

Determinants of Market Exclusivity for Prescription Drugs in the United States

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The high prices of brand-name prescription drugs are a growing source of controversy in the United States. Manufacturers of brand-name drugs can command high prices because they are protected from generic competition by two types of government-granted monopoly rights. The first are patents on the drugs that generally define the basic period of brand-name-only sales. The second is awarded at the time of US Food and Drug Administration (FDA) approval and usually defines the minimum time until a generic can be sold. The initial patents last for 20 years and may be extended to account for time spent in clinical trials and regulatory review; other laws prevent approval of other manufacturers' versions of new drugs for about 6 to 7 years, and for new biologics for 12 years. Overall, most new drugs receive about 12 to 16 years of market exclusivity from both kinds of monopoly protection combined. We reviewed the peer-reviewed medical and health policy literature to identify studies that described the different types of patent protection and regulatory exclusivities that shield brand-name prescription drugs from competition and thus help to sustain high drug prices. We also identified potential policy reforms intended to modify exclusivity periods to address public health needs by balancing drug affordability and industry revenue. The goal of policy in this area should be to ensure that drug market exclusivity periods provide for fair return on investment but do not indefinitely block availability of lower-cost generic drugs.

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High prices for brand-name prescription drugs are made possible in large part by government-granted monopolies that protect companies from generic competition in 2 ways: patents (defining the basic market exclusivity period) and regulatory exclusivity (defining the minimum time before another manufacturer's version can be approved). In this article, we review the laws and regulations that protect brand-name manufacturers from competition in these ways, as well as various policy proposals intended to adjust those time periods to help make drugs more affordable to patients and health care systems.

Spending on prescription drugs in the United States reached over \$450 billion in 2015, accounting for about 17% of total health care spending.¹ Net spending on pharmaceuticals has increased 42% since 2006,² and current per capita spending for US patients far outpaces that in other high-income countries around the world.^{3,4} The high price of brand-name drugs is an important reason for rising pharmaceutical expenditures. Though comprising only about 10% all dispensed prescriptions, brand-name drugs account for 72% of drug spending.⁵ One analysis found that a group of commonly used brand-name drugs increased in price by 164% from 2008 to 2015.⁶ High prices make drugs less affordable for patients, thus contributing to reduced patient adherence and worse health outcomes.⁷

Manufacturers of brand-name drugs can command high prices because they are protected from competition by legally mandated monopolies or market exclusivity periods.² After these periods end, generic drugs, which are interchangeable and usually cost much less, can

enter the market. With generic competition, the prices of drugs are usually closer to the cost of production.^{8,9} Such exclusivities are defined both by patent law and other laws that block generic or biosimilar drug approval by the US Food and Drug Administration (FDA). The approach to determining drug prices in the United States differs from that in virtually every other nation with an advanced industrial economy, where prices are determined in large part by negotiation between the manufacturer and the government or other payor.

We reviewed the peer-reviewed medical and health policy literature from January 2006 to December 2016 to identify articles describing prescription drug market exclusivity periods, determinants of their length, and their effects on drug costs, patient access, and related health outcomes. We identified additional articles from the listed references. We also reviewed recent prominent proposals designed to reduce or extend these exclusivity periods.

Patent Exclusivity

The US government awards pharmaceutical manufacturers 2 forms of monopoly protection against competition: patent protection, which dates back to the Patent Act of 1790,¹⁰ and protection against the sale of interchangeable generic drugs, enforced by the FDA (also called regulatory exclusivity, which applies to all new drugs regardless of whether they are covered by patents). Patent protection is usually the longer of the 2 and therefore defines the basic duration of such

monopoly rights for most drugs.¹¹ Patents are government-enforced rights that were put in place to encourage and reward innovation. They allow the patent holder to exclude others from making, using, or selling the invention described in the patent for 20 years from the filing date, which in the case of drugs usually occurs around the date of first synthesis or discovery of the product.¹² The original intention of the framers of the Constitution was to encourage innovation by providing legal protection for an inventor to reward and incentivize their work, while putting a limit on that protection to eventually make the discovery more readily available to the public.¹³ In the pharmaceutical market, patents are considered essential to provide sufficient return on investment in drug development, which can take many years.¹³

