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Evaluating and Valuing Drugs for Rare Conditions: No Easy Answers

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ABSTRACT

We find ourselves in an era of unprecedented growth in the development and use of so-called "orphan" drugs to treat rare diseases, which are poised to represent more than one-fifth of pharmaceutical expenditures by 2022. This widespread use has been facilitated by legislative and regulatory incentives in both the United States and abroad, yet US payers and health systems have not yet made a concerted effort to understand whether and how rare diseases require special considerations on their part and how to adapt traditional methods of health technology assessment and economic evaluation to accommodate these situations. In this article, we explore the general ethical dilemmas that rare diseases present, steps taken by health technology assessment bodies worldwide to define the level of rarity that would necessitate special measures and the modifications to their assessment and valuation processes needed, and the contextual components for rare-disease evaluation that lie outside of the assessment framework as a guide to US decision makers on constructing a formal and relevant process stateside.

Keywords: orphan drug production, rare diseases, neglected diseases, orphan diseases, economics, financing.

Introduction

The National Organization for Rare Diseases estimates that approximately 30 million Americans are affected by one of 7,000 rare diseases, typically defined as affecting fewer than 200,000 individuals, or approximately 60 per 100,000 population [1]. Biopharmaceutical products targeted at these rare conditions are often called "orphan drugs." In recent years, approvals of orphan drugs for serious, disabling, and often rapidly fatal diseases such as cystic fibrosis, dystrophic syndromes, and certain cancers such as lymphoma and melanoma have improved prognosis and provided new hope to patients with few or no existing treatment options [2].

Following on these successes, the market for orphan drugs is in a period of significant acceleration. Worldwide sales of orphan drugs first reached $100 billion in 2015 but are expected to more than double by 2022 and will represent more than one-fifth of all prescription drug sales by that time [3]. One factor driving the trend in spending on orphan drugs has been higher acquisition cost. A recent estimate that considered publicly available prices before insurer rebates or discounts calculated an average annual cost for orphan drugs that is five times higher than for non-orphan medications ($140,443 vs. $27,756, respectively) [3].

Historically, higher prices for orphan drugs have not been associated with greater barriers to insurance coverage in the United States, in part because it was widely recognized by insurers that even very high prices, when multiplied by small patient numbers, would produce a limited impact on budgets and insurance premiums. In addition, there has been a general sense that what can be termed "orphan prices" needed to be high per patient for innovators to make a reasonable profit after recouping research and development costs. Both considerations are subject to great uncertainty, however. First, there is no universal agreed on definition of what constitutes a "rare" disease. A recent survey of definitions from more than 1,100 organizations worldwide found significant variation, ranging from prevalence thresholds of five to 76 cases per 100,000 population [4]. Variation was correlated with stakeholder type, with patient groups and payers employing the most liberal and restrictive definitions, respectively. In addition, there is no clear threshold for what a "reasonable" innovator profit might be, a discussion further complicated by the presence of government subsidies for orphan drug development that offset significant clinical development costs, provide tax incentives, and extend patent protections.

Beyond these practical considerations has always been the strong societal impulse to prioritize treatment for conditions that are severe, are often inherited, and disproportionately affect the very young, a health care application of the "rule of rescue" [5,6]. Whether and how much the rule of rescue should drive policy-making regarding pricing and access to orphan drugs is a topic of

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ongoing debate among ethicists because concepts of disease severity, young age, and genetic predisposition are not unique to rare diseases, and reimbursement decisions should in theory be made without recognition of the identity of affected individuals [7–9].

For many years, the market for orphan drugs has reflected a sort of unwritten agreement that small patient numbers could allow public and private insurers to maintain reasonable access to orphan drugs despite much higher prices. With a limited number of orphan drugs, this approach allowed innovation to be given suitable rewards, patients could receive rapid insurance coverage, and insurers could absorb high per-patient costs without experiencing destabilizing impacts to their overall budgets. However, the orphan drug landscape is shifting rapidly, with great promise for patients, but also with a growing sense of peril for health care budgets. As illustrated earlier, orphan drugs no longer are a small minority of drug approvals. The number of new regulatory submissions for orphan indications is at an all-time high; Food and Drug Administration (FDA) orphan designations totaled 350 in 2015 [8], and 41% of the drugs the agency approved in 2016 carried an orphan designation [10]. With increasing numbers of orphan drugs coming into the health system at high orphan prices, and with some drugs moving from initial orphan status to command much broader indications and "blockbuster" revenues, US decision makers have significant challenges but also an opportunity—to create an explicit framework for evaluating and pricing orphan drugs that is informed both by experiences in other countries and US-specific ethical and contextual considerations.

