1.5% of Total Drug Spending (0.15% of Total Health Spending)

Reforming the Orphan Drug Act

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Issue Summary: The Orphan Drug Act (ODA) is designed to encourage the biotech sector to invest in the development of treatment for rare conditions and diseases. Because, by construction, rare diseases do not have large patient populations and will not have treatments that get sold in large quantities, for-profit firms may not face strong enough incentives to invest in developing treatments for these conditions. The ODA employs two policy levers to incentivize private firms to invest in developing treatments for rare conditions and diseases. First, the law offers tax credits that defray the costs of research and development (R&D) for drugs used to treat orphan conditions. Second, the ODA offers drugs with an orphan designation a seven-year period of market exclusivity from the date of FDA marketing approval instead of the usual three to five years given to other drugs. When firms get extended market exclusivity for a product, this extends the period in which they can charge monopoly prices, even if their patents have expired. As a result, the ODA provides a pathway to increase the returns to firms that develop drugs for rare conditions relative to the returns available to firms for developing products that treat more common diseases.

Unfortunately, in its current form, the ODA rewards some drug manufacturers for bringing drugs to market or finding indications for existing drugs that, in all likelihood, would have been produced without additional incentives. Many drugs have multiple indications (including some for orphan conditions and some for more common non-orphan conditions). The ODA allows manufacturers to get extended patent protection for products that mainly treat non-orphan conditions, but also have indications for orphan conditions. As a result, some of the most widely prescribed drugs in the US—Humira®, Enbrel®, Keytruda®, Biktarvy®, Remicade®, and Stelara®—receive extended patent protection from the ODA even though they primarily treat non-orphan conditions (IQVIA 2020; US Food and Drug Administration 2020).

Policy Proposal: This brief proposes three updates to the ODA. First, rather than providing market exclusivity, firms should only be incentivized to invest in orphan diseases via the provision of R&D tax credits. Second, these R&D tax credits should be subject to a "clawback" provision for drugs that earn enough to suggest, ex post, that they could have been developed without such R&D tax credits. Third, firms receiving R&D tax credits for developing an orphan drug should agree to some form of price regulation on the drug after patent expiration if there is no generic or biosimilar competition.

Potential Savings: To give a back-of-the-envelope estimate of savings, among the top 10 highest-revenue drugs in the US, six have received an orphan drug designation. A 10% reduction in prices of those products alone would reduce health spending by $5.24 billion (approximately 1.5% of total drug spending).

Related Literature and Evidence

Bagley, Nicholas, Benjamin Berger, Amitabh Chandra, Craig Garthwaite, and Ariel D. Stern. 2018. "The Orphan Drug Act at 35: Observations and an Outlook for the Twenty-First Century." *Innovation Policy and the Economy*, Vol. 19 University of Chicago Press and NBER.

Bagley, Nicholas, Amitabh Chandra, Craig Garthwaite, and Ariel D. Stern. 2018. "It's Time to Reform the Orphan Drug Act." *New England Journal of Medicine Catalyst*.

Background

In 1983, Congress passed the ODA. The ODA was designed to incentivize firms to increase their development of treatments for rare diseases and conditions. In general, absent intervention, for-profit firms often do not have sufficiently large incentives to invest in treatments for rare conditions. By definition, rare diseases have small patient populations, so the treatments for rare diseases often cannot be sold at sufficiently large volume and generate large enough profits to justify the costs of their development.

The ODA used two policy levers to encourage firms to invest in "orphan drugs" used to treat rare diseases and conditions. First, the law provides R&D tax credits to offset the costs of developing orphan drugs. Up until recently, firms that produced an orphan drug could recoup up to 50% of their R&D costs. In 2017, the R&D credit was halved, so firms could only recoup 25% of their R&D costs (26 US Code § 45C). Second, the ODA extends the market exclusivity of products used to treat orphan conditions. Whereas most products have market exclusivity for three to five years, the ODA granted orphan drugs a seven-year fixed period of market exclusivity from the approval date of the product (US Food and Drug Administration 2013). This extended patent protection increases the returns to orphan drugs by extending the period that their manufacturers can charge monopoly prices.

By most accounts, the ODA significantly increased investment in and the development of orphan drugs. In 1983, when the ODA was passed, there were approximately 40 orphan drugs available (Institute of Medicine 2010). From 1984 to 2003, there were approximately 63 orphan drug designations per year; in the 2000s, there have been approximately 200 per year (Kesselheim et al. 2017).

