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The Role of Patents and Regulatory Exclusivities in Pharmaceutical Innovation

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January 15, 2014

Congressional Research Service
7-5700
www.crs.gov
R42890

CRS REPORT
Prepared for Members and
Committees of Congress

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Summary

In combination, patents and regulatory exclusivities provide the fundamental framework of intellectual property incentives for pharmaceutical innovation in the United States. Patents, which are administered by the United States Patent and Trademark Office (USPTO), provide their owner with the ability to exclude others from practicing the claimed invention for a limited time. In contrast, regulatory exclusivities are administered by the Food and Drug Administration (FDA). Alternatively known as marketing exclusivities, data exclusivities, or data protection, regulatory exclusivities establish a period of time during which the FDA affords an approved drug protection from competing applications for marketing approval.

Although patents and regulatory exclusivities are separate entitlements that are administered by different federal administrative agencies and that depend upon distinct criteria, they both create proprietary rights in pharmaceutical and biologics innovation. These rights allow innovators to receive a return on the expenditure of resources leading to a discovery. Once these proprietary interests expire, the marketplace for that drug is open to generic or follow-on competition.

Congressional interest in promoting both innovation and competition in the pharmaceutical industry has focused attention on both patents and regulatory exclusivities. For example, the 112th Congress proposed but did not enact the Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network Cures Act, or MODDERN Cures Act (introduced both as H.R. 3901 and H.R. 3116). This bill confronted policy makers with a debate previously conducted by legal academics over the relative role of patents and regulatory exclusivities in promoting pharmaceutical and biotechnology R&D. In addition, the Obama Administration has proposed a reduction in the regulatory exclusivity offered to brand-name biologic drugs to seven years, down from the 12 years incorporated in the Biologics Price Competition and Innovation Act of 2009 (enacted as Title VII of the Patient Protection and Affordable Care Act). Controversy has surrounded the award of regulatory exclusivities to colchicine, an ancient remedy for gout that was subject to the FDA's Unapproved Drugs Initiative.

International agreements require each World Trade Organization (WTO) member state to treat all patented inventions in the same manner. This rule seemingly prohibits discrimination both against and in favor of patents on drugs as compared to other technologies. As a result, regulatory exclusivities provide Congress with a more flexible option for stimulating specific sorts of desirable private activity than do patents. The WTO Agreements, as well as certain Free Trade Agreements to which the United States is a signatory, also obligate nations to provide some manner of protection to pharmaceutical test data. Discussion over the inclusion of regulatory exclusivity requirements within the Trans-Pacific Partnership (TPP) is ongoing.

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Background

Congressional interest in stimulating innovation within the pharmaceutical industry has been reflected in legislative activity in the areas of patent law and regulatory exclusivities. In particular, the 112th Congress enacted the Leahy-Smith America Invents Act, P.L. 112-29, which made numerous changes to the nation's patent laws. The 112th Congress also enacted the Food and Drug Administration Safety and Innovation Act, P.L. 112-144. That statute in part addressed so-called pediatric exclusivity and also allowed a "qualified infectious disease product" to be eligible for an extended period of regulatory exclusivity.[1]

In combination, patents and regulatory exclusivities create a relatively complex landscape of intellectual property rights intended to encourage firms to develop and market new drugs. Patents, which are administered by the U.S. Patent and Trademark Office (USPTO), provide firms with exclusive rights to an invention for a limited time in exchange for disclosure of the invention to the public. In contrast, regulatory exclusivities are administered by the Food and Drug Administration (FDA). They consist of a period of time during which the FDA affords an approved drug protection from competing applications for marketing approval.

Although regulatory exclusivities have been available within the healthcare industry for three decades, commentators have raised a number of innovation policy issues in this context. Some observers question the need for innovators to obtain both regulatory exclusivities and patents.[2] Others have expressed concern over the duration of particular regulatory exclusivities.[3] Issues have also arisen with respect to the use of regulatory exclusivities to encourage specific sorts of innovation and with the obligations of other nations to grant regulatory exclusivities in the manner of U.S. law.[4]

This report introduces and analyzes innovation policy issues concerning intellectual property rights in pharmaceutical innovation. It begins with a review of the policy and procedures relating to both patents and regulatory exclusivities. The report then discusses current domestic and international issues that exist at the intersection of these two proprietary rights. The report closes with a summary of congressional issues and potential alternatives.

