VIEWPOINT

The Orphan Drug Act Revisited

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The Orphan Drug Act (ODA) was first passed in 1983 to address the concern that pharmaceutical manufacturers were not pursuing drug development for diseases that affect limited patient populations. The concern was in part that companies viewed pursuing these therapies as undesirable because the markets for them are small in comparison with the markets for more widespread chronic diseases. To promote the development of orphan drug therapies, the ODA provided companies that engaged in research for drugs with populations of fewer than 200 000 patients with tax incentives, research subsidies, and extended patent protection. With the new incentives in place, drug companies began developing more of these drugs. As of August 2018, a total of 503 new orphan therapies had been approved following the passage of the act.[1]

While the ODA was successful at inducing drug companies to conduct research and develop therapies for rare diseases, there are some concerns that the success of the ODA has adversely affected the overall pharmaceutical market and the integrity of the US system for drug approval.[2] The incentives established by the act are so appealing, and the requirements of traditional drug approval so onerous, that some pharmaceutical companies have disproportionately shifted their focus to orphan drug development.[3-5] Rare diseases, as defined in the Act, affect less than 10% of individuals in the United States.[3] However, between 2015 and 2016, therapies focused on these diseases constituted 30 products (45%) of the 67 new drugs approved by the Food and Drug Administration (FDA).[4,5]

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Critics of the act highlight 2 concerns. First, companies applying for orphan drug approval can often avoid the cost of large-scale, randomized clinical trials that are standard for traditional drug development. An analysis of trials used for orphan and nonorphan drug approval between 2005 and 2012 found that orphan drug trials were more likely to have smaller numbers of participants (mean of 98 for orphan drug studies vs mean of 294 for nonorphan drug studies) and were less likely to be randomized trials.[6]

Second, pharmaceutical companies can charge substantial prices for orphan disease therapies because the market lacks generic competition. This can lead to astronomical prices and profits. For example, glycerol phenylbutyrate (Ravicti, manufactured by Horizon Pharma), which is used to treat a rare urea cycle disorder, has a list price of approximately $793 000 per year for a single patient.[7] Such prices make orphan drugs comparable with nonorphan drugs in terms of revenue. The top 10 orphan therapies each generated more than $1 billion in sales for their manufacturer in 2017,[3] which is the threshold for a nonorphan "blockbuster" drug. Overall, orphan drug products generated an industry-wide estimated $125 billion in sales in 2017. This represented approximately 16% of the total prescription drug market.[3] By 2024, orphan drug sales are projected to be $262 billion and are forecast to comprise almost 22% of the prescription drug market.[3] These impressive revenues do not consider the substantial financial incentives companies receive in fee waivers and extended patent exclusivity. Because orphan drugs can be less expensive to develop[8] and just as profitable once they are on the market, these products have expanded to be far more of the pharmaceutical pipeline than Congress intended, and they constitute a larger share of the pharmaceutical market every year.

The rise of precision medicine and molecular genetics means the increasing emphasis on orphan drug development will continue. Molecular genetics has made substantial breakthroughs in the last few decades, elucidating disease mechanisms and genetic associations with an unprecedented level of detail. For some diseases, scientists are on the verge of understanding the precise genetic combinations that produce the alterations in gene products that result in disease-state phenotypes. One consequence of this enhanced understanding is that it is disrupting 20th-century disease definitions and, in doing so, slowly dismantling the distinction between orphan diseases and common ones.

Fifty years ago, cancer was defined primarily by its location: cancer in the pancreas was pancreatic cancer, cancer in the lung was lung cancer. While this nomenclature persists today, cancers are increasingly subclassified by the underlying genetic mutations involved in the disease process. It is now known that cancers vary by various genetic mutations, for example, there are cancers with p53 mutations, cancers with rb mutations, cancers with *BRAF* mutations, cancers with *MEK* mutations, and cancers with *ERBB2* mutations. Molecular genetics has shown that what was previously thought of as a single disease affecting millions of people is a collection of rarer cancer diseases each affecting much smaller populations, potentially fewer than 200 000 patients, making them orphan diseases under the ODA definition. For example, Vitrakvi (larotrectinib) received approval and orphan drug designation from the FDA in

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November 2018 for treatment of adult and pediatric cancers with a specific neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion. The drug proved remarkably effective in clinical trials, with a response rate of 75%, but only for tumors with this particular genetic biomarker.

Genetic research on Parkinson disease has similarly found that what was once thought of as a single disease entity is a collection of at least 5 distinct illnesses, each caused by its own unique genetic mutation.[9] As these diseases are further disaggregated, the patient subpopulations affected by each will likely be fewer than 200 000, and new therapies targeting them will be orphan drugs.

Why does this matter? What is the concern if ultimately every drug is an orphan drug?

As more pharmaceutical research targets subpopulations of common diseases, fewer drugs will go through the traditional approval process. The entire drug approval system will change due to the redefinition of disease, not as a result of any shift in thinking about the value of standard randomized clinical trials. Other unintended changes will occur as well. For example, fewer pharmaceutical companies will be paying all of the required fees for the drugs they are developing (only 31% of the FDA's drug approval budget comes from the federal government, the other 69% is supposed to come from industry fees),[10] and fewer will be performing sufficiently powered randomized clinical trials to substantiate the safety and efficacy of these products, that is, more drugs will come to market based on potentially inadequate premarket evidence. The FDA may have insufficient resources to meet its obligations, and because smaller and less rigorous study designs will be used to approve drugs, there will not be the same detailed data about the efficacy and safety of novel therapies. This tradeoff perhaps made sense when Congress was trying to incentivize rare disease research, but the ODA was never intended to change the entire drug approval process.

Is it time to abolish the orphan drug classification? Pharmaceutical companies can charge exceptionally high prices for orphan drugs, so it is unclear that there is still a need to incentivize research into rare disease therapies. Precision medicine is doing that on its own. The billion-dollar market for many of these emerging drugs is likely incentive enough to ensure continued research on diseases affecting small populations. Accommodations to the clinical trial process for some rare diseases or disease subtypes may still be required because finding eligible participants for rare disease trials is more difficult than it is for common disease studies. However, the arbitrary patient population threshold that currently exists for defining "rare" diseases (ie, fewer than 200 000 patients), and all of the financial benefits that accompany it, seems outdated, unnecessary, and flawed.

If legislation promoting orphan disease therapies is to continue, instead of focusing on the number of patients in a population, which will become an increasingly less meaningful metric over time, the definition should focus on diseases that have to date been ignored by major pharmaceutical companies. The benefits of the ODA should accrue to companies that conduct drug development research that other companies have long neglected. For example, the first entrant into a research area could reap incentivizing benefits, whereas the third or fourth company to enter the disease space once that first company has already developed a successful drug should be required to follow the traditional approval process. Another possibility would be to enact price regulations for orphan drugs after their extended patent exclusivity expires, if no generic competition has arisen.[2] This would enable companies to leverage the orphan drug benefits for a reasonable period of time while ensuring that patients had long-term access to affordable therapies. Price controls would only apply to drugs that took advantage of the ODA incentives so companies that have concerns about price controls curtailing exorbitant profits in the future could opt for the nonorphan drug development pathway.

Any update to the ODA needs to include a new definition of "orphan drug" for the 21st century. Congress should not be providing financial benefits and extended market exclusivity to every new drug with a small patient population. It is quite possible that before long those will be the only new drugs available.

ARTICLE INFORMATION

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