However, in the more than three decades since the ODA was passed, the market for therapies to treat rare diseases has changed significantly. First, the price of orphan drugs has increased dramatically. The average price for the top 100 orphan drugs was estimated to be $150,854 per patient per year in 2018, and the median price was estimated to be $109,723 per patient per year, which is approximately seven times the median price of a non-orphan drug (Pomeranz 2019). Orphan drugs account for six of the 10 top-selling drugs in the US based on annual sales data (IQVIA 2020; US Food and Drug Administration 2020).

Second, the rise of precision medicine and the use of genomic biomarkers have allowed firms to target medications at smaller populations. This has raised concerns that firms are securing orphan drug designations for products that are likely to be used to treat large populations.

Third, changes in the R&D process in general and the use of surrogate endpoints in particular have lowered the cost of drug development. The FDA offers four primary expedited programs for the development and review of drugs that address unmet medical needs: accelerated approval, breakthrough therapy designation, fast track designation, and priority review. Approximately 71% of orphan drug marketing approvals from 2008 to 2017 benefited from at least one type of these expedited programs (US Government Accountability Office 2018).

As a result of these trends, the ODA rewards some drug manufacturers for bringing drugs to market that in all likelihood would have been produced without additional incentives. Indeed, a sizeable share of drugs approved for additional market exclusivity via the ODA have a range of non-orphan disease indications and are used to treat wider populations. From 2008 to 2017, 38.5% of orphan drug marketing approvals were for a new indication for a drug previously approved to treat a rare or non-rare disease (US Government Accountability Office 2018).

For example, the blockbuster product Humira® (adalimumab) initially received FDA marketing approval on December 31, 2002, for rheumatoid arthritis, which is a non-orphan disease (Tribble and Lupkin 2017). Subsequently, between 2008 and 2016, the FDA approved Humira® to treat five orphan indications in the areas of dermatology, gastroenterology, ophthalmology, and rheumatology (US Government Accountability Office 2018). Indeed, based on our calculations, less than 10% of total spending on Humira® is on orphan disease populations.

As orphan drug uses are approved, manufacturers can "stack" orphan designations to receive extended periods of patent protection.[1] For example, Sigma-Tau Pharmaceuticals enjoyed more than 20 years of market exclusivity for its product, Carnitor®, as a result of the ODA (Tribble and Lupkin 2017). This metabolic disorder drug was approved for three orphan drug exemptions for three different conditions. The second and third exemptions were obtained in the year patent protections were about to expire.

Improving the Orphan Drug Act

This brief outlines three reforms to modernize the ODA.

First, R&D tax credits should be the only incentives provided to firms to produce orphan drugs, rather than the current mix of tax credits and market exclusivity. Many orphan drugs are economically viable without extended market exclusivity. Moreover, when firms are given additional market exclusivity, the higher costs from this exclusivity are borne by a narrow sliver of the public. Added exclusivity translates into higher drug prices. These higher drug prices result in higher insurance premiums and higher cost sharing for the individuals who consume the drugs. By contrast, tax credits are funded via general tax revenue. As a result, the costs of them are spread more evenly across the population.

Second, R&D tax credits should be subject to a "clawback" provision if it becomes clear, ex post, that a drug would have been developed in the absence of the tax credits. This type of system has been shown to be effective outside the US. In Japan, for example, manufacturers must begin to repay R&D subsidies

for drugs with annual sales that exceed 100 million yen (Bagely et al. 2018). A similar threshold could be adapted for the US market. A change of this type would focus government subsidies on drugs that would otherwise have not been developed, rather than subsidizing products that had broader uses outside of their orphan designation.

Third, firms that receive R&D tax credits for developing an orphan drug should agree, as a condition of receiving the tax credits, to some form of price regulation after their patent expires if there is no generic or biosimilar competition. For some orphan drugs, there is not a sufficiently large market to justify generic entry. As a result, firms that produce branded orphan products can recoup monopoly rents even after their patent expires. One potential form of price regulation would be to require these manufacturers to set rates that generate a prespecified margin above the production costs of the orphan drug. In general, while across-the-board regulation of the mark-ups that firms could charge would discourage innovation, in this setting, policy makers would only be regulating the prices of products that already received high returns during the period they had patent protection.

Estimated Savings

It is difficult to calculate precisely the potential savings from these three interventions. However, to give a back-of-the-envelope estimate of savings from amending the ODA, it is vital to note that among the top 10 highest-revenue drugs in the US, six have received an orphan drug designation. A 10% reduction in prices of those products alone would reduce health spending by $5.24 billion (approximately 1.5% of total drug spending).

Footnotes

1. Orphan designations are indication-specific; manufacturers receive seven years of exclusivity for each newly approved orphan indication. However, generic and biosimilar entry for the expired indications is possible after the first seven-year exclusivity period ends. Doctors are able to prescribe these alternatives off-label, even when the FDA grants a secondary indication for a drug.

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