Fundamentals of the Patent System

The Patent Act of 1952 (also known as the Patent Act) requires innovators to prepare and submit applications to the USPTO if they wish to obtain patent protection.[5] USPTO officials known as examiners then assess whether the application merits the award of a patent. In deciding whether

[1] P.L. 112-144 at §801.

[2] See Yaniv Heled, "Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?," 18 *Michigan Telecommunications and Technology Law Review* (2012), 419.

[3] See Benjamin N. Roin, "Unpatentable Drugs and the Standards of Patentability," 87 *Texas Law Review* (2009), 503.

[4] See Jerome H. Reichman, "Rethinking the Role of Clinical Trial Data in International Intellectual Property Law: The Case for a Public Goods Approach," 13 *Marquette Intellectual Property Law Review* (2009), 1.

[5] 35 U.S.C. §111.

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to approve a patent application, a USPTO examiner considers whether the submitted application fully discloses and distinctly claims the invention.[6]

The examiner will also determine whether the invention itself fulfills certain substantive standards set by the patent statute. To be patentable, an invention must consist of a process, machine, manufacture, or composition of matter that is useful, novel, and nonobvious.[7] The requirement of usefulness, or utility, is satisfied if the invention is operable and provides a tangible benefit.[8] To be judged novel, the invention must not be fully anticipated by a prior patent, publication, or other knowledge within the public domain.[9] A nonobvious invention must not have been readily within the ordinary skills of a competent artisan at the time the invention was made.[10]

If the USPTO allows the patent to issue, the patent proprietor obtains the right to exclude others from making, using, selling, offering to sell or importing into the United States the patented invention.[11] The term of the patent is ordinarily set at twenty years from the date the patent application was filed.[12]

Once a patent issues, its proprietor bears responsibility for monitoring its competitors to determine whether they are using the patented invention or not. Patent owners who wish to compel others to observe their intellectual property rights must usually commence litigation in the federal district courts.[13] The U.S. Court of Appeals for the Federal Circuit ("Federal Circuit") possesses exclusive national jurisdiction over all patent appeals from the district courts,[14] while the U.S. Supreme Court possesses discretionary authority to review cases decided by the Federal Circuit.[15]

Fundamentals of Regulatory Exclusivity

The U.S. government regulates the marketing of pharmaceuticals and agricultural chemicals in the interest of public health. Under this regime, 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.[16] This showing requires a sponsor to conduct both preclinical and clinical investigations of drugs that have not been previously tested.[17] In deciding whether to issue

[6] 35 U.S.C. §112.

[7] 35 U.S.C. §111.

[8] Ibid.

[9] 35 U.S.C. §102.

[10] 35 U.S.C. §103.

[11] 35 U.S.C. §271.

[12] 35 U.S.C. §154(a).

[13] 28 U.S.C. §1339(a).

[14] 28 U.S.C. §1295(a)(1).

[15] 28 U.S.C. §1254(1).

[16] 21 U.S.C. §355.

[17] Development and Approval Process (Drugs), Food and Drug Administration, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm.

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marketing approval or not, the FDA evaluates the test data that the sponsor submits in a so-called New Drug Application (NDA).[18]

The FDA maintains the test data incorporated into an NDA in confidence.[19] 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.[20]

Until 1984, federal law contained no separate provisions addressing 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."[21] 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.[22]

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 equivalents often causes prices to decrease, the interest of consumers was arguably not being served through these observed costs and delays.[23]

In response to these concerns, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984,[24] more commonly known as the Hatch-Waxman Act. This legislation created a new type of application for market approval of a generic drug. This application, termed an "Abbreviated New Drug Application" (ANDA), may be filed at the FDA.[25] 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

[18] 21 C.F.R. §314.50.

[19] 21 C.F.R. §20.61.

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

[21] See Colleen Kelly, "The Balance Between Innovation and Competition: The Hatch-Waxman Act, the 2003 Amendments, and Beyond," 66 *Food & Drug Law Journal* (2011), 417.

[22] 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.

[23] 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.

[24] P.L. 84-417, 98 Stat. 1585 (1984).

[25] 21 U.S.C. §355(j)(1).

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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.[26]

The Hatch-Waxman Act placed certain limits upon the ability of generic competitors to reference the data generated by the manufacturers 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.[27] 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, and biologics. This report will describe each of these regulatory exclusivities below.

