Competition and Innovation Act of 2009 (BPCIA), which was enacted as Title VII of the Patient Protection and Affordable Care Act, P.L. 111-148, introduced new regulatory exclusivities for a category of biologically derived preparations known as “biologics.”⁵⁷ Biologics consist of such products as vaccines, antitoxins, blood components, and therapeutic serums.⁵⁸ For the most part, the FDA regulates biologics under Section 351 of the Public Health Service Act,⁵⁹ as compared to the Federal Food, Drug, and Cosmetic Act⁶⁰ which applies to small-molecule, traditional pharmaceuticals.

The BPCIA established two periods of regulatory exclusivity applicable to brand-name biologics, one with a duration of 4 years and the other with a duration of 12 years. The BPCIA specifically provides:

(7) EXCLUSIVITY FOR REFERENCE PRODUCT.—

(A) EFFECTIVE DATE OF BIOSIMILAR APPLICATION APPROVAL.—Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a).

(B) FILING PERIOD.—An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).⁶¹

Some discussion has occurred about whether the 12-year regulatory exclusivity period identified in the statute operates as a data or marketing exclusivity. In the FDA’s public hearing notice, the agency referred to a “12-year period of marketing exclusivity.”⁶² Several Members of Congress drafted letters to the FDA explaining that the 12-year period instead acted as a data exclusivity. One letter explained:

The Act does not provide market exclusivity for innovator products. It provides data exclusivity, which prohibits FDA from allowing another manufacturer of a highly similar biologic to rely on the Agency’s prior finding of safety, purity and potency for the innovator product for a limited period of time. It does not prohibit or prevent another

⁵⁴ P.L. 97-414, §526(a)(2), 96 Stat. 2049 (1982).

⁵⁵ Health Promotion and Disease Prevention Amendments of 1984, P.L. 98-551, 98 Stat. 2815 (1984).

⁵⁶ 21 U.S.C. §360bb(a)(2).

⁵⁷ CRS Report R41483, *Follow-On Biologics: The Law and Intellectual Property Issues*, by John R. Thomas.

⁵⁸ 42 U.S.C. §262(i).

⁵⁹ This provision has been codified as 42 U.S.C. §262.

⁶⁰ P.L. 98-417, 98 Stat. 1585.

⁶¹ 42 U.S.C. §262(k)(7).

⁶² Department of Health and Human Services, FDA, “Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments,” *75 Federal Register* (Oct. 5, 2010), 61497.

manufacturer from developing its own data to justify FDA approval of a full biologics license application rather than an abbreviated application that relies on the prior approval of a reference product.⁶³

Similarly, other Members of Congress explained that the 12-year regulatory exclusivity acts as data exclusivity that “only protects the FDA from allowing another manufacturer to rely on the data of an innovator to support another product. Importantly, it does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a similar of competitive product.”⁶⁴ A third letter from some Members of Congress stated their belief that “the statute is clear that the FDA can begin reviewing biogeneric applications during the 12 year exclusivity period.”⁶⁵ The FDA subsequently issued a draft guidance document that appeared to align the agency’s view with that of the congressional correspondents.⁶⁶

Pediatric Studies

Brand-name firms may qualify for a six-month pediatric exclusivity upon the completion of studies on the effects of a drug upon children.⁶⁷ This six-month period begins on the date that the existing patent or data exclusivity protection on the innovator drug would otherwise expire. Pediatric exclusivity extends to any drug product with the same active ingredient. The purpose of the pediatric regulatory exclusivity is to improve the availability of appropriate pediatric labeling on drug products.⁶⁸

Congress first established pediatric regulatory exclusivities with the Food and Drug Administration Modernization Act of 1997 (FDAMA).⁶⁹ Although the FDAMA included a sunset provision, Congress subsequently reauthorized these provisions.⁷⁰ In the 112th Congress, the Food and Drug Administration Safety and Innovation Act, P.L. 112-144, made the pediatric exclusivity permanent.⁷¹

