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POLICY FORUM

Policymaking for Orphan Drugs and Its Challenges

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In the United States, rare diseases (e.g., cystic fibrosis and leukemia) are defined by the Food and Drug Administration (FDA) as diseases that affect fewer than 200,000 people [1]. The roughly 6,000-8,000 diseases defined as rare collectively affect approximately 25 million US citizens [2]. About 80 percent of rare diseases are genetic in origin (e.g., caused by defects in a single gene or mutations in several genes) [2]. Because rare diseases are "life-threatening and/or chronically debilitating" and many people "die before reaching adulthood," treating patients with rare diseases should be a significant public health concern [3].

Before the advent of the Orphan Drug Act (ODA) of 1983 [4], biotechnology and pharmaceutical companies did not invest much in developing drugs and biologics (hereafter referred to as drugs) for rare diseases or conditions because "there [was] no reasonable expectation [that] the sales of the drug[s would] recover the costs" [5]. Such drugs are often referred to as orphan drugs because they were neglected. Only 10 drugs were available to treat rare diseases in the 1970s before the enactment of the ODA [1].

Due to the rarity of the conditions and limited demand for treatments, biotechnology and pharmaceutical companies were unlikely to develop orphan drugs without government intervention [6]. As a result of advocacy from public and special interest groups (e.g., the National Organization of Rare Disorders) in the late 1970s, the Orphan Drug Act (ODA) of 1983 was signed into law to provide several incentives to encourage biotechnology and pharmaceutical companies to develop orphan drugs. Through subsequent amendments to the act, incentives include: (1) seven years of market exclusivity for any unpatented drugs designated as treatments for rare conditions; (2) tax credits for certain research and development costs; (3) elimination or reduction of procedural fees; (4) fast-tracking of FDA review and approval of applications pertaining to orphan drugs; and (5) federal and state grants for drug development (e.g., research grants from the National Institutes of Health) [2, 7].

Successes of the ODA

Since the enactment of the ODA, the FDA has granted approval for marketing to more than 400 orphan drugs [1]. Considering that only ten orphan drugs were available between 1973 and 1983, this is great progress. Stimulating rare disease research through the ODA not only led to scientific breakthroughs but also "permit[ted] enough

freedom of movement for sponsors [(e.g., biotechnology and pharmaceutical companies)] to recycle [or re-purpose] previously discontinued products" [8]. Moreover, through the ODA and its amendments, orphan products became more diverse. For example, they include not only traditional (i.e., chemically based) drugs, but also biologics (e.g., "natural sources such as human cells or microorganisms") and medical devices [9].

The increase in availability of orphan drugs had a positive impact on health. Approved orphan drugs are shown to reduce premature mortality rates in patients with rare diseases [10]. Using longitudinal, disease-specific data from 1996-2006, for example, Lichtenberg found that the cumulative number of orphan drugs approved three to four years earlier was significantly inversely associated with premature mortality rates in patients with rare diseases (e.g., rare cancers, Huntington disease, Tourette syndrome, and Lou Gehrig's disease) [10, 11]. While a relationship between mortality and cumulative number of drugs approved up to two years earlier was not found, this may be because "most patients probably do not have access to a drug until several years after it has been launched" [12].

Problems Remaining after the ODA

Despite recent successes in developing orphan drugs, less than 10 percent of patients with rare diseases are treated today [2]. While the ODA had some benefits, there are major problems it did not address.

Medications are available, but they may not be always accessible due to high costs. Several studies indicate that orphan drugs are very expensive and that their accessibility can be a huge concern [13]. For example, cerzyme was developed by Genzyme to treat Gaucher disease. There are about 2,000 patients with Gaucher disease in the US [13], and the medication costs as much as $400,000 every year for an adult patient [14]. There is a concern that pharmaceutical companies can create a monopoly market [6], precluding payers' ability to negotiate prices, by "splitting up a disease into several sub-diseases that qualify as rare diseases (a practice called 'disease sub-setting,' 'salami-slicing' or disease stratification')" [15]. Furthermore, drug manufacturers are "free to set their own introductory prices" [16], and "establishing a price that maximizes its profit is legal" [17]. Such high medication costs can be burdensome to payers and, especially but not only if reimbursement is denied, to patients.

The incentives may not be doing enough. Some researchers also raise the question of whether, even when given incentives to focus on rare diseases, the pharmaceutical industry concentrates only on commercially lucrative areas. At least 95 of the aforementioned 400-plus orphan drugs were for cancer treatment; orphan drugs used to treat rare cancer are the most profitable [13, 18-20]. Haffner and colleagues ask, does the "development [of orphan drugs] actually take place for the truly rare diseases, or only for the more common ones" within the rare group, like the rare cancers [21]?

Wellman-Labadie and Zhou question whether these "oncology products should qualify for orphan drug designation and whether so many cancers should be considered as rare diseases" [22].

Conclusion

To improve the accessibility of orphan drugs for patients with rare diseases, relevant policies should be altered in ways that promote fairness and equity. As Côté and Keating state, fairness requires "a positive action by the state [or government] when the market does not provide a good match between investments and health [care] needs. Finally, fairness requires that the barriers to access should be morally justifiable" [23].

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