Data Exclusivity Versus Market Exclusivity

Regulatory exclusivities are, regrettably, 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."[28] This report will instead follow the approach of a second group of writers who ascribe distinct meanings to these terms.[29] Under this 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.[30]

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.[31] The difference between data and marketing exclusivity is of greater moment to firms that can afford to generate their own data packages for submission to the FDA.

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[26] See Martin S. Masar III, "Effects of the Federal Circuit Judges on Hatch-Waxman Litigation," 19 *DePaul Journal of Art, Technology & Intellectual Property Law* (2009), 315.

[27] 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.

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

[29] 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.

[30] See McMahon, supra.

[31] See Rebecca S. Eisenberg, "The Role of the FDA in Innovation Policy," 13 *Michigan Telecommunications and Technology Law Review* (2007), 345.

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New Chemical Entity Exclusivity

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.[32] 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 approval of the NDA for that active moiety.[33]

A drug is judged to be an NCE if the FDA has not previously approved that drug's active ingredient.[34] 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.[35]

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 patents that the generic 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.[36] The apparent purpose of this provision is to allow additional time for brand-name and generic pharmaceutical firms to put their patent affairs in order prior to generic marketing.

The practical effect of NCE exclusivity is to restrict a potential generic manufacturer from bringing a product to market for 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.[37] In this respect NCE exclusivity operates differently from other forms of FDA-administered exclusivities. These exclusivities generally prevent the FDA from approving applications, rather than accepting them in the first instance.

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[32] 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.

[33] 21 U.S.C. §355(j)(5)(F)(ii).

[34] 21 C.F.R. §314.108(a).

[35] See Timothy A. Cook, "Pharmaceutical Patent Litigation Settlements: Balancing Patient & Antirust Policy Through Institutional Choice," 17 *Michigan Telecommunications and Technology Law Review* (2011), 417.

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

[37] See Joyce Wing Yan Tam, "Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation," 98 *Georgetown Law Journal* (2010), 535.

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New Clinical Study Exclusivity

In order to encourage improvements upon drugs that are already in use, the Hatch-Waxman Act also provided for a three-year new clinical study exclusivity period. New clinical study 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 new clinical study exclusivity for such changes as new dosage forms, new indications, or for a switch from prescription to over-the-counter status for the drug.[38]

The Hatch-Waxman Act imposes four requirements that an investigation must fulfill in order to qualify for new clinical study exclusivity.[39] 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. FDA regulations stipulate that an applicant that has provided "substantial support" for the investigation fulfills this requirement. The statement of a certified public accountant that the applicant provided 50% or more of the cost of conducting the study qualifies as substantial support, and the FDA will also entertain explanations of why the applicant should be considered to have "conducted or sponsored" the study if the applicant provided less than half of the funding for that study.[40]

Finally, the study must be "essential to the approval" of the application or supplement. 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 new clinical study exclusivity.[41]

As with NCE exclusivity, new clinical study exclusivity acts as data exclusivity.[42] It therefore does not preclude the FDA from approving a full NDA. If the sponsor of that 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, new clinical study exclusivity does not prevent the FDA from accepting a generic application with respect to the drug. If the new clinical study exclusivity continues to bar the issuance of marketing approval at the close of FDA review, the FDA will issue a tentative approval for the generic product that will become effective once the new clinical study exclusivity has run its course.[43]

In addition, new clinical study exclusivity only applies to the use of the product that was supported by the new clinical study. 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

[38] See Elizabeth H. Dickinson, "FDA's Role in Making Exclusivity Determinations," 54 *Food and Drug Law Journal* (1999), 195.

[39] 21 U.S.C. §355(j)(5)(F)(iii)-(iv).

[40] 21 C.F.R. §314.108(a).

[41] Ibid.

[42] See Anna B. Laakmann, "Collapsing the Distinction Between Experimentation and Treatment in the Regulation of New Drugs," 62 *Alabama Law Review* (2011), 305.

[43] See Dickinson, supra.

