**PROTEIN REPLACEMENT THERAPIES FOR RARE DISEASES: A BREEZE FOR REGULATORY APPROVAL?**

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Protein replacement therapies for rare monogenic diseases have a higher probability of regulatory approval compared with biologics, small molecules, and grant-funded orphan drugs.

**ORPHAN DRUG APPROVALS ON THE RISE**

Diseases with a prevalence of less than 200,000 affected individuals in the United States and less than approximately 250,000 affected individuals in the European Union (EU) can be designated as orphan diseases. The passage of the U.S. Orphan Drug Act in 1983 provided regulatory, tax, and commercial incentives to companies developing drugs for orphan diseases in the United States. Similar legislation was passed in the EU in 2000, and several other countries now provide regulatory and commercial benefits to products for rare diseases. Activism by rare-disease advocacy organizations—for example, the National Organization for Rare Disorders (NORD) and Rare Diseases Europe (EURODIS)—and patient associations, as well as the cooperation between academic institutions, companies, and regulatory agencies, has led to an increase in the number of orphan drug designations over time. In the United States, the U.S. Food and Drug Administration (FDA) designated 1 orphan drug in 1983, 70 in 2000, and 199 in 2011. In the EU, the EMA designated 10 orphan drugs in 2000 (first year of designations) and 104 in 2011 (www.fda.gov and www.ema.europa.eu, respectively; a single drug may have an orphan designation for more than one indication). Three areas within orphan diseases have the most orphan drug approvals: pediatric indications, rare types of cancer, and genetic diseases. Protein replacement therapies have proven to be a valuable treatment for rare monogenic diseases.

The first monogenic protein replacement therapies (MPRTs) in the orphan drug space to receive regulatory approval in the United States and EU were blood factors and enzyme replacement therapies for lysosomal storage disorders. These MPRTs introduced a new commercial model called “orphan drug pricing,” in which high premiums are applied to life-changing therapies. Currently, the annual cost for MPRTs, such as Fabryzyme, Elaprase, and Naglazyme, generally exceeds $200,000 (1), and sales of orphan MPRTs exceed $100 million per year.

There has been considerable attention given to the high prices of orphan drugs and the challenges with reimbursement (2, 3). MPRTs are reimbursed in the United States, in many countries of the EU, and in Japan, and they are often supplied at no cost in the developing world or through patient assistance programs. In order to continue to support orphan drug pricing and obtain reimbursement, it is important for developers of MPRTs to make a case to payers for cost-effectiveness of these therapies. Although certain MPRTs have shown long-term safety, clinical efficacy, and improvements in health-related quality of life (4–6), more data are needed to demonstrate cost-effectiveness (a net reduction in health-care costs from MPRTs) to justify reimbursement in certain countries (2).

**LOW DEVELOPMENT RISK**

The Tufts Center for the Study of Drug Development (CSDD) has published several reports on clinical approval success rates. In 2010, DiMasi et al. published the results of a study evaluating the clinical approval success rates for investigational compounds that entered clinical testing between the mid-1990s and the early 2000s from the 50 largest pharmaceutical firms (as determined by 2006 sales) (7). This study stratified data by product type (large versus small molecule). The authors reported the overall probability of clinical approval success at 19%, with biologic drugs having a higher success rate (32%) than that of small-molecule drugs (13%). Tufts CSDD also published a report in 2010 that looked specifically at approval probabilities for orphan drugs. In this study, sponsors engaged in orphan grant–funded development reported that 22% of their clinical programs led to approvals (8). The probability of regulatory approval for MPRTs, which comprise only a small fraction of the total number of approved drugs, has not been determined.

We conducted an analysis to determine whether MPRTs would have a higher probability of success through clinical trials, compared with all orphan drugs and all other drug classes. If these therapies have a higher probability of success than those of other new molecular entities (NMEs), a case could be made for expanded investment to develop MPRTs for orphan diseases that currently have no approved therapeutic products.

**MPRT: APPROVED OR TERMINATED?**

To conduct our analysis, we consulted several data sources. We began by reviewing all U.S. and EU orphan product designations and identifying monogenic protein replacement therapy candidates (www.fda.gov and www.ema.europa.eu). Because companies may not seek orphan designations for certain protein replacement therapies (for example, follow-on therapies or plasma-derived therapies reviewed at the national level in the EU), we supplemented our orphan drug designated product search by conducting candidate searches in the Adis R&D Insight database (http://bi.adisinsight.com), reviewing public domain candidate data from Tufts CSDD (http://csdd.tufts.edu/research/databases), reviewing product listings from the World Federation of Hemophilia (www wfh.org), and by reviewing the pipelines of companies we know are active in the MPRT space. Our analyses were restricted to MPRTs for the treatment of orphan diseases that had entered or completed clinical trials, filed for or received regulatory approval as of 30 November 2011. For inclusion in the study group, therapies had to meet certain criteria, as described in the Supplementary Methods.