In establishing pediatric exclusivity, Congress responded to concerns that many FDA-approved drugs had not yet been clinically tested upon children. Investigations upon a pediatric population tends to raise a number of complexities, including issues of informed consent, the changes that occur in children as they grow, and the inability of children to describe accurately the effect of a medication. As a result, most drugs are tested solely upon adults. By establishing a pediatric

⁶³ Letter of January 7, 2011, from Senator Michael Enzi et al., to Dr. Margaret Hamburg, Commissioner, FDA (available at <http://www.hpm.com/pdf/1-7-11%20Senate%20Biologics%20letter%20to%20FDA.pdf>) (signed by Senators Enzi, Hagan, Hatch, and Kerry).

⁶⁴ See Letter of December 21, 2010, from Representative Anna G. Eshoo et al., to FDA (available at <http://patentdocs.typepad.com/files/letter-to-fda.pdf>) (signed by Representatives Barton, Eshoo, and Inslee).

⁶⁵ See Letter of January 24, 2011, from Senator Sherrod Brown et al., to Dr. Margaret Hamburg, Commissioner, FDA (available at <http://patentdocs.typepad.com/files/senator-letters-exclusivity.pdf>) (signed by Senators Brown, Harkin, McCain, and Schumer).

⁶⁶ FDA, Guidance for Industry, Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Feb. 2012), 3.

⁶⁷ 21 U.S.C. §355a.

⁶⁸ See Michael J. Malinowski & Grant G. Gautreaux, “Drug Development—Stuck in a State of Puberty?: Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability,” 56 *St. Louis University Law Journal* (2012), 363.

⁶⁹ P.L. 105-115, 111 Stat. 2296, at §11 (1997).

⁷⁰ See John R. Thomas, *Pharmaceutical Patent Law* (Bureau of National Affairs, 2d ed. 2010), p. 461.

⁷¹ P.L. 112-144 at §501.

regulatory exclusivity, Congress hoped to encourage additional pediatric testing, which in turn could allow medications to be labeled for use by children.⁷²

Pursuant to its statutory authority, the FDA issues written requests to NDA applicants and holders of approved NDAs to perform pediatric studies with respect to the drug. An FDA written request contains such information as the indications and the number of patients to be studied, the labeling that may result from such studies, the format of the report to be submitted to the FDA, and the timeframe for completing the studies. Response to this written request is wholly voluntary. If the innovative drug company submits a report to the satisfaction of the FDA, however, then it will be awarded the six-month regulatory exclusivity.⁷³

Notably, the food and drug laws do not condition pediatric exclusivity upon the success of the study. The six-month regulatory exclusivity period may be obtained whether or not the study successfully demonstrates safety and effectiveness in children. Thus, the pediatric exclusivity is intended to create incentives for drug sponsors to conduct research and submit their results to the FDA.⁷⁴

The effect of a pediatric exclusivity is to extend the approved manufacturer's existing regulatory exclusivity or patent protection for an additional 6 months. If the pediatric exclusivity applied to an orphan drug, for example, the result would be 7 years and 6 months of marketing exclusivity; if applied to an NCE exclusivity, the drug's sponsor would obtain 5 years and 6 months of data protection. If applied to a patent, that pediatric exclusivity does not actually extend the term of a patent; rather, it is a regulatory exclusivity administered by the FDA.⁷⁵

Qualified Infectious Disease Products

Congressional concern over the spread of antibiotic-resistant “superbugs” led to the enactment of the Generating Antibiotic Incentives Now (GAIN) Act, enacted as Title VIII of the FDA Safety and Innovation Act, P.L. 112-144.⁷⁶ That statute allows the FDA to designate a drug as a “qualified infectious disease product” (QIDP) if it consists of an antibacterial or antifungal drug intended to treat serious or life-threatening infections.⁷⁷ The GAIN Act stipulates that QIDPs include drugs that address drug-resistant tuberculosis, gram negative bacteria, and *Staphylococcus aureus*.⁷⁸

Along with other measures intended to provide pharmaceutical and biotechnology companies with incentives to develop innovative antibiotics,⁷⁹ the GAIN Act adds five years to the term of the new chemical entity, clinical investigation, and orphan exclusivities for any QIDP.⁸⁰ The

⁷² See Scott Tillett, “Off-Label Prescribing of SSRIs to Children: Should Pediatric Testing Be Required, or Are There Other Means to a Safer End for Children?,” 19 *Southern California Review of Law & Social Justice* (2010), 447.