The Ethical Context of Funding Decisions for Treatments of Rare Diseases

There are many reasons why pricing and coverage decisions for rare diseases involve considerations that differ from those of more prevalent conditions. Many of these considerations stem from practical challenges with evidence development and with recouping development costs, given the small size of these populations. On a per-patient basis, the high research and development costs and possibility of a low return on investment make rare-disease treatments a less attractive commercial target, in principle, than interventions for more prevalent conditions [11]. This is particularly true for "ultra-rare" conditions, a term that has no formal definition, but with reported prevalence ranging from 1 per 50,000 to 1 per 1 million population [4]. The high prices that have been set for orphan drugs are in part an outgrowth of the desire to extract a profit from a small patient base, but these higher prices have meant that these orphan drugs often do not meet commonly cited cost-effectiveness thresholds for medical interventions [12].

The fact that treatments for rare and ultra-rare conditions often fail to meet cost-effectiveness thresholds that are used to consider what a reasonable value would be for other treatments raises important ethical questions of fairness. Some ethicists and health economists have argued that fairness requires using the same standards to judge the value of treatments for all individuals [5]. In this view, the primary goal of health insurance and the health system is to use available resources to maximize the health of the population, and if resources are spent systematically for patients with rare diseases in a way that produces less health gain than could have been obtained by using the same resources to help other patients even more, this represents an unfair opportunity cost. Therefore, spending for orphan treatments that exceeds the cost-effectiveness threshold applied to other treatments means that, ultimately, other "invisible" patients will be harmed.

Nevertheless, as mentioned earlier, many countries have carved out decisions regarding orphan, and particularly ultra-orphan, treatments from usual considerations of cost effectiveness. From an ethical perspective, this has been justified in several ways. First, some have argued that the goal of a health system, or of a society more broadly, is not simply to maximize health gains across the entire population. In this view, fairness can be defined as ensuring that all patients get some chance at a meaningful health gain (e.g., surviving a universally fatal childhood disease), even if this exceeds standards for what would be considered a cost-effective use of health resources [13]. This perspective on fairness is sometimes accompanied by arguments that prioritization of resources should embody the value of "fair innings"—the notion that, all things being equal, preference for curative therapy should be given to younger individuals whose circumstances have denied them the ability to live a full life, over older individuals [14,15].

There are, therefore, competing ethical interpretations of "fairness" in the context of spending on expensive treatments for rare and ultra-rare conditions. This ethical tension is captured well by Hughes et al [5]:

> A key issue around whether … funding should support the provision of ultra-orphan drugs is whether the rarity and gravity of the condition represents a rational basis for applying a different value to health gain obtained by people with that condition. That ultra-orphan drugs are reimbursed at all, illustrates the fact that budget impact, clinical effectiveness and/or equity issues are given precedence over cost-effectiveness in decisions on resource allocation in some countries. The consequence, however, is that the opportunity cost of supporting the use of ultra-orphan drugs necessitates that patients with a more common disease, for which a cost-effective treatment is available, are denied treatment.

There is no simple solution to this tension; many, but not all, ethicists argue that some preference, some premium, is due to treatments for very rare conditions. But no ethicist or manufacturer, clinician, insurer, or citizen would argue that treatments for rare conditions should command an unlimited premium. To decide how much preference, how high the price for a treatment should go, is a question whose answer requires us to find an elusive balance between two different views of fairness.

Rare Disease Landscape in Health Technology Assessment and Payer Systems

For private payers in the United States, the increase in orphan drug approvals, often depending on small, noncomparative studies and surrogate endpoints, coupled with rising prices and frequent expansion beyond orphan indications, has created an atmosphere of deep concern. A recent survey of leaders at seven private insurers that comprise 75% of the US market found that more than two-thirds were concerned and monitoring the current orphan drug pipeline [16]. Despite this concern, most respondents reported that their strategic plans to manage orphan drugs are either in the earliest stages of development (initial dialogue with providers and facilities) or that they are unsure of what to do. Most payers reported the use of prior authorization requirements that are tied to FDA labeling, but relatively few described other utilization management efforts, such as requirements for genetic/diagnostic testing or ongoing monitoring for clinical improvement [16].

As the largest single insurer of children in the United States, Medicaid has a particularly important role in coverage and reimbursement for many orphan drugs, especially those that treat ultra-rare conditions. Among the 50 most costly drugs to