**Misuse of the Orphan Drug Act of 1983 by the Modern Pharmaceutical Industry and the Cost Implications for Society**

In the United States (US), an estimated 30 million individuals are afflicted with a rare disease, half of whom are children (Rare Genomics Institute, 2023). A rare disease is defined as a disease that affects fewer than 200,000 individuals in the US and it is estimated that there are a total of 7,000 rare diseases (Rare Genomics Institute, 2023). Prior to the 1980s, it proved difficult for these patient populations to receive innovative treatment because pharmaceuticals simply had no monetary incentive to develop drugs that would target these small populations. These unique pharmaceutical markets contain two defining features that delineate them from the mass pharmaceutical market: the cost of research and development (R&D) for rare-disease drugs is presumably lower than that for non-rare-disease drugs and the market for rare-disease drugs is considerably smaller. Addressing the former feature, pharmaceuticals are subject to an exhaustive process before an optimal drug is marketed which includes pharmacophore identification and both preclinical and clinical development. Notably, clinical development consists of in-vivo studies that allow for exploration of drug safety and efficacy. For rare diseases, there are less subjects available for human studies and pharmaceuticals are held to lower standards in terms of sample size, which in turn lowers their costs for clinical development. A recent study has shown a 40% reduction in out-of-pocket clinical costs for rare-disease drugs when compared to non-rare-disease drugs (Jayasundara et al, 2019). Additionally, marketing costs are lower because companies need to reach a smaller number of medical specialists and the information diffuses quickly as the drug is in many cases the only treatment option available (Seoane-Vazquez et al, 2008). However, the small number of potential consumers makes it very difficult for companies to substantiate investment in R&D

when projected revenue either may not be enough to cover costs or will result in less profit than could be made investing an equivalent amount of capital in non-rare-disease drug development. The latter feature is therefore responsible for the rare disease pharmaceutical market failure, wherein, assuming no external incentives are present, pharmaceuticals will always opt to operate in the considerably more lucrative non-rare-disease market. This market failure disadvantaged patients with rare diseases by severely limiting their treatment options and facilitated the persistence of negative health outcomes for these individuals. Clearly, additional incentives to pharmaceuticals were necessary to protect this vulnerable patient population against the adverse consequences of market failure and in 1983, patient advocates successfully lobbied for the implementation of the Orphan Drug Act (ODA)- a policy that aimed to foster innovation and the development of pharmaceutical agents to treat patients afflicted with rare diseases (Herder, 2017).

To understand the reason for the misuse of the ODA by the modern pharmaceutical industry, we must first explore the three main incentives that the ODA provides. First, federal research grants are given to companies engaged in clinical testing of drugs that can treat rare diseases (Department of Health and Human Services [HHS], 2001). Additionally, if a drug is granted orphan drug designation by the Food and Drug Administration (FDA), the company is given a 50% tax credit of the total cost of conducting human clinical trials and most notably, is protected from competition through a 7-year market exclusivity (HHS, 2001). This exclusivity disallows the entry of competing firms (unless clinical trials can overwhelmingly support drug superiority), giving monopolistic market power to pharmaceuticals which enables them to gain from higher pricing opportunities and from lack of competition. The ODA is considered by many to have successfully attained its goal of stimulating orphan drug development- a mere 10

orphan drugs were developed in the decade prior to the ODA; contrast this to the approximate 200 approved orphan drugs by the year 2000 and the success of the ODA becomes strikingly apparent (HHS, 2001). However, the ODA fails to protect against abuse of orphan drug designation and the lack of strict provisions has recently transformed a previously overlooked market into the most popular.

