Expert Opinion on Orphan Drugs

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EXPERT OPINION

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Access and availability of orphan drugs in the United States: advances or cruel hoaxes?

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The Orphan Drug Act of 1983 in the United States collapsed the barrier between patients with rare diseases and promising drug treatments. Over the subsequent 30 years, > 400 'orphan drugs' became available to them. However, with thousands of rare diseases still left with no treatments at all, many efforts are being put toward generating more investment for discovery, new clinical trial methods and more efficient approval processes. But, a new threat to access has emerged from the costs patients increasingly must bear. We call for a coordinated systems engineering approach that makes more treatments available to more people without unintended negative consequences on individual elements of the process.

Keywords: access, economics, orphan drugs, rare diseases, regulation, research

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1. A barrier to access falls

Western industrial nations, certainly the United States, have left pharmaceutical development mostly to for-profit, commercial organizations. Operating under market-driven economic behaviors, pharmaceutical research and manufacturing companies have traditionally focused their drug development programs on the largest patient populations that can produce the largest returns on investment. Utilitarian impulses to do the most good for the most people may be at work to some degree as well. Both motivations are rational, *prima facie*, but they work against the interests of people with rare diseases who seek new treatments.

This dynamic dominated pharmaceutical development during the latter half of the 20th century. Diseases with large patient populations drew the attention of most pharmaceutical developers: diabetes, cardiovascular diseases, asthma, arthritis, infectious diseases and cancer to name a few. Indeed, very few drugs were developed and marketed for diseases affecting very small populations during that time [1]. The more discernable pathophysiology of certain rare diseases with unambiguous targets for treatment development could not overcome the allure of the large populations more common diseases offered, even among those associated with multifactorial causes that complicate drug development and approval. People with rare diseases saw that this paradox would persist until incentives were in place that made the business case for developing treatments as inviting for small populations as it was for large populations. They knew they needed a big idea for a big breakthrough [2].

For a small group of rare disease patient advocates, the big idea was to package a set of incentives for rare disease drug development into a federal law. The Orphan Drug Act of 1983 resulted from their efforts, and which worked to remove a formidable barrier to new treatment access for rare disease patients through a series of tax benefits and market exclusivity provisions among other incentives. Thirty years later, over 400 drugs had been made available for nearly 450 rare disease indications [3]. For some rare diseases, there is even competition within drug categories. However, patient access to these therapies is again threatened, though not for lack

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of scientific breakthroughs or compelling business cases for developers, but rather because of financial barriers posed by payer policies and requirements. To many patients with rare diseases, new treatments without viable access look more like cruel hoaxes than medical advances. Action with the impact of the Orphan Drug Act is needed now to address this impending crisis.

2. A new barrier to access rises

Within the first 3 years following the Orphan Drug Act becoming law, the pharmaceutical industry obtained between 50 and 100 orphan drug designations every year until 2003 when the Human Genome Project (HGP) was completed. The information, tools and efficiencies HGP made available enabled researchers to discern the molecular and genetic basis of rare diseases and to design targeted treatments. The rate of orphan drug designations increased accordingly, reaching a record of 260 new designations in 2013, and orphan drugs have consistently comprised 30 – 40% of total new drug approvals over the last several years [4,5]. The commercial success of orphan drug products has further spurred orphan drug designation growth rates.

And yet, thousands of rare diseases still remain without treatments. This state of affairs has worked to attract legislative, regulatory and patient advocacy group involvement toward increasing the development and approval rate of new treatments. As examples, federal legislation such as the FDA Safety and Innovation Act facilitates the use of new tools and methods for emerging treatments for rare diseases and makes mechanisms available to speed approvals. The US FDA has created guidance and procedures to address challenges generated by small populations requiring complex treatments [6]. Patient advocacy groups are helping to de-risk treatment development through venture philanthropy [7]. Academic researchers and leading investor groups are developing new methods to attract investment capital for research and development [8,9].

All of these efforts and others like them will increase the rate of new treatments available for rare diseases. This should come as good news to people with rare diseases, and it does, but they greet the news with some trepidation. Their cautious optimism comes mostly from fears about whether they will get access to these new treatments because of the costs they have to bear and the often bewildering distribution processes they have to master.

Payer reactions to orphan drug costs are behind much of the patient fears over access problems related to costs. None of the work being done to increase the number of treatments for rare diseases is taking patient cost barriers into account. These new treatments are fed into a payment environment that is not configured to incorporate very high cost treatments for rare diseases. As more of these highly expensive products have become available, the payment environment has been contorted into irrational and unjust forms. Many payers pass proportions of orphan drug costs onto rare disease patients that exceed the proportions of costs patients pay for less expensive products. If patients needing orphan drugs cost the payer more, then these patients should pay more, goes a common explanation. That these patients do not have alternatives - be they biomedical or behavioral - or that this approach is antithetical to basic insurance principles either goes unnoticed or is unpersuasive.

