

## PRICING ORPHAN DRUGS

A 1983 law created incentives to develop drugs to treat rare diseases that might otherwise not justify commercial investment.

Many of the drugs developed by companies relying on incentives created by the Orphan Drug Act have high prices. This has made the law controversial, though the relationship between those high prices and the incentives in the law is not always clear. One prominent incentive in the Act is a special period of market exclusivity that prohibits the Food and Drug Administration (FDA) from approving a competing version of the drug for seven years—in essence, a statutory protection that increases pricing power for a drug marketer. In some prominent cases, however, the orphan drug exclusivity has been used to provide protection for drugs that have been available in unapproved forms for many years. The resulting increase in the price of those products has garnered significant attention from policy makers and the public.

### Background

The [Orphan Drug Act of 1983](#) created a class of therapies defined not by biology or medical specialty, but by the prevalence of the treated condition in the population. The act was driven by concern that pharmaceutical companies would not develop drugs to treat diseases with a small number of patients and therefore a limited commercial market. Examples of diseases to which the Orphan Drug Act applies include cystic fibrosis and muscular dystrophy.

The law established economic incentives—including tax credits, research grants, and special market exclusivity protections—to encourage drug developers to invest in drugs for rare diseases. Market exclusivity was believed to be particularly important for orphan drugs at the time of the law's passage. Then as now, most new pharmaceuticals have patent protection at the time of approval, which blocks competition broadly. The exclusivity provision in the Orphan Drug Act was intended to offer nonpatent (statutory) protection against competition to encourage companies to invest in products that do not have patents or where there might be questions about the ability to enforce a patent.

Since 1983 the FDA has granted more than 3,500 orphan “designations” (see below) and approved more than 500 orphan drugs. Recently, as the biopharma business model has evolved and the science of targeted therapies has advanced, orphan drug designations have increased dramatically. The FDA [received](#) a record 440 requests for such designation in FY 2015, more than double the

WITH SUPPORT FROM:



The  
Commonwealth  
Fund

DrugPricing Lab

Memorial Sloan Kettering

number five years ago. This has occurred even though the threshold for orphan status is fixed at 200,000 patients, and is therefore an ever smaller percentage of the growing US population.

The Orphan Drug Act was supported by the [National Organization for Rare Disorders](#), a coalition built on the premise that because there are so many different

the idea of a sponsor that actually intends to market a drug for a large patient population—for example, people with lung cancer—but seeks orphan designations first for one slice of the market (stage 4 lung cancer), then for another (stage 3).

As understanding of genomic markers of disease has advanced, there have been new questions about when a specific subset of a common disorder should qualify for orphan status. The FDA [updated](#) its orphan drug regulations in 2013, defining a new concept for designation requests, known as an “orphan subset,” for determining when a specific use is or is not an appropriate orphan indication.

A single product can have multiple orphan designations for different rare diseases and can also be approved for use in non-orphan diseases. Sponsors with an orphan drug designation receive tax credits to support clinical development and are eligible for grants administered by the FDA. Upon approval, an orphan drug is awarded seven years of “market exclusivity,” meaning that no other sponsor can market the same drug for the same orphan-designated use. (The same drug can be marketed by a different sponsor for *other* uses, and *different* drugs can be marketed for the same orphan use.)

Another provision allows the FDA to approve the same drug for the same orphan-designated use if a sponsor demonstrates that its product conveys a clinically meaningful benefit, compared to the already marketed version. Those exceptions (known as “breaking” the orphan exclusivity of the first product) are rare and generally relate to differences in the formulation that may affect safety, efficacy, or convenience.

## “A single product can have multiple orphan designations for different rare diseases.”

rare diseases, collectively they have a broad societal impact. Those advocates view the law as a success—one reason the market exclusivity approach has been imitated in other incentive programs enacted over the past three decades (Exhibit 1).