⁷³ See Barbara A. Noah, “Just a Spoonful of Sugar: Drug Safety for Pediatric Populations,” 37 *Journal of Law, Medicine and Ethics* 280 (2009).

⁷⁴ See Leslie Kushner, “Incentivizing Postmarketing Pharmaceutical Product Safety Testing with Extension of Exclusivity Periods,” 19 *Fordham Intellectual Property, Media and Entertainment Law Journal* (2009), 519.

⁷⁵ *Ibid.*

⁷⁶ P.L. 112-144, §801 (introducing 21 U.S.C. §505E).

⁷⁷ 21 U.S.C. §505E(g).

⁷⁸ 21 U.S.C. §505E(f).

⁷⁹ See “Antibiotics Resistance Rising; Can New Drugs Keep Pace?,” *BioWorld Insight* (September 17, 2012).

⁸⁰ 21 U.S.C. §505E(a).

statute stipulates that the five-year QIDP extension is cumulative with the pediatric exclusivity.⁸¹ As a result, a QIDP that qualified as a new chemical entity, and was also awarded a pediatric exclusivity, would be entitled to a data exclusivity period of 10 years and 6 months.

Enantiomers

Enantiomers are molecules that possess the same molecular formula but are mirror images of each other—like left and right hands. Frequently, only one of a pair of enantiomers is pharmacologically active, while the other is inactive or nearly so. Sometimes only one member of a pair of enantiomers will demonstrate toxicity.⁸² The term “racemate” refers to a compound that has equal amounts of the two sorts of enantiomers.⁸³

The FDA traditionally held the view that the single enantiomer of a previously approved racemate contained a previously approved active moiety and was not a new chemical entity.⁸⁴ This situation changed with the enactment of the FDA Amendments Act (FDAAA) of 2007.⁸⁵ This legislation incorporated provisions that allowed the FDA to grant new chemical entity (NCE) exclusivity to enantiomers of previously approved racemates if the NDA applicant so elects. Under the FDAAA, enantiomer exclusivity only applies where the applicant seeks approval for an indication in a different therapeutic class from that of the previously approved racemate.

In addition, approval of the non-racemic drug must be based upon different studies than the racemic one for exclusivity to be awarded. Finally, in the event of applicant election for enantiomer exclusivity, the labeling of the non-racemic drug “shall include a statement that the non-racemic drug is not approved, and has not been shown to be safe and effective, for any condition of use of the racemic drug.” The FDAAA limits the availability of enantiomer exclusivity to applications submitted to the FDA after September 27, 2007, and before October 1, 2017.⁸⁶

Antibiotics

An antibiotic is “any drug ... composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.”⁸⁷ Prior to 1997, the FDA reviewed most applications for antibiotic drug marketing approval under section 507 of the Federal Food, Drug, and Cosmetic Act (FFDCA).⁸⁸

⁸¹ 21 U.S.C. §505E(b).

⁸² Kyle Faget, “Why FDCA Section 505(u) Should Not Concern Us Greatly,” 15 Mich. Telecomm. Tech. L. Rev. 453 (2009).

⁸³ See *Sanof-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1080-81 (Fed. Cir. 2008).

⁸⁴ FDA, Policy on Period of Marketing Exclusivity for Newly Approved Drug Products With Enantiomer Active Ingredients; Request for Comments, 62 Fed. Reg. 2167 (Jan. 15, 1997).

⁸⁵ P.L. 110-85, 121 Stat. 823 (2007).