Pharmaceuticals have manipulated the system in two stark manners. First, they have begun to sub-categorize diseases for access to ODA benefits that they would otherwise not qualify for. The medical community often recognizes subpopulations that have a disease as a subtype of a common disease (Lee, 2017). Companies will thus logically try to obtain orphan status for a subtype of a disease rather than for the common disease to obtain ODA benefits and companies can then continue to attain orphan status for other subtypes of the disease and maintain monopolistic power. Hybrid repurposing is another strategy used by pharmaceuticals to maintain market power well after their patent exclusivity for a mass market drug expires. Repurposing is widely seen with blockbuster drugs, or drugs that are widely successful, generating sales of at least 1 billion USD (Collier, 2011). Commonly, these drugs will initially be FDA approved for non-rare diseases and then be repurposed to serve a subpopulation- usually for pediatric use as this subpopulation is typically small enough for a common disease to be considered a rare disease (Lee, 2017). Pharma company AbbVie is a recent example of engagement in hybrid repurposing. Humira is the brand name for Adulimumab, a monoclonal antibody originally approved in 2002 to treat rheumatoid arthritis- a condition affecting more than 1 million individuals in the US alone (Xu et al, 2021). In 2008, Humira gained FDA orphan drug status for juvenile rheumatoid arthritis which affects approximately 50,000 children in the US (Tribble et al, 2017). This status was then followed up with 4 additional orphan drug

designations, extending Humira’s market exclusivity until 2023 for a total of 21 years (Tribble et al, 2017). Unfortunately, AbbVie is just one of many pharmaceuticals abusing orphan drug designations; Sigma-Tau Pharmaceuticals also maintained orphan drug market exclusivity over one of its metabolic disorder drugs for approximately 20 years (Tribble et al, 2017). Pharmaceuticals are finding loopholes to grant their drugs orphan status and do so just before prior exclusivity terminates in a seemingly never-ending circle that lengthens their monopoly power and profitability. Furthermore, these strategies offer no innovation in the pharmaceutical industry- the original intent of the ODA- and instead are a mere relabeling of drugs for extended profitability opportunities.

The gains that pharmaceuticals experience with retention of monopolistic market power come with costs to society. Normally, once patent exclusivity expires, additional companies can enter the market through the development of generic drugs (Kefalas et al, 2011). This increases competition and lowers prices. However, when pharma companies file for and obtain orphan drug designation just prior to termination of patent exclusivity, these companies retain market power for longer periods of time and delay the entry of generic drugs into the market. Prices are artificially kept high and consumers are forced to unnecessarily continue facing inflated prices. More concerning is the rise in medical expenditures on orphan drugs. In 2017, 25% of prescription drug spending was for orphan drugs (Chua et al, 2021). In the government program, Medicare, the majority of the highest-expenditure drugs have been approved for at least one orphan designation, many of which were originally mass market drugs (HHS, 2021). These increased expenditures place a burden on both US taxpayers and private insurance companies. Insurances profit from risk pooling where high cost individuals are offset by low cost individuals. At the launch of the ODA, insurances only had to pay higher prescription drug

prices for individuals afflicted with rare diseases, but now that pharmaceuticals are finding ways to monopolistically price mass market drugs, insurances are now faced with higher prices for a larger proportion of their enrollees, which can lead to increased premiums and potentially restricted access to orphan drugs, disadvantaging those for which the ODA served to protect.

In addition to these monetary costs, society also has to face costs to overall health. The pharma strategy of sub-categorizing diseases is the main contributor to these health status losses. Essentially, companies are incentivized to first only carry out clinical studies in narrow populations to gain ODA benefits, even though the drug could potentially have been proven to benefit the larger population (Daniel et al, 2016). This results in the delay of treatment for many individuals and the persistence of unnecessary negative health outcomes.

Pharmaceuticals have faced increased public scrutiny in recent years for these exploitative strategies and reform efforts have been made to combat misuse of ODA benefits. The Fairness in Orphan Drug Exclusivity Act was introduced to the US House of Representatives in 2023 and stipulates that a “...drug shall be granted the seven-year exclusivity period only if the sponsor demonstrates that there is no reasonable expectation that it will recover…costs within its first 12 years of U.S. sales…” (H.R.456, 2023). The road ahead may be long, but there is an evident need for stricter provisions to be implemented that will halt orphan drug designation abuse, remove unfounded monopolistic market power, and reinstate the initial goal of the ODA- to protect highly vulnerable patient populations by encouraging innovative treatments for rare diseases.

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