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that particular use or dosage form. The FDA is not barred from approving generic drugs for other indications or dosage forms.[44]

A drug product may be subject both to NCE exclusivity and new clinical study 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 exclusivities.[45]

Orphan Drug Exclusivity

In 1982, Congress enacted the Orphan Drug Act[46] 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. Congressional encouragement takes a number of forms under the Orphan Drug Act, including FDA protocol assistance, tax breaks, and a grants program through which researchers may compete for grants to conduct clinical trials to support the approval of orphan drugs.[47]

The most commercially significant of all of these benefits is a seven-year term of marketing exclusivity.[48] This period commences from the date the FDA issues marketing approval on the drug. The original version of the Orphan Drug Act extended marketing approval only to drugs that were not patented. However, Congress amended the statute in 1985 to provide for regulatory exclusivity both for patented and unpatented products.[49]

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. Orphan drug regulatory exclusivity applies only to the indication for which the drug is approved, however. 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.[50]

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 States of such drug."[51] In 1984, Congress changed the definition to its present form.[52] Currently, in order to qualify for orphan drug status, the drug must treat a rare disease or condition (1)

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[44] See Rebecca S. Eisenberg, "The Problem of New Uses," 5 *Yale Journal of Health Policy, Law and Ethics* (2005), 717.

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

[46] P.L. 97-414, 96 Stat. 2049 (1982).

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

[48] 21 U.S.C. §360cc.

[49] Orphan Drug Amendments of 1985, P.L. 99-91.

[50] 21 U.S.C. §360cc(b).

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

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

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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.[53] As can be appreciated, the effect of this change was to allow drug sponsors to avoid making a showing of unprofitability if the target population consisted of less than 200,000 persons.

The original version of the Orphan Drug Act allowed a sponsor to request orphan drug status at any time prior to FDA marketing approval. Congress amended the statute in 1988, however, to require that the sponsor make this designation request prior to the submission of an application for marketing approval.[54]

Biologics Exclusivity

The Biologics Price Competition and Innovation Act of 2009 (BPCIA), which was enacted as Title VII of the Patient Protection and Affordable Care Act, introduced new regulatory exclusivities for a category of biologically derived preparations known as "biologics." Biologics consist of such products as vaccines, antitoxins, blood components, and therapeutic serums.[55] For the most part, the FDA regulates biologics under Section 351 of the Public Health Service Act,[56] as compared to the Federal Food, Drug, and Cosmetic Act[57] 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).[58]

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."[59] Several Members of Congress

[53] 21 U.S.C. §360bb(a)(2).

[54] Orphan Drug Amendments of 1988, P.L. 100-290, 102 Stat. 90 (1988).

[55] 42 U.S.C. §262(i).

[56] This provision has been codified as 42 U.S.C. §262.

[57] P.L. 98-417, 98 Stat. 1585.

[58] 42 U.S.C. §262(k)(7).

[59] Dept. Health & Human Servs., FDA, "Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments," 75 *Federal Register* (Oct. 5, 2010), 61497.

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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 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.[60]

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."[61] A third letter from 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."[62] The FDA subsequently issued a draft guidance document that appeared to align the agency's view with that of the congressional correspondents.[63]

Pediatric Exclusivity

Brand-name firms may qualify for a six-month pediatric exclusivity upon the completion of studies on the effects of a drug upon children.[64] 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 (also known as the drug's "active moiety"). The purpose of the pediatric regulatory exclusivity is to improve the availability of appropriate pediatric labeling on drug products.[65]

Congress first established pediatric regulatory exclusivities with the Food and Drug Administration Modernization Act of 1997 (FDAMA).[66] Although the FDAMA included a sunset provision, Congress subsequently reauthorized these provisions.[67] In the 112th Congress, the Food

[60] 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).

[61] 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).

[62] 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).

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

[64] 21 U.S.C. §355a.

[65] 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.

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

[67] See Thomas, supra, at 461.

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and Drug Administration Safety and Innovation Act, P.L. 112-144, made the pediatric exclusivity permanent.[68]

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 regulatory exclusivity, Congress hoped to encourage additional pediatric testing, which in turn could allow medications to be labeled for use by children.[69]

Pursuant to its statutory authority, the FDA issues written requests to NDA applicants and holders 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 pediatric regulatory exclusivity.[70]

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.[71]

The effect of a pediatric exclusivity is to extend the approved manufacturer's existing regulatory exclusivity or patent protection for an additional six months. If the pediatric exclusivity applied to an orphan drug, for example, the result would be seven years and six months of marketing exclusivity; if applied to an NCE exclusivity, the drug's sponsor would obtain five years and six 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.[72]

Qualified Infectious Disease Products

Congressional concern over the spread of antibiotic-resistant "superbugs" recently 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.[73] That statute allows the FDA to designate a drug as a "qualified infectious disease product" (QIDP) if it consists of an antibacterial or antifungal

[68] P.L. 112-144 at §501.

[69] 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.

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

[71] 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.