⁸⁶ 21 U.S.C. §355(u).

⁸⁷ 21 U.S.C. §321(jj).

⁸⁸ 21 U.S.C. §357.

The FDA Modernization Act of 1997⁸⁹ repealed section 507 and instead required agency to review antibiotic drugs under section 505 of the FDCA. Stated differently, antibiotics were no longer covered by a distinct statute, and instead were brought into the mainstream of pharmaceutical regulation. The FDA Modernization Act considered the ramifications for intellectual property rights in so-called “old antibiotics”—that is to say, antibiotics that were subject to applications for marketing approval prior to the statute’s enactment. Under that legislation, marketing applications for drugs containing an antibiotic that the FDA received on or before November 20, 1997, were exempted from certain patent listing, patent certification, and regulatory exclusivity provisions of the Hatch-Waxman Act.⁹⁰ These provisions essentially maintained the status quo with respect to the expectations of antibiotics manufacturers who had sought marketing approval prior to the enactment of the FDA Modernization Act.

Congress revisited the issue in 2008 with the QI Program Supplemental Funding Act of 2008.⁹¹ This legislation introduced changes to the Medicare and Medicaid programs, but also altered the rules pertaining to patents and regulatory exclusivities for antibiotics. The QI Act clarified that antibiotic drugs approved before November 21, 1997, may obtain a three-year exclusivity for a new condition of use for an “old antibiotic.” The statute also stipulated that marketing approval applications for antibiotic drugs submitted before November 21, 1997, but not yet approved by the FDA, may elect to become eligible for three-year clinical investigation exclusivity, five-year NCE exclusivity, or a patent term extension under section 156 of the Patent Act. Should this election be made, the other features of the Hatch-Waxman Act, such as its patent dispute resolution system, apply to that “old antibiotic.”⁹²

Generic and Follow-On Exclusivity

Most of the regulatory exclusivities operate in favor of brand-name firms. However, federal law also establishes regulatory exclusivities designed to encourage generic and follow-on firms to market their products. The Hatch-Waxman Act allows generic firms to obtain a 180-day period of “generic exclusivity” if they are the first to file an ANDA challenging a brand-name firm’s patents.⁹³ Generally speaking, this regulatory exclusivity precludes the FDA from approving another ANDA for the same product for the 180-day period.⁹⁴

In addition, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) establishes a regulatory exclusivity that operates in favor of manufacturers of follow-on biologics. Under the BPCIA, the first follow-on product deemed to be “biosimilar” to or “interchangeable” with the brand-name product is entitled to a period of exclusivity before the FDA will make a determination for a competing product. Follow-on exclusivity ends at the earlier of one year after first commercial marketing, 18 months after a final court decision in a patent infringement action against the applicant or dismissal of such an action, 42 months after approval if the applicant has been sued and the litigation is still ongoing, or 18 months after approval if the applicant has not been sued.⁹⁵

⁸⁹ P.L. 105-115.

⁹⁰ FDA, *Guidance for Industry: Submission of Patent Information for Certain Old Antibiotics*, November 2008.

⁹¹ P.L. 110-379.

⁹² 21 U.S.C. §355(v).

⁹³ 21 U.S.C. §355(j)(B)(iv).

⁹⁴ See, e.g., David E. Korn et al., “A New History and Discussion of 180-Day Exclusivity,” 64 *Food and Drug Law Journal* (2009), 335.

⁹⁵ 42 U.S.C. §262(k)(6).

Competitive Generic Therapies

Under the Hatch-Waxman Act as originally enacted, the first generic drug company that challenges patents relating to a brand-name drug may obtain a 180-day period of regulatory exclusivity. The FDA could not award a generic exclusivity when patents on the brand-name drug have already expired, however. Some observers believed that this circumstance discouraged generic drug companies from offering products to compete with drugs that were off-patent.