However, the Orphan Drug Act has also generated debate, often tied to the very high prices of many drugs for rare diseases. In some cases, the price of an orphan drug may limit access for the patients the law is intended to serve. Even when the direct cost to patients is low (because of insurance, patient assistance programs, or both), the commercial success of some orphan drugs calls into question the need to incentivize their development in the first place.

### ■ The Orphan Drug Act: What You Need To Know

Sponsors may request, and the FDA generally grants, an orphan drug designation for any product intended to treat a disease that affects fewer than 200,000 patients in the US. (The law also allows a designation for a disease that affects more than that number if a sponsor can demonstrate that a potential treatment would not make a profit. The latter approach has been used only a handful of times.) In some instances, there have been disagreements about whether a proposed patient population has been defined arbitrarily to create an orphan indication—a practice referred to as “salami slicing.” The metaphor is intended to convey

### ■ Important Concepts For Pricing And Coverage Policy

Several important concepts relate to how (or whether) orphan drug status affects prices and coverage policy.

#### VARIED UNDERLYING PRICING DYNAMICS

Orphan drug status applies to diverse products with different pricing dynamics, complicating efforts to craft policies to address costs. In contrast to

expedited pathways such as [Accelerated Approval](#) or [Breakthrough Therapy Designation](#), orphan drug status is not tied to the severity of the disease or the perceived effects of the therapy; instead, it is simply a matter of counting potential patients. A drug to treat a mild condition can qualify, as can a drug that offers only mild symptomatic benefits for a serious disease.

Further complicating pricing, many orphan approvals are new indications for drugs with broader approved uses; for example, the top-selling drug in the world, AbbVie's Humira (adalimumab), has several orphan drug indications but is also approved for arthritis and related rheumatology uses. In those cases, pricing reflects the dynamics of the broader market, not the rare disease use.

Drugs approved exclusively for rare diseases often have extremely high prices (hundreds of thousands of dollars per patient per year). Sponsors may explain

those prices by citing the need to generate an appropriate return on investment based on the costs of development. However, there are a number of examples of drugs approved solely for orphan indications that generate sales in excess of \$1 billion annually—a common standard for commercial success for products intended for common diseases. While those are a relatively small number of the 500 orphan drug approvals, they call into question the underlying premises of the incentives: that there is no viable commercial market to treat rare diseases.

### VALUE OF MARKET EXCLUSIVITY

Despite the long-standing view of the value of market exclusivity, the seven-year protection has become less important over time, resulting from subsequent changes in market protections for all new therapies. In fact, most successful orphan drugs do not rely on these protections. The 1984 Hatch-Waxman Act gives *any* never-before-approved drug a minimum

## EXHIBIT 1

### Exclusivity Incentives For Drug Developers

| Type/Legislation   | What Products Qualify?   | Scope Of Exclusivity   | Duration   |
|--|--|--|--|
| <b>Orphan drug</b><br>Orphan Drug Act, 1983  | Drugs to treat diseases affecting fewer than 200,000 patients in the US, or for which there is "no reasonable expectation that the cost of developing and making available" the therapy will be recovered. | The FDA cannot approve the same drug for the same use until exclusivity expires, unless the second applicant can show clinical superiority to the first. | <b>7 years</b>   |
| <b>New molecular entity</b><br>Hatch-Waxman Act, 1984                              | Drugs with "an active ingredient that has never before been marketed in the U.S. in any form."   | The FDA cannot receive an Abbreviated New Drug (generic) Application (ANDA) until exclusivity expires.   | <b>5 years</b><br><i>(4 years if the ANDA is challenging a patent)</i> |
| <b>New formulation</b><br>Hatch-Waxman Act, 1984                                   | New formulations of previously approved drugs that require clinical data to support approval.  | The FDA cannot approve a generic application until the exclusivity expires.  | <b>3 years</b>   |
| <b>Innovator biologic</b><br>Affordable Care Act, 2010                             | Novel biologic therapies, upon FDA approval.   | No biosimilar application may be approved until exclusivity expires.   | <b>12 years</b>  |
| <b>Pediatric exclusivity</b><br>FDA Modernization Act, 1997                        | Any new drug for which a sponsor completes a pediatric study subject to an FDA written request.  | Added to all patent and exclusivity protections. Each new drug is eligible for only one extension.   | <b>6 months</b>  |
| <b>Qualified infectious disease product</b><br>FDA Safety and Innovation Act, 2012 | New antibacterial or antifungal drugs intended to treat serious or life-threatening infections.  | Added to all other exclusivities.  | <b>5 years</b>   |
| <b>Single-enantiomer products</b><br>FDA Amendments Act, 2007                      | Single-isomer formulations of drugs previously available solely as racemic mixtures.   | The same protection as the new molecular entity exclusivity.   | <b>5 years</b>   |