Although in recent years the US Patent and Trademark Office has been reported to be more stringent in its patent review process,¹⁴ the issue of what chemical or biological products merit initial patent protection remains controversial. Patents on a new drug are usually obtained close to the time of discovery or initial synthesis; it can then take a number of years to complete preclinical research, with an additional 5 to 7 years for clinical trials.¹⁵ As a result, pharmaceutical manufacturers typically would have considerably less than 20 years remaining on their original patents if and when their drugs reach the market.¹⁶ Importantly, the original patent is rarely the last one that covers the drug to expire. Drug manufacturers often obtain patents that cover methods of manufacturing a drug or its use in clinical care; such patents, known as "secondary patents," can significantly extend a product's market exclusivity period.

In principle, a patent should be issued only for a new product that is a "nonobvious" advance over already-described products. However, this has led to controversy over the US Patent and Trademark Office authorizing patent protection for products such as esomeprazole (Nexium; AstraZeneca). Esomeprazole is simply the S-isomer of an existing product, omeprazole (Prilosec; AstraZeneca), with no compelling clinical advantage. Yet this new patent protection allowed it to become a separate multibillion-dollar per year blockbuster drug with a patent life of its own.

Patent Term Restoration

The Hatch-Waxman Act of 1984 was designed to facilitate the market entry of generic drugs as well as to compensate pharmaceutical manufacturers for the time involved in clinical testing by creating a period of patent term restoration.¹⁷ This Act permitted pharmaceutical manufacturers to petition the government to extend the term of one key patent by one-half the time from the initiation of clinical trials to the filing of the new drug application (NDA), plus the full time the FDA took to review the NDA. Patent term restoration is capped at 5 years and the resulting patent term cannot extend more than 14 years after the date of the drug's FDA approval for the basic patent.¹⁸

Pediatric Exclusivity

In the 1990s, there was concern that many drugs were being widely prescribed to children even though they had never been formally tested in that age group. The FDA sought to have companies study their approved drugs in children; manufacturers argued that they had no legal obligation to do so but might perform these trials if provided with sufficient economic incentive. As a result, in 1997, Congress enacted legislation that awarded 6 additional months of patent protection, added to existing market exclusivity periods, for the success-

Key Points

Question How is the market exclusivity period for brand-name prescription drugs defined?

Findings Brand-name prescription drug market monopoly periods are usually defined both by patents and regulatory exclusivity earned at the time of approval by the US Food and Drug Administration (about 6-7 years or 12 years for new biologics). In total, most new drugs receive about 12 to 16 years of market protection from the time of US Food and Drug Administration approval.

Meaning Government-granted market exclusivity protection for brand-name prescription drugs prevent entry of low-cost generic drugs and therefore allow manufacturers to set high prices, recoup their investments, and earn profits. These are hotly contested decisions, with considerable pressure from interested groups. Policy makers frequently try to lengthen these periods to increase pharmaceutical company revenues with the hope that some of these increased revenues will eventually lead to more research and innovation.

ful completion of pediatric trials.¹⁹ Although additional trials may lead a single drug to obtain multiple new pediatric indications, only one 6 month pediatric extension is awarded per drug, which is added to the end of existing market exclusivity periods. The 2002 Best Pharmaceuticals for Children Act continued and modified this additional period of patent protection, and the program was made permanent in 2012.²⁰ Hundreds of drugs have been granted pediatric exclusivity since the program was created.²¹ One study²² found that, of nearly 200 drugs studied in pediatric populations between 1998 and 2012, 57% resulted in new or expanded pediatric indications for the drugs being studied, although the clinical utility of some of the trials conducted to earn the extension has been criticized.²³

Pediatric exclusivity, however, is a very costly means of ensuring that the needed clinical research in children is performed. An analysis found that the revenues collected because of the additional monopoly protection granted to manufacturers from pediatric exclusivity far exceeded their cost for performing these trials; the net economic benefit was \$134 million per drug (range, -\$9 million to \$508 million), a profit ratio of more than 10 to 1.¹⁷