To address this concern, the FDA Reauthorization Act of 2017, P.L. 115-52, established a 180-day “competitive generic therapy” exclusivity period in circumstances of “inadequate generic competition.” The FDA Reauthorization Act defines “inadequate generic competition” to exist where no generic competition exists for a particular drug, or where a single generic drug has been approved but the brand-name drug is no longer marketed. In addition, the “competitive generic therapy” must not be subject to relevant patents or regulatory exclusivities. The “competitive generic therapy” exclusivity blocks competing generic applications from initial FDA approval for 180 days. It is forfeited if its holder does not market its generic drug within 75 days from the date of FDA approval.⁹⁶

Transitional Exclusivity

The Hatch-Waxman Act established two “transitional” exclusivities for applications for marketing approval, other than ANDAs, that the FDA approved between January 1, 1982, and September 24, 1984.⁹⁷ These periods of exclusivity expired some years ago and are of historical interest today.

Proposed Reforms in the 115th Congress

Legislation introduced in the 115th Congress would modify the current system of regulatory exclusivities. None of this legislation has been enacted as of the publication of this report.

Duration of Protection

The Improving Access to Affordable Prescription Drugs Act, introduced as both H.R. 1776 and S. 771, would modify the NCE exclusivity period. Under current law, the FDA may not accept an ANDA proposing to market a generic version of a brand-name drug subject to NCE exclusivity for five years from the date the brand-name drug was approved for marketing. This period may be reduced to four years if the ANDA applicant challenges patents pertaining to the brand-name drug.⁹⁸

H.R. 1776 and S. 771 would instead allow the FDA to accept a generic drug application for the brand-name product three years after the brand-name product was approved. This earlier date would apply whether or not the ANDA applicant challenges any relevant patents. However, under

⁹⁶ P.L. 115-52 at §808.

⁹⁷ 21 U.S.C. §§355(j)(5)(F)(i), 355(j)(5)(F)(v).

⁹⁸ See C. Scott Hemphill & Mark A. Lemley, “Earning Exclusivity: Generic Drug Incentives and the Hatch-Waxman Act,” 77 *Antitrust Law Journal* (2011), 947.

this proposed legislation, the agency may not approve the ANDA until five years have passed since the brand-name product's approval date.⁹⁹

As noted earlier in this report, in select instances the practical effect of NCE exclusivity is to restrict a potential generic manufacturer from bringing a product to market for the period of NCE exclusivity—currently either four or five years—plus the length of the FDA review of the generic application. By reducing the period during which generic firms must wait before filing ANDAs, H.R. 1776 and S. 771 would potentially allow the FDA to approve generic drugs pertaining to NCEs more quickly.

This legislation would also reduce the regulatory exclusivity period for biologics from 12 to 7 years. This proposal is consistent with those previously made by the Obama Administration¹⁰⁰ and in legislation introduced in the 114th Congress.¹⁰¹

Entitlement to the Three-Year Clinical Investigation Exclusivity

This report previously described the four requirements that the Hatch-Waxman Act imposes upon an investigation for it to qualify for clinical investigation exclusivity. In particular, the study must be new; consist of a clinical study on humans; been “conducted or sponsored” by the applicant; and be “essential to the approval” of the application.¹⁰² H.R. 1776 and S. 771 would also limit the award of the three-year clinical investigation exclusivity to drugs that show “a significant clinical benefit over existing therapies manufactured by the applicant in the 5-year period preceding the submission of the application.”¹⁰³ This proposed additional requirement appears to address concerns that brand-name firms have obtained multiple awards on three-year clinical investigation exclusivity with respect to variations upon the same drug in order to thwart generic competition.