[72] Ibid.

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

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drug intended to treat serious or life-threatening infections.[74] The GAIN Act stipulates that QIDPs include drugs that address drug-resistant tuberculosis, gram negative bacteria, and Staphylococcus aureus.[75]

Along with other measures intended to provide pharmaceutical and biotechnology companies with incentives to develop innovative antibiotics,[76] the GAIN Act adds five years to the term of the new chemical entity, new clinical study, and orphan exclusivities for any QIDP.[77] The statute stipulates that the five-year QIDP extension is cumulative with the pediatric exclusivity.[78] 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 ten years and six months.

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.[79] Generally speaking, this regulatory exclusivity precludes the FDA from approving another ANDA for the same product for the 180-day period.[80]

In addition, the Biologics Price Competition and Innovation Act of 2009 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 interchangeable with the brand-name product is entitled to a period of exclusivity before the FDA will make a determination of interchangeability 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.[81]

Innovation Policy Issues

The Term of Regulatory Exclusivities

The Obama Administration has proposed a reduction in the regulatory exclusivity offered to brand-name biologic drugs to seven years, down from the 12 years incorporated in the Biologics Price Competition and Innovation Act of 2009. The Obama Administration's Fiscal Year 2013

[74] 21 U.S.C. §505E(g).

[75] 21 U.S.C. §505E(f).

[76] See "Antibiotics Resistance Rising; Can New Drugs Keep Pace?", *BioWorld Insight* (September 17, 2012).

[77] 21 U.S.C. §505E(a).

[78] 21 U.S.C. §505E(b).

[79] 21 U.S.C. §355(j)(B)(iv).

[80] 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.

[81] 42 U.S.C. §262(k)(6).

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Budget asserted that the shorter periods of data exclusivity will "encourage faster development of generic biologics while retaining appropriate incentives for research and development for the innovation of breakthrough products."[82] This change would purportedly result in $4 billion in savings over 10 years to federal health programs including Medicare and Medicaid. This proposal has yet to be enacted.

Regulatory Exclusivity for Colchicine

Controversy surrounded the award of regulatory exclusivities to colchicine, an ancient remedy for gout that had been marketed for decades in the United States without FDA approval.[83] In 2006, the FDA launched an Unapproved Drugs Initiative to encourage manufacturers of old drugs that were sold prior to current premarket approval requirements to test the drugs for safety and efficacy and to seek formal agency approval.[84] The FDA had previously approved two combination products including colchicine as one of multiple ingredients, but had never approved a single-ingredient colchicine product.[85]

In response to the FDA request, one firm submitted NDAs for the use of colchicine to treat familial Mediterranean fever and acute gout flares. The FDA approved both applications and awarded seven years of orphan drug exclusivity for the use of colchicine to treat familial Mediterranean fever and three years of new clinical study exclusivity for the treatment of acute gout flares. The FDA subsequently announced its intention to take enforcement action against unapproved single-ingredient colchicine products.[86] With other suppliers removed from the market, the new sole provider reportedly increased the price of its colchicine product, Colcrys®, from $0.09 to $4.85 per tablet.[87]

As a practical matter, regulatory exclusivities ordinarily apply only to products that are coming to the market for the first time. The colchicine incident nonetheless illustrates that, unlike patent protection, regulatory exclusivities may be awarded to products that are not necessarily new or innovative. This case also illustrates the costs that regulatory exclusivities may impose upon patients and payors for drugs that might have been sold far more cheaply in a competitive market.

The MODDERN Cures Act

As a historical matter, patents have long served as a primary incentive for health care innovation in the United States. Regulatory exclusivities are a relatively more recent form of intellectual property right, first coming into being in the 1980s with the Orphan Drug and Hatch-Waxman

[82] Office of Management and Budget, *Fiscal Year 2013 Budget of the U.S. Government,* at 37.

[83] Aaron S. Kesselheim & Daniel H. Solomon, "Incentives for Drug Development—The Curious Case of Colchicine," 362 *New England Journal of Medicine* (2010), 2045.

[84] FDA, *Guidance for FDA Staff and Industry: Marketed Unapproved Drugs: Compliance Policy Guide* (2011), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070290.pdf.

[85] FDA, Letter to Gary L. Veron, Esq. from Janet Woodcock, Director, Center for Drug Evaluation and Research (May 25, 2011), available at http://www.regulations.gov/#!documentDetail;D=FDA-2010-P-0614-0072.