Patent Challenges

A generic manufacturer is expected to wait for the expiration of any patents on FDA-approved drugs before it can market its competing product. Alternatively, a generic manufacturer can certify that its version of the drug either does not infringe these patents, that the patents were invalid, or both.²⁴ The response to such a certification (called a Paragraph IV certification) is usually a lawsuit from the manufacturer of the brand-name drug.²⁵ If the patent is invalidated in the subsequent litigation, generic entry into the market can commence. The first generic manufacturer to successfully challenge a patent for a brand-name drug in this way obtains a special 180-day period of generic exclusivity as the sole competitor on the market. If the legal proceedings continue for more than 2.5 years, generic manufacturers are permitted to enter the market at that point. During the duopoly period after a successful challenge, drug prices usually do not fall substantially because the sole generic competitor lacks a sufficient incentive to lower its price.^{26,27} Typically, generic drug prices decrease only with the entry of multiple new competitors²⁸: according to data

from the FDA, 2 competitors decrease the price to about 55% of the brand-name price, with further decreases to 33% with 5 generic competitors and 13% with 15 competitors.²⁹

Summary

The duration of monopoly protection for a branded drug through patent laws depends on the time remaining on its initial patents after the drug is approved. This time can be extended by patent term restoration and a 6-month exclusivity for conducting trials in children. Additional patents granted on other aspects of a drug, such as its mechanisms of use or the pill coating, can further extend this period of protection.³⁰

Regulatory Exclusivity

Market-wide regulatory exclusivity has its origins in the Hatch-Waxman Act of 1984, which created a pathway for abbreviated testing and FDA review for approval of low-cost generic drugs.³¹ As part of a political compromise with the brand-name drug industry, the Hatch-Waxman Act also instituted a guaranteed period of time for all newly approved drugs after FDA approval in which a generic version cannot be approved no matter how much time is left on a drug's patent.³² Regulatory exclusivity therefore provides the minimum bound of a prescription drug's competition-free period.³³

This regulatory exclusivity period was set at 5 years after approval for new drugs.³⁴ The 5-year mark, however, represents the first date generic drug manufacturers can submit their applications; marketing approval is typically not granted for another year or more. From 2015 to 2016, the FDA reported that it provided an initial response to such generic drug applications by about 15 months after submission (though final approval may take more time).³⁵ Thus, manufacturers of brand-name drugs usually have a minimum of 6 years or more of regulatory exclusivity for new drugs.

An exception is generic manufacturers that submit a patent challenge; they can file for approval after only 4 years.³⁶ Such patent challenges, however, are often subject to lengthy litigation, although generic manufacturers can enter the market if the litigation extends past 2.5 years, as discussed above.³⁷ In recent years, many such challenges have led to financial settlements between the brand-name and generic manufacturers, which a generic manufacturer receives payment from the brand-name manufacturer and in exchange agrees to withhold its marketing of a generic competitor (so-called "pay for delay" arrangements).³⁸

The Hatch-Waxman Act also created additional 3-year exclusivity periods for drugs on which a brand-name manufacturer conducts new studies of small differences in the products, such as new formulations or dosages, or new uses for the products. Unlike the 5-year exclusivity period for new drugs, generic manufacturers can be ready to sell their versions as soon as the 3-year period ends.

Antibiotics

In 2012, Congress approved the Generating Antibiotic Incentives Now (GAIN) Act,³⁹ which provides incentives for the development of new antibiotics based on the FDA awarding a Qualifying Infectious Disease Product (QIDP) designation. Under the GAIN Act, products intended to treat certain pathogens of high public health importance, such as methicillin-resistant *Staphylococcus aureus* (MRSA)

and multidrug resistant gram-negative bacteria, could earn the QIDP designation, which includes the potential for expedited regulatory review in addition to 5 additional years of regulatory exclusivity. The 5 years would be added to the original Hatch-Waxman Act regulatory exclusivity period, thus providing new antibiotics with a minimum market exclusivity of at least 10 years. Of 109 QIDP requests from July 2012 to December 2015, the FDA granted 101.⁴⁰