Termination of Regulatory Exclusivities

H.R. 1776 and S. 771 would also call for the termination of a regulatory exclusivity if its proprietor engages in one of certain specified activities, including adulteration, misbranding, illegally marketing a drug, making false statements to the FDA, or entering into an anticompetitive settlement of patent infringement litigation.¹⁰⁴

Abuse-Deterrent Opioids

The Abuse-Deterrent Opioids Plan for Tomorrow Act of 2017, H.R. 2025, would limit the scope of the three-year clinical investigation exclusivity with respect to section 505(b)(2) applications that relate to abuse-deterrent opioids. Firms have begun to market opioid formulations that deter abuse through physical or chemical barriers; antagonists that reduce the euphoria associated with abuse; additional substances that produce an unpleasant effect, such as nasal irritation, if the dosage is manipulated; and other techniques. Often these products involve the use of newer abuse deterrent technologies applied to a previously marketed opioid. In such circumstances, firms have

⁹⁹ H.R. 1776 at §303(a)(1), S. 771 at §303(a)(1).

¹⁰⁰ Office of Management and Budget, *Fiscal Year 2013 Budget of the U.S. Government*, p. 37.

¹⁰¹ H.R. 5573 in the 114th Congress.

¹⁰² 21 U.S.C. §355(j)(5)(F)(iii)-(iv).

¹⁰³ H.R. 1776 at §303(a)(2), S. 771 at §303(a)(2).

¹⁰⁴ H.R. 1776 at §304(a), §402; S. 771 at §304(a), §402.

used the section 505(b)(2) pathway to obtain FDA marketing approval. Under this approach, they rely upon the safety and efficacy studies associated with the old opioid, and then conduct additional clinical trials with respect to the newer abuse-deterrent formulation. If approved, the product includes labeling describing its specific abuse-deterrent properties.

Observers have criticized the impact of the three-year clinical investigation exclusivity in these circumstances. An example illustrates concerns that this exclusivity may be too generously awarded with respect to abuse-deterrence labeling.¹⁰⁵ Suppose that Company A files a 505(b)(2) application with respect to the combination of an old opioid in a nasal abuse deterrence formulation. Company A relies upon the safety and efficacy data generated years ago by sponsor of the old opioid and also conducts its own clinical trials with respect to its in-house nasal abuse deterrence technology. If the FDA approves the 505(b)(2) application, then it will award a three-year clinical investigation exclusivity with respect to the “condition of approval”—namely, the nasal abuse deterrence labeling.

Company B later also files a 505(b)(2) application with respect to the combination of the same old opioid and its distinct nasal abuse deterrence technology. In doing so, Company B relies upon the old opioid’s safety and efficacy data, along with its own clinical trials with respect to its abuse-deterrent formulation. Because the FDA has already approved Company A’s application with nasal abuse deterrence labeling, then the clinical investigation exclusivity owed to Company A would bar Company B’s application from FDA approval for three years. The clinical investigation exclusivity would apply even though the two abuse deterrence technologies may differ, and even though Company B did not in any way reference or otherwise rely upon Company A’s application.

To address this issue, H.R. 2025 would add the following language to the Federal Food, Drug, and Cosmetic Act:

A drug for which [a section 505(b)(2)] application ... is submitted shall not be considered ineligible for approval under this subsection on the basis that its labeling includes information describing the abuse-deterrent properties of the drug ... that otherwise would be blocked by [three-year clinical investigation] exclusivity ... if—

(I) the investigation or investigations relied upon by the applicant for approval of the labeling information were conducted by or for the applicant or the applicant has obtained a right of reference or use from the person by or for whom the investigation or investigations were conducted; and

(II) the drug has meaningful technological differences compared to the drug otherwise protected by exclusivity....¹⁰⁶

This amendment would affect any 505(b)(2) application filed on or after January 1, 2017.

Orphan Drugs

The Orphan Products Extension Now Accelerating Cures and Treatments Act (OPEN ACT) of 2017, S. 1509, would build upon the incentive structure of the Orphan Drug Act. The bill endeavors to encourage drug companies to repurpose existing medications in order to address rare diseases. That statute would require the FDA to extend by six months each existing exclusivity period for an approved drug or biological product when the product is additionally approved to

¹⁰⁵ This example is based upon the FDA approval of ARYMO ER. FDA, *Impact of Exclusivity on Approval of Arymo ER*, January 9, 2017, <https://www.fda.gov/Drugs/DrugSafety/ucm535708.htm>.