**SOURCE** Prevision Policy LLC.

five-year exclusivity period for all uses—which in practice typically means at least a seven-year period before generic competition can begin.

The law also provides for restoration of patent life to make up for time in development and under FDA review, so a product with any remaining patent life at the time of FDA approval is almost certain to have a patent term longer than the seven-year orphan protection. In addition, the biosimilar provisions in the Affordable Care Act (ACA) give new biologic medicines a minimum twelve-year exclusivity period. As a result, most drug developers—whether granted orphan status or not—can be assured of at least seven years of exclusivity for any novel molecule or biologic.

### CONTROVERSY AROUND MARKET EXCLUSIVITY

Drugs that *do* depend on market exclusivity have been controversial. KV Pharma's preterm labor drug Makena (4-aminopyridine, or 4-AP) and Marathon's steroid approved for Duchenne muscular dystrophy, Emflaza (deflazacort), are recent examples in which sponsors sought orphan status and subsequent FDA approval for therapies that many patients were accessing previously in unapproved forms (pharmacy compounding for 4-AP and importation from Europe for deflazacort).

The seven-year market protection was a key factor in the decision to seek FDA approval with orphan status, since neither product had patent protection that would otherwise allow a premium price. Both

sponsors faced significant resistance from patients and payers based on the much higher price point compared to the older source of supply. That has led to the unusual dynamic of patient and consumer advocates urging the FDA to allow continued access to an "unapproved" product instead of using its enforcement powers to cut off the alternative supply once an approved version is available.

### ADDITIONAL BENEFITS OF ORPHAN STATUS

Orphan drug status conveys other benefits not originally included in the law. Sponsors of applications for orphan drugs are exempt from user fees to support that review. Although user fees did not exist at the time of the 1983 Orphan Drug Act, non-orphan sponsors now pay a fee of more than \$2 million for review of a new drug application. The ACA also exempted products with an orphan drug designation from otherwise mandatory discounted pricing for certain payers under the federal [340B drug pricing program](#).

In addition, the ACA exempted drugs that are approved solely for orphan indications from their portion of the [annual market-share fee](#) paid by pharmaceutical companies. (The annual fee, negotiated by the pharmaceutical industry as part of the ACA debate, amounted to a total of \$4 billion in 2017.) Finally, developers of drugs to treat rare diseases receive enhanced attention within the FDA from a dedicated office for orphan products and a rare disease specialist.

## HealthAffairs

Health Policy Briefs are produced under a partnership of *Health Affairs* with the generous support of the Commonwealth Fund and Memorial Sloan Kettering Cancer Center. Text highlighted in blue is hyperlinked to outside sources in the online version of this brief.

Written by **Michael McCaughan**, Prevision Policy LLC. Editorial review by **Aaron Kesselheim**, Harvard Medical School and Brigham and Women's Hospital; **Allan Coukell**, The Pew Charitable Trusts; **Laura Tollen**, consulting editor, *Health Affairs*.

Cite as: "Health Policy Brief: Pricing Orphan Drugs," *Health Affairs*, July 21, 2017. DOI: 10.1377/hpb20173

7500 Old Georgetown Road, Suite 600 | Bethesda, Maryland 20814-6133 USA | © 2017 Project HOPE—The People-to-People Health Foundation, Inc.