[86] FDA, "Single-Ingredient Oral Colchicine Products; Enforcement Action Dates," 75 *Federal Register* (October 1, 2010), 60768.

[87] Kesselheim & Solomon, supra.

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Acts. Because regulatory exclusivities have traditionally offered shorter periods of protection than the 20-year patent term, patents are often viewed as the principal R&D incentive mechanism for the pharmaceutical and biotechnology sectors. However, legislation has been introduced in the 112th Congress that would establish a distinct framework of innovation incentives that emphasizes regulatory exclusivity over patents.

Under the proposed Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act (MODDERN Cures Act) (introduced both as H.R. 3901 and H.R. 3116), a drug sponsor could submit a request to FDA for "dormant therapy" designation for a therapy that fulfills "one or more unmet medical needs."[88] The request must include a list of patents covering the therapy and a conditional waiver of the right to enforce those patents after the termination of regulatory exclusivity. If the FDA agrees that the indication for which approval is sought addresses an unmet medical need, it will grant the dormant therapy designation and the patent waiver will become effective. The sponsor then obtains 15 years of marketing exclusivity. All of the identified patents are given an extended term of up to 15 years after the product is approved, but pursuant to the patent waiver, the sponsor of the drug disclaims any patent term after the 15-year exclusivity period.[89]

The MODDERN Cures Act confronts policy makers with a debate previously conducted by legal academics over the relative role of patents and regulatory exclusivities in promoting pharmaceutical and biotechnology R&D. Regulatory exclusivity arguably provides a better temporal fit with the life cycle of a pharmaceutical or biologic product than does a patent. Regulatory exclusivity periods typically do not begin until a drug is on the market, while much or all of a patent term may run before the FDA grants marketing approval.[90] The scope of regulatory exclusivities may also correspond more closely to relevant product markets than do patents. Regulatory exclusivity tracks the terms of FDA product approvals, while patent claims, drafted to distinguish an invention from the prior art, may not correspond as closely to any actual commercial product.[91]

In addition, patents provide not so much the right to exclude as the right to sue to exclude.[92] Generic firms frequently make successful arguments that the brand-name firm's patents are invalid or not infringed. In contrast, regulatory exclusivity keeps competitors off the market without the need for patent owners to bring expensive and uncertain infringement lawsuits.

On the other hand, regulatory exclusivities arguably possess disadvantages in comparison to patents. For example, the U.S. Supreme Court recently explained that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts."[93] Yet as suggested by the colchicine incident, regulatory exclusivities are available for old products based upon the completion of routine clinical trials that would not qualify for additional patent rights. Denying patent rights to "ordinary innovation" in order to promote progress seems inconsistent with granting analogous protection via regulatory exclusivity in the context of drug testing.

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[88] See §201(a) of both bills.

[89] Ibid., at §201(i).

[90] Eisenberg (2007), supra.

[91] Ibid.

[92] Mark A. Lemley & Carl Shapiro, "Probabilistic Patents," *Journal of Economic Perspectives* (Spring 2005), 75.

[93] KSR International Co. v. Teleflex Inc., 550 U.S. 398, 427 (2007).

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Regulatory exclusivities may also place public health officials in the potentially uncomfortable position of denying patients access to safe and effective generic substitutes for unpatented medications. They require the FDA to devote considerable time and effort towards drafting regulations, issuing guidance documents, and adjudicating disputes involving multiple regulatory exclusivity regimes.[94] These resources might be more effectively spent in pursuit of the agency's core mission of protecting public health.

International Issues

The agreements comprising the World Trade Organization (WTO) impose certain requirements with respect to both patents and regulatory exclusivities. The WTO Agreement on Trade-Related Aspects of Intellectual Property (TRIPS Agreement) requires signatories to provide patent protection "without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced."[95] This provision in part required WTO member states to eliminate provisions in their national laws that disallowed patents on pharmaceutical products. But the TRIPS Agreement apparently prohibits discrimination in favor of pharmaceutical patents as well as against them.

The TRIPS Agreement also requires each WTO member state to establish protections for pharmaceutical test data under certain conditions. Article 39.3 of the TRIPS Agreement specifically provides:

> Members, when requiring as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use.