¹⁰⁶ H.R. 2025 at §2.

prevent, diagnose, or treat a new indication that is a rare disease or condition. The six-month extension would be cumulative with other sorts of regulatory exclusivity, such as pediatric or qualified infectious disease product exclusivity, that might apply to the product.¹⁰⁷

S. 1509 would also modify the Orphan Drug Act in one respect. The current statute explains that when a drug is subject to an orphan drug exclusivity, the FDA cannot approve the same drug made by another manufacturer for the same use, unless the original sponsor approves or the original sponsor is unable to provide sufficient quantities of the drug to the market.¹⁰⁸ S. 1509 would clarify that the orphan drug exclusivity also does not bar the FDA from approving a new, clinically superior drug with the same active ingredient that will be marketed for treatment of the same disease or condition.¹⁰⁹

Scope of the Clinical Investigational Exclusivity

Congress placed one limitation on the three-year exclusivity, as well as patents, that relate to the use of a drug in pediatric populations. As provided by 21 U.S.C. §355a(o)(1):

A drug for which an [ANDA] application has been submitted or approved ... shall not be considered ineligible for approval ... or misbranded ... on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by three-year exclusivity.

Stated differently, the statute permits generic drugs to omit pediatric labeling and therefore bypass relevant patents and the three-year clinical investigation exclusivity. The statute further requires the labels of generic drugs to indicate that they are not approved for pediatric use and provide a statement of any contraindications, warnings, or precautions that the FDA deems necessary.

Under current law, this possibility of a “labelling carve out” for pediatric indications applies only to ANDA applications. The OPEN ACT, S. 1509, would extend the scope of this exemption to include section 505(b)(2) applications.¹¹⁰

Concluding Observations

Congress has increasingly turned to regulatory exclusivities in order to encourage the development and distribution of new drugs. In comparison with the broadly oriented patent system, which pertains to virtually every innovative industry in the United States, regulatory exclusivities allow Congress to direct attention to more focused issues. This shift holds a number of implications for innovation and public health policy. In particular, the growing number of regulatory exclusivities has caused the FDA to move beyond its traditional focus upon food and drug safety, and instead become an agency that must administer numerous intellectual property rights. They have also created a more complex landscape of proprietary rights in the area of pharmaceuticals and biologics.

The ultimate assessment of regulatory exclusivities depends upon whether they have encouraged the discovery and public availability of new medicines. Orphan and pediatric drug exclusivity

¹⁰⁷ S. 1509 at §2(a).

¹⁰⁸ 21 U.S.C. §360cc(b).

¹⁰⁹ S. 1509 at §3(a).

¹¹⁰ *Ibid.* at §4.

have been widely lauded as successful programs,¹¹¹ although some observers have expressed concern over their operation.¹¹² More recently established exclusivities, such as those pertaining to enantiomers and qualified infectious disease products, have arguably not attracted the same level of interest from industry. Continued congressional monitoring may help ensure that regulatory exclusivities provide appropriate incentives for innovation in the crucial area of public health.

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¹¹¹ See Christopher D. Moen, “Helping “Orphans” Grow: Fostering Rare Disease Drug Development,” *Delaware Lawyer*, vol. 33 (Spring 2015), p. 24; U.S. Congress, House Committee on Energy and Commerce, *Evaluating the Effectiveness of the Food and Drug Administration Modernization Act*, 107th Cong., May 3, 2001 (including the testimony of Dr. Richard Gorman describing the pediatric testing provisions as “one of the most extraordinarily successful federal initiatives that have ever been accomplished for children.”).

¹¹² See Pamela Politis, “Transition from the Carrot to the Stick: The Evolution of Pharmaceutical Regulations Concerning Pediatric Drug Testing,” *Widener Law Review*, vol. 12 (2005), p. 271.; David Duffield Rhode, “The Orphan Drug Act: An Engine of Innovation? At What Cost?,” *Food and Drug Law Journal*, vol. 55 (2000), p. 125.