The Unintended Consequences of the Orphan Drug Act

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If you look up the word “orphan” in the dictionary it is commonly used to convey loss and abandonment. However, when orphan is used in the pharmaceutical industry, it conveys dollar signs. Big dollar signs.

The world’s 10 most expensive drugs are all classified as orphan drugs and the orphan drug market is expanding rapidly. Projected worldwide sales are expected to outpace conventional drugs by twofold over the next six years. Moreover, orphan drugs are projected to account for 21.4 percent of global prescription sales in 2022, up from 6 percent in 2000.

For patients, this growth trend may be interpreted as a sign that an increased number of treatment options are being approved for rare diseases. While the number of approved treatment options for rare diseases continues to increase, there are indicators that the growth trend in the orphan drug market is also driven by big pharma’s strategic use of the Orphan Drug Act (ODA) to maximize its profits, which is an unintended result of the legislation.

The original mission of the ODA, passed in 1983, was to encourage development of drugs for rare diseases that would likely have limited potential for profitability. To receive an orphan designation, the disease or condition for which the drug is intended must affect fewer than 200,000 people in the U.S.; or if the disease or condition affects more than 200,000 people, the manufacturer must demonstrate there is no reasonable expectation that research and development costs can be recovered by U.S. sales. Orphan-designated drugs are eligible for a range of financial incentives and seven years of market exclusivity, which starts at the time of approval.

While the ODA successfully created an incentive for manufacturers to invest in developing treatments for rare diseases, the legislation’s provision of market exclusivity is a key driver of the high cost of orphan drugs and big pharma’s abuse of the ODA.

The market exclusivity provision of the ODA bars the FDA from approving any new or abbreviated application for the same drug for the same indication during the period of exclusivity and the manufacturer is able to price the drug at what the market can bear. In 2016, the average cost per patient per year for orphan drugs was 5.5 times higher than non-orphan drugs, using median prices.

The unrestricted cost of orphan drugs has historically been accepted as a necessary tradeoff for the development of drugs for rare diseases. However, there is evidence that the orphan drug market has become a profitable business, as the return on investment is 1.89 times greater for an orphan drug than a nonorphan drug. Critics suggest manufacturers are finding creative ways to manipulate the ODA to maximize their profits. These practices include:

1. **Repurposing mass-market drugs as orphan drugs.** A recent investigation found that the FDA approved more than 70 orphan-designated indications for drugs initially approved for nonrare conditions.
2. **Disease slicing.** A closer examination of recent approvals suggests the surge in orphan drug development in the past five years is not due to an increase in approvals for drugs to treat traditionally rare diseases, but rather is a byproduct of a practice commonly referred to as "salami slicing" or disease slicing. This occurs when manufacturers tailor drugs to treat a subset of patients within a nonrare disease population. Under the ODA, this practice is permissible as long as the manufacturer can demonstrate that only the "orphan subset" of the larger nonorphan population is an appropriate candidate for treatment with the drug.
3. **Off-label use.** Another potential abuse of the ODA is strategically positioning drugs for the treatment of rare diseases that might otherwise have been tested and approved for a nonorphan indication. Subsequent to approval, off-label use for common conditions is widespread.
4. **Repurposing of old compounds.** The ODA also grants orphan status to both new and existing molecular entities. In some instances, an older drug is granted orphan status in spite of the manufacturer incurring little or no research and development costs. This often occurs if a manufacturer repurposes a drug for a rare disease and its effectiveness for the rare disease is published in the literature prior to the application for orphan designation.

Due to the prevalence of these practices, the Government Accountability Office is preparing to launch an investigation into potential abuses of the ODA. The investigation is slated to start later this year.

While it’s clear that reform of the ODA is needed to curb some of these practices, it’s unclear how the ODA might be amended. Once a drug exceeds the basic tenets of the ODA, e.g. it’s for a small population or it’s unprofitable, the drug should no longer be subsidized by the government. This type of reform might be achieved through taxes, reduced exclusivity or pricing adjustments. In the case of true orphan drugs, moving toward value-based payments will likely help curb costs.

In any case, it’s too soon to predict the future of orphan drugs and how the government will regulate them. The only thing we can predict with any certainty is that their prices, if left unchecked, will continue to rise dramatically.
**About the author.** As senior director of drug information at Vizient, Lauderdale oversees the development of clinical resources for the pharmacy membership, which includes education and formulary support. Prior to her current position, she served as assistant professor of drug information at Samford University and a drug information specialist at the Samford University Global Drug Information Service. Lauderdale also has authored several publications and is a recognized speaker on drug information.

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