Some commentators have observed that Article 39.3 establishes broad parameters using vague language. In particular, terms such as "new chemical entities," "considerable effort," and "unfair commercial use" receive no further definition within the TRIPS Agreement. As a result, some debate has occurred over the precise nature of the obligations Article 39.3 imposes upon WTO member states.[96]

Perhaps given the uncertainties with respect to Article 39.3 of the TRIPS Agreement, the United States has entered into certain Free Trade Agreements (FTAs) that require signatories to provide five years of regulatory exclusivity for pharmaceuticals that utilize new chemical entities. For example, Article 15.10:1(a) of the Dominican Republic-Central America-United States FTA provides:

> If a Party requires, as a condition of approving the marketing of a new pharmaceutical or agricultural chemical product, the submission of undisclosed data concerning safety or efficacy, the Party shall not permit third persons, without the consent of the person who

[94] Eisenberg (2007), *supra*.

[95] Agreement on Trade-Related Aspects of Intellectual Property Rights, April 15, 1994, Annex 1C, 33 I.L.M. 1197 (1994), Art. 27.

[96] See Trudo Lemmens & Candice Telfer, "Access to Information and the Right to Health: The Human Rights Case for Clinical Trials Transparency," 38 *American Journal of Law & Medicine* (2012), 63.

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> provided the information, to market a product on the basis of (1) the information, or (2) the approval granted to the person who submitted the information for at least five years for pharmaceutical products and ten years for agricultural chemical products from the date of approval in the Party.

The term "new product" is generally defined as "one that does not contain a chemical entity that has been previously approved in the territory of the Party."[97]

More recently, the United States has entered into negotiations with respect to the Trans-Pacific Partnership (TPP), a multilateral free trade agreement that aims to liberalize trade within the Asia-Pacific region. The TPP reportedly calls for its signatories to adopt a period of exclusivity for biologics. Some Members of Congress have encouraged U.S. negotiators to incorporate a 12-year period of exclusivity that would align the TPP with the Biologics Price Competition and Innovation Act of 2009.[98] However, other Members of Congress have expressed concern over the impact of regulatory exclusivity provisions in the TPP on healthcare in developing countries.[99]

Concluding Observations

In combination, patents and regulatory exclusivities provide the fundamental framework of intellectual property incentives for pharmaceutical innovation in the United States. Due to the TRIPS Agreement's obligation of technological neutrality with respect to the patent system, regulatory exclusivities provide Congress with a more adaptable option for stimulating specific sorts of hoped-for private activity than do patents. As such, regulatory exclusivities have been, and likely will continue to be, the most widely used option for encouraging the development of discrete classes of products regulated by the FDA.

The potential for expanded use of regulatory exclusivities in turn raises a number of innovation policy issues. In the United States, regulatory exclusivities are viewed primarily as supplementing patent protection, in that they provide more limited protections for inventions that do not meet Patent Act requirements, or effectively delay the onset of patent litigation for inventions that do. Expanding the availability of regulatory exclusivities, in addition to lengthening their term, increases the possibility that regulatory exclusivities will trump patents as the primary form of intellectual property protection for certain FDA-regulated products.

The decision to supplant the primacy of the current regime of USPTO-procured and judicially enforced patent rights with a system of automatic, FDA-administered regulatory exclusivities presents a number of trade-offs that policy makers may wish to consider. Among them are the impact of the contemplated exclusivity periods upon incentives for pharmaceutical innovation; the cost and availability of medications to consumers; the desirability of individualized determinations about the technical merits of the pharmaceutical invention; the expense and uncertainty of patent enforcement proceedings; and whether the USPTO or FDA is the better institution for awarding proprietary rights to pharmaceutical innovators.

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[97] Dominican Republic-Central America-United States Free Trade Agreement, January 1, 2006, 119 Stat. 462, at Chapter 15, footnote 15.

[98] Letter from Senators Patty Murray and Maria Cantwell to President Barack Obama (July 12, 2012) (available at http://www.hpm.com/pdf/blog/WA%20TPP%20letter.pdf).

[99] Letter from Rep. Jan Schakowksy et al., to Ambassador Ron Kirk, Office of the U.S. Trade Representative (August 2, 2011) (available at http://infojustice.org/wp-content/uploads/2011/08/Ten-Representatives-on-TPP-08022011.pdf).

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International harmonization provides another significant issue with respect to regulatory exclusivities. While some observers have expressed concerns over the use of free trade agreements to encourage trading partners to establish longer regulatory exclusivity periods, others believe that doing so lies in the best interest of the United States. Future dialogue may concern setting global regulatory exclusivity standards in view of national goals and priorities.

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