The existence of patient assistance programs lays bare the failure of payer environments to adapt coverage policies that accommodate highly expensive orphan drugs. These programs provide a secondary or shadow financial support system for patients who do not have enough money to pay for their prescriptions. The gaps arise for people who do not have any, or have only inadequate insurance coverage, such as can be the case with policies requiring patients to pay a percentage of the prescription costs. Even with annual caps on the amount patients spend now, the amounts they must still pay can push the drugs they need out of reach. The extent of this problem is evidenced by an expansive and burgeoning patient assistance program industry - an industry that has grown as large as $5 billion by some estimates [10]. Many people depend on these programs as the only means they have to get their medications, but these programs perpetuate the underlying causes for access challenges. Drug developers, in an effort to improve access to those who qualify, often provide the funds for these programs putting upward pressure on drug pricing, which then drive patient payment requirements correspondingly. Some payers looking to reduce their costs will exclude coverage of drugs where there are patient assistance programs, thus further dissembling basic insurance constructs that spread the costs of rare but catastrophic events across large pools of people [11]. Indeed, even hospitals will use these programs to lessen the burden of uncompensated care [12].

3. A coordinated systems approach

Thus, the current efforts to accelerate development of rare disease treatments need to be expanded in scope to incorporate patient access related to costs. And, importantly, any mechanisms aimed at preventing access barriers cannot create new barriers to research and development investment or require new burdens on regulatory review processes. We are suggesting that a more coordinated systems approach by which orphan drugs are discovered, developed and delivered to patients be adopted so that no efforts to improve individual elements unintentionally work against the effectiveness of other elements [13,14].

Coordinated systems approaches to orphan drug development apply at both macro (system) and micro (individual product) levels, and will require involvement from patient groups, clinicians, regulatory agencies, payer organizations, research methodologists, scientists, ethicists and developers, among others. People from industries other than health care can offer ideas that may otherwise be obscured by entrenched

perspectives within health care. However, bringing in people representing the various aspects of a coordinated approach does not produce a coordinated process itself. Process engineering experts are necessary to ensure that all the required input is obtained and simultaneously integrated and reconciled so that effects on certain elements of the process are not countered by unintended consequences. Well-engineered processes will include design scenarios and simulations to test a range of configurations that minimize waste and inefficiency, and that optimize value for all stakeholders. Success will yield higher rates of effective rare disease treatments approved through more streamlined regulatory approval steps, be easily accessible to patients, and encourage new investments in research.

Our urging for a coordinated systems approach to orphan drug development is not a matter of fine-tuning or working around the margins of an adequate system. Leading figures from across the health care system warn that the costs of developing, approving, covering and accessing orphan drugs will eventually become 'unsustainable.' Alas, there are signs that they are becoming unsustainable now. Clearly, patients struggle with the costs as they either forgo treatments or are forced to seek support from patient assistant programs, and clinicians are now publicly admitting that they will not prescribe certain treatments because of cost considerations. Investment money is always at risk of moving away from rare diseases or to other financial sectors in search of more efficient or effective returns. Payer organizations are continuing to push more costs onto patients and at the same time restricting coverage policies. Most ominously, legislators are voicing concerns about these costs, and beginning to consider possible actions. Major advances are on the horizon, such as gene therapies, and others yet unknown that will undoubtedly put even more pressure on costs and intensify these responses.

A systems engineering approach to orphan drug development is thus needed now. The National Organization for Rare Disorders, the MIT Center for Biomedical Innovation (CBI) and the MIT Laboratory for Financial Engineering are jointly leading an effort to create a framework for a coordinated approach to the development, delivery and financing of new orphan drugs. We will assemble a group of cross-sector leaders, all of whom share a commitment to and will work together toward creating a sustainable environment that facilitates important discoveries, and reliably turns them into accessible therapies.

Building on the methodologies successfully applied by MIT CBI and its NEWDIGS consortium to regulatory innovation [15,16], this initiative will start with the goal of improved patient 'outcomes.' Outcomes considered will not only be medical needs but patient health status, quality-of-life indicators and economic consequences to list just a few. The group will aim to ultimately generate a set of frameworks, tools and validated models for application across scientific discovery through clinical adoption and payment policies, and for assuring rare disease patients that orphan drugs will be easily within their grasp.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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