We identified 144 replacement therapies approved or investigated for 40 unique proteins that are deficient or dysfunctional owing to mutations in a single gene associated with an orphan disease (table S1). We then determined whether these therapies were at the preclinical stage, clinical stage,
or currently marketed. For those in clinical trials, we determined whether the candidates were active or terminated. Candidate status was recorded as the most advanced clinical phase or approval in either the United States or EU. To determine the probability of approval for candidates that have entered clinical trials, the 23 active preclinical programs (for 21 protein targets) were not included in the analysis. The removal of these candidates left 121 total therapies directed to 29 targets. Eighty-five of these therapies have received regulatory approval for 21 monogenic diseases, and 25 are active clinical candidates directed to 14 targets (Table 1). Eleven terminated candidates were identified. Our analysis shows that once MPRTs enter clinical trials, the probability of regulatory approval is 88%, compared with Tufts CSDD’s rates of 19% for all drugs (7) and 22% for grant-funded
orphan drugs (8). [The probability of regulatory approval for monogenic protein replacement therapies of 88% was calculated as follows: (85 × 100) / (85 + 11).]

To reduce the influence of the large number of approved candidates for Factor VIII and Factor IX, we also calculated the probability of approval for a first-in-class protein replacement therapy. Here, we considered the number of targets that had at least one approved MPRT (21 targets) with the total number of targets for which a candidate’s ultimate fate (approval or termination) was known (23 targets). Only two targets, arylsulphatase A and porphobilinogen deaminase, had candidates terminated in clinical trials, with no approved therapies (table S1). Thus, first-in-class MPRTs have a 91% probability of regulatory success.

**BLOOD FACTORS AND LYSOSOMAL ENZYMES DOMINATE**

If we consider the 27 targets from Table 1 that have active clinical stage and/or approved programs, 85% of MPRTs to these targets can be classified as blood components (12 targets) or lysosomal enzymes (11 targets). The remaining 15% of MPRTs are targeted to metabolic disorders. These target classes may represent the “low-hanging fruit,” and the >85% probability of regulatory success for MPRTs is high because the clinical pathogenesis, mechanism of action, and ability to manufacture the MPRT are well understood for blood components and many lysosomal enzymes. It is possible that the probability of regulatory success of MPRTs for targets outside of these classes will decrease with challenging targets, such as structural proteins, or difficult methods of delivery, such as for central nervous system disorders.

Similarly, lysosomal enzymes and blood products make up 78% of the identified preclinical programs (18/23), with 22% (5 programs) directed toward targets outside of these classes. New MPRT preclinical targets include structural proteins in dermatology (collagen VII in dystrophic epidermolysis bullosa and ectodysplasin-A1 in X-linked hypohidrotic ectodermal dysplasia), mitochondrial enzymes (thymidine phosphorylase in mitochondrial neurogastrointestinal encephalopathy and frataxin in Friedreich’s ataxia), and a nonlysosomal metabolic enzyme [lecinthin-cholesterol acyltransferase (LCAT) in LCAT deficiency].

**CLINICAL AND COST ADVANTAGES**

MPRTs have the advantage of receiving regulatory approval with smaller clinical trials and after shorter development times. For example, the total number of patients evaluated in clinical trials for the MPRTs Elaprase, Vpriv, Fabrazyme, and Naglazyme, were 108, 94, 73, and 56, respectively. Clinical trials for biologics in larger indications generally evaluate >1000 patients. Additionally, the time from Investigational New Drug (IND) application to approval for the MPRTs above were 5.6, 6.2, 6.0, and 4.7 years, respectively, compared with 8.3 years, which is the median time reported for NMEs and significant biologics for the period from 1980 to 2009 (Supplementary Methods) (9).

Paul et al. (10) developed an R&D model to estimate the cost of discovering and developing a single new molecular entity from lead discovery through preclinical and clinical studies to commercial launch. If the high (88%) probability of clinical success for MPRTs was used in this model, it would substantially reduce the out-of-pocket costs and total capitalized costs for the clinical development of an MPRT, compared with small molecules and other biologics.

**OPPORTUNITIES REMAIN**

The commercial potential of MPRTs and the unmet need for new drugs for orphan diseases has led to increasing attention from the pharmaceutical and biotechnology industries, as well as from the investment community owing to the potential returns within this sector. Several companies that focused on the development and commercialization of MPRTs have been acquired for large sums. For instance, in 2011 Sanofi-Aventis acquired Genzyme for ~$20 billion, and Alexion acquired Enobia for ~$1.1 billion.

There are many monogenic diseases that do not have approved protein replacement therapies. Federal agencies such as the National Institutes of Health and the FDA have developed specific guidelines to accelerate regulatory approval and provide incentives for orphan drug development. In addition to the commercial success of MPRTs, we hope the observation that MPRTs demonstrate a high probability of regulatory approval will provide another incentive to develop additional MPRTs for diseases for which no therapy is available, as well as to create improved follow-ons for existing treatments.

**SUPPLEMENTARY MATERIALS**

Methods Table S1. Active MPRT preclinical candidates and MPRTs that have entered clinical development or received regulatory approval.

**REFERENCES AND NOTES**


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