Biologic Products

Biologic products represent some of the most important therapeutic advances in recent years, such as the anemia treatment epoetin α (Epogen; Amgen) and infliximab (Remicade; Janssen Biotech, Inc) for rheumatoid arthritis. These products can be more expensive to produce than small-molecule drugs, and spending on biologic therapeutics by patients and payors has accounted for a growing share of drug costs. The regulatory exclusivities for drugs in the Hatch-Waxman Act applied to small-molecule drugs rather than to these newer products, and there was no abbreviated pathway to approval for follow-on versions of biologics, known as "biosimilars."⁴¹ This changed with the passage of the Biologics Price Competition and Innovation Act (BPCIA) in 2010 as part of the Affordable Care Act,⁴² which created a biosimilar approval pathway modeled after Hatch-Waxman.⁴³

In contrast to the 5 years of protection granted for new drugs, the BPCIA provided originator biologic manufacturers with a guaranteed regulatory exclusivity period of at least 12 years.⁴⁴⁻⁴⁶ Follow-on biologic manufacturers are permitted to submit abbreviated applications starting at year 4 after approval of the originator product.⁴⁷ The BPCIA also included provisions intended to prevent awarding of 12-year regulatory exclusivity periods to noninnovative products, such as those merely based on structural modifications to previously approved biologics.^{48,49} Once fully implemented, the new pathway could contribute to some reductions in spending on biologic drugs, although its utilization has been modest thus far. In Europe, widespread use of biosimilar products has occurred with little to no evidence of diminished clinical benefit or increased risk and has led to substantial cost savings, although the marketplace for pharmaceutical reimbursement in Europe is much different than in the United States.⁵⁰

Orphan-Designated Drugs

Prior to the mid-1980s, there was concern that the business model of the pharmaceutical industry provided little incentive to develop drugs for rare conditions that had small markets providing less opportunity for revenues. To address this concern, the Orphan Drug Act of 1983 created a special designation for such drugs—later defined as treatment for conditions with an annual prevalence of fewer than 200 000 people in the United States.^{51,52} Among the incentives provided was a guarantee of 7 years of market exclusivity from the date of FDA approval. This 7-year period is granted separately from and runs concurrently with other regulatory exclusivities. In 2016, 41% of new drug approvals had received an Orphan Drug Act designation.⁵³ Orphan-designated drugs can still be among top revenue-generating drugs on the market; for example, imatinib (Gleevec; Novartis), approved to treat 7 rare cancers, earned over \$4.5 billion in revenues in 2015 alone. The emerging capacity to define specific genotypes of common conditions, such as lung cancer, increases the possibility that treatments for subtypes of conditions that are not rare will soon meet the criteria for a rare disease and be granted orphan status.

Exclusivity under the Orphan Drug Act is stronger than a patent because it cannot be truncated in court. But this exclusivity is also narrower because it applies only to the approved use of the product for a given orphan-designated indication. As a result, in theory, a drug could be first approved for a rare disease indication as well as a common disease indication at the same time, and a generic manufacturer could seek approval to market a version of the drug only for the common condition before expiration of the orphan drug exclusivity for the rare disease indication. In such a case, physicians could then prescribe the generic formulation off-label for the rare disease indication.⁵⁴ This chain of events has not happened for a new drug, but it could prevent manufacturers from obtaining orphan drug exclusivity for a supplemental indication late in a drug's market exclusivity period and delaying generic entry.⁵⁵ For example, AstraZeneca was unsuccessful when it tried this strategy after receiving approval for its cholesterol-lowering drug rosuvastatin (Crestor) to treat familial homozygous hypercholesterolemia, a rare condition, in the months leading up to loss of market exclusivity for its main indications, primary hypercholesterolemia and mixed dyslipidemia.⁵⁶

Summary

Regulatory exclusivity for prescription drugs is a form of monopoly protection awarded at the time of FDA approval and prevents the introduction of lower-cost generic competitors regardless of any patents covering the drug. At present, regulatory exclusivity establishes a market exclusivity floor for new drugs of about 6 to 7 years and for new biologics of 12 years.

Total Market Exclusivity Time

One study⁵⁷ of drugs approved between 2001 and 2010 found the average duration of patent exclusivity was 15.9 years; by comparison, the average market exclusivity periods—that is, the time until a generic drug was introduced—for those same drugs was 12.2 years, with successful patent challenges primarily accounting for the difference. This estimate of total market exclusivity duration is compatible with results from 2 other recent studies.^{58,59} The first was a review of the total of patents, patent term restoration, and market exclusivity extensions for a sample of widely used drugs from 2000 to 2012 that found a median (interquartile range [IQR]) exclusivity duration of 12.5 (8.5-14.8) years⁵⁸; a subsequent study had similar findings for drugs approved from 1995 to 2014.⁵⁹

Evidence shows that the current system favors innovative, first-in-class therapeutics, which earn more market exclusivity time. For first-in-class therapeutics, the median (IQR) exclusivity period was 14.5 (13.3-15.8) years.⁵⁷ Such longer exclusivity periods are likely attributable in part to various pathways the FDA offers⁶⁰ to expedite the development or review of innovative new drug products, permitting the drugs to reach the market with more time remaining on their original patents. They may also be attributable to the greater strength of patents covering more novel products in the face of patent challenges.

Changes to Market Exclusivity Periods

Extending or strengthening market exclusivity periods can provide incentives for certain types of drug development. This was the rationale for pediatric exclusivity and the Orphan Drug Act and has been the ba-

sis for other more recent proposals as well (Table). Advocates for longer periods of government-granted monopolies for the marketing of new drugs argue that the potential for financial benefit from longer periods of exclusivity is necessary to encourage additional investment in drug discovery and development. Critics argue that the current situation is overly generous to the already-lucrative biotechnology and pharmaceutical industries. Moreover, critics argue that further expansion of market exclusivity could discourage innovation if it served to reward continued marketing of older drugs rather than the discovery and marketing of new drugs that provide meaningful therapeutic advances to patients. A separate objection relates to the fact that current exclusivity arrangements, combined with other federal and state rules that require public and private insurers to include certain drugs on their formularies,⁶¹ reduce payor ability to effectively negotiate lower drug prices.⁶²

For certain drug classes, adjustments to the regulatory exclusivity floor may have little practical effect. For example, the antibiotic exclusivity extension in the GAIN Act added 5 years to existing regulatory exclusivity periods as an incentive to develop new antibiotics. But since the average total market exclusivity time was already about 12 to 13 years—and was 14 years (IQR, 10.4-16.0 years) for top-selling anti-infectives and antifungals⁴⁴—such an alteration is unlikely to have affected manufacturers' investments in antibiotic research. Some have suggested extending regulatory exclusivity for small molecule drugs to 12 years,⁶³ although such a move would be much more likely to offer market protection to less innovative drugs.

Similarly, proposals to decrease the regulatory exclusivity period may not facilitate price reductions. Reducing the 12-year regulatory exclusivity period afforded to biologic products has been widely discussed, with some estimates that such a move could reduce drug spending by \$7 billion cumulatively from 2017 to 2026.⁶⁴⁻⁶⁶ However, manufacturers considering the development and marketing of biosimilar products would still have to contend with the patents covering innovator biologic drugs.⁶⁷ Indeed, delays in introducing the first wave of biosimilars in the US market have stemmed in part from ongoing litigation over the patents remaining on innovator products approved by the FDA in the 1980s and 1990s.⁶⁸

In 2017, legislation seeking to speed generic competition (the Improving Access to Affordable Prescription Drugs Act) would make specific changes to the regulatory exclusivity rules, such as allowing earlier submissions by generic manufacturers for tentative approval, prior to the 5-year mark for small-molecule drugs.⁶⁹ Patents lasting considerably longer than 5 years, however, cover most new drugs. Thus, the practical impact of such a change would likely be limited. The legislation would also require manufacturers seeking the additional 3-year exclusivity period under Hatch-Waxman for new trials related to changes in already-approved drugs, such as a new formulation or strength, or a new use of the product, to demonstrate enhanced efficacy over the prior version.⁶⁹

In general, extending market exclusivity by expanding the period of patent protection is a more powerful means of preventing the entry of generic drugs than changes to regulatory exclusivity. However, proposals to extend patent protection also risk overcompensating manufacturers for the actual investments they have made. For example, one proposal would have provided a 6-month patent extension for manufacturers that receive supplementary approvals for rare diseases.⁷⁰ A recent study⁷¹ concluded that a manufacturer's median net return per drug would have been \$82.4 million, with higher returns for drugs with higher annual sales, far surpassing the actual cost of conducting the trials.

Table. Policy Proposals Affecting Market Exclusivity Periods for Prescription Drugs

Proposal	Source/Status	Details
Extending Market Exclusivity		
Patent extension voucher	21st Century Cures “discussion draft” (proposal removed before final law enacted).	Would create a voucher worth 12 additional months of exclusivity earned based on approval of a qualified infectious disease product. This can be transferred (sold) to another company for use with a different drug of its choice.
Guaranteed protection for dormant therapies	First introduced in the Modernizing Our Drug & Diagnostics Evaluation and Regulatory Network Cures Act of 2013 and the Dormant Therapies Act of 2014, then included in the 21st Century Cures “discussion draft” (proposal removed before final law enacted).	15 Years of regulatory exclusivity offered to repurposed products lacking patent extension that treat unmet medical needs. To receive exclusivity, the sponsor would agree to waive patent rights to the drug.
Regulatory exclusivity extension for drug modifications	Promoting Access for Treatments Ideal in Enhancing New Therapies Act of 2015, 21st Century Cures “discussion draft” (proposal removed before final law enacted).	2 Years of additional regulatory exclusivity on top of 3-year period normally granted to modified formulations of a drug if there is some evidence of improvement in safety or efficacy (eg, improve adherence, decrease abuse, or make the drug safer to take).
6-Month patent extension for rare disease approvals	First introduced in the Orphan Product Extensions Now Accelerating Cures and Treatments Act of 2014, later included in 21st Century Cures Act of 2015 (H.R. 6), but not in final version. Filed as an amendment to FDA Reauthorization Act of 2017 but not offered during Senate committee debate.	6-Month patent extension for drugs approved for a new rare disease indication.
5-Year “new drug” exclusivity for fixed-dose combination drugs	Combination Drug Development Incentive Act of 2013 (reintroduced in 2015).	Allows a 5-year period of market exclusivity to combination drugs, even if all the components are already generic, as long as they present reports of new clinical studies essential to approval of the application.
Reducing Market Exclusivity		
Change market exclusivity for biologic drugs (domestic policy)	Obama administration budgets to Congress (2012-2016) but edited out of all final budgets; Price Relief, Innovation and Competition for Essential Drugs Act of 2016; Improving Access to Affordable Prescription Drugs Act (Introduced in Senate in 2017).	Would have cut the exclusivity period on biologics from 12 to 7 y.
Change market exclusivity for biologic drugs (international policy)	Trans-Pacific Partnership (United States withdrew in January 2017).	Would have required the United States to reduce its exclusivity period for biologics to between 5 and 8 years.
Small changes to rules for implementing or earning regulatory exclusivity	Improving Access to Affordable Prescription Drugs Act (introduced in Senate in 2017).	Allows FDA to accept generic drug applications after three years rather than five (maintains market exclusivity at five years) and requires a manufacturer seeking the 3-year New Clinical Investigation Exclusivity to show significant clinical benefit over existing therapies.

Abbreviation: FDA, US Food and Drug Administration.

Though others have countered that this short-term perspective on financial returns ignores the long-term cost savings (including lives saved) of an orphan drug extension,⁷² it is important to ensure that proposals to extend patent protection are narrowly tailored to achieve their desired goals.

Conclusions

The market exclusivity protections offered to prescription drugs are intended to provide manufacturers with exclusive rights to

the marketing of their products for a defined period of time, during which they charge higher prices, recoup their investments in research and development, and earn profits. When the monopoly period expires, generic competition allows the public to gain wider access to the drugs, usually at a considerably lower cost. At that point, to maintain their revenue streams, manufacturers of brand-name drugs must develop and market new products. Public policy for prescription drugs in the United States should strike a balance between rewarding past innovations, while also ensuring the affordability of this very important component of patient care.

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