Drug development for orphan diseases in the context of personalized medicine

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Orphan diseases are diseases that are found in less than 200,000 patients in the United States, which is the cutoff point for the number of patients for a drug to be profitable. Because many thousands of orphan diseases exist in the aggregate (about 20 to 30 million Americans have orphan diseases), these patients are disenfranchised from drug development by the pharmaceutical industry. Orphan drugs are a large part of personalized medicine. The orphan diseases are often so rare that a physician may observe only 1 case a year or less. So proper treatment is a personalized encounter between doctor and patient. Academic physician-scientists have tried to fill this therapy vacuum by working on developing orphan drugs. But many disincentives are involved, which include career disincentives, lack of funding, and the multiple areas of expertise that are required. Positive developments include formation of the National Organization for Rare Diseases, the Orphan Drug Act, the development of a grant program to fund orphan drug development, the formation of the National Institutes of Health Office of Rare Diseases, and the passage of orphan drug legislation by other countries. Progress has increased, but the 300 orphan drugs and devices approved in the last 25 years are still only a drop in the bucket compared with the many thousands of orphan diseases. I believe we must do better. I present my own 2 examples of the positive and the negative aspects of orphan drug development, and I end this article by giving recommendations on how we might succeed both in developing more orphan drugs and in rescuing the pharmaceutical industry from its impending economic collapse. (Translational Research 2009;154:314–322)

Abbreviations: FDA = U.S. Food and Drug Administration; IRB = Institutional Review Board; NDA = new drug application; NIH = National Institutes of Health; NORD = National Organization for Rare Diseases; ORD = NIH Office of Rare Diseases; SQNS = semiquantitative neurologic scoring; TM = tetrathiomolybdate

Orphan diseases are defined by the U.S. Food and Drug Administration (FDA) as diseases numbering 200,000 cases or less in the United States.[1] The term ''orphan'' for these diseases has been adopted because it is roughly the cutoff point for willingness by pharmaceutical companies to work on treatments for a disease. If less than 200,000 cases exist in the United States, the potential return on an effective therapy is traditionally not deemed worth the research and development expenditures to bring a product to market. Hence, these diseases are called orphans.

Literally thousands of orphan diseases exist (the National Institutes of Health (NIH) Office of Rare Diseases (ORD) mentions that 6800 rare diseases are known today),[1] which range from the extremely rare (only a few

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cases described) to diseases that are common in the experience of many physicians, particularly specialized physicians, such as multiple sclerosis, cystic fibrosis, and muscular dystrophy, but still fall below the 200,000 cutoff. And, of course, many rare diseases are still to be discovered. If we assume an average 5000 patients in the U.S. per orphan disease, and 4000 orphan diseases that need treatment, this number adds up to 20 million patients with orphan diseases needing treatment in the United States. ORD estimates there are 25 to 30 million people in the United States with a rare disease.[1] Thus, in the aggregate, patients with orphan diseases represent a large number of patients, whose pharmaceutical needs have largely gone unmet by the pharmaceutical industry.

Personalized medicine is particularly relevant in any discussion of treatment for orphan diseases. For the most part, these diseases are so rare that the average physician may observe only 1 case in a year, or perhaps only 1 case in a career. Thus, the treatment of that case becomes a personalized experience between physician and patient. Furthermore, research in the design of drugs for patients with rare diseases is of a necessity personalized, because the researcher must use methods that will identify the specific rare patients for which the drug is being designed, and then test the therapy in those rare patients. Medical care becomes an important part of the researcher's role. This care becomes very personalized between researcher and patient.

As we have already pointed out, this type of research is generally not of interest to pharmaceutical companies because of the lack of profit potential. This result leaves this area of research in the hands of academicians, usually physician-scientists, who have to overcome multiple problems if they are to make progress. These scientists, if they are going to develop a treatment idea into a marketed drug, generally without pharmaceutical company help until the last stages, have to reproduce the functions that a large drug company goes through to develop a drug. These functions include chemical synthesis, purification, formulation, animal toxicity testing, animal efficacy studies, preparing drug for first human use, FDA interactions and investigational new drug approval, phase I human testing, then phase II clinical trials in the disease, which might include dose ranging, pharmacokinetic and pharmacodynamic studies, and finally phase III double-blind trials against the best alternative drug, which are usually multi-institutional. The problems that develop are that the physician scientists are not trained in most of these areas, and in fact, it would be difficult for any scientist to have expertise in all these areas. Furthermore, funding is generally not available for many of the more mundane steps such as chemical synthesis, purification, formulation, animal toxicity testing, and dose ranging studies in humans.

After perusing the above introductory remarks, the average reader is probably feeling rather pessimistic about the prospects of drug development for orphan diseases, and indeed, gloom is appropriate for some areas. However, there are positive developments. We will next review these various positive aspects.

REVIEW OF POSITIVE DEVELOPMENTS

National Organization for Rare Diseases (NORD). In 1982, Dr. Jesse Thoene and I organized the first orphan disease conference, in Ann Arbor, to bring together scientists interested in orphan drugs with drug company representatives, representatives of lay organizations involved with orphan diseases, and various types of administrators and political representatives. The results of this meeting were published.[2] Two subcommittees of this meeting recommended formation of an umbrella organization concerned with all orphan diseases.[2] From this recommendation, NORD was founded in 1983.

Over the years, NORD has done many good things. Early after its formation, it successfully lobbied Congress, and others, for the passage of an improved orphan drug act, some aspects of which we will review shortly. NORD has extended its umbrella to include a large number of lay organizations (over 2000), each of which is involved with a specific disease.[3] In this way, these small and relatively unfunded organizations have a voice in the area of orphan disease activities. NORD has developed a Rare Disease Database, which includes reports on more than 1150 rare diseases. It publishes The NORD Guide to Rare Disorders and a Physician's Guide booklet. NORD has been instrumental in influencing the development of other legislation, such as the formation of the National Commission on Orphan Diseases, and in helping the passage of orphan drug laws in other countries. Finally, NORD has accumulated enough funds to offer a small grant program in the area of treatment development for orphan diseases.

The Orphan Drug Act. In 1983, Congress passed the Orphan drug Act, which was signed into law by President Reagan. This act provided tax relief for companies investing in clinical research for orphan drugs, and it provided for 7 years of exclusivity for a product approved for an orphan disease, even though the product might be otherwise in common use. For example, a pharmaceutical company and I received approval for zinc to treat Wilson's disease, which is an orphan disease. The company that received the approval had 7 years of marketing exclusivity for zinc treatment of Wilson's disease, even though zinc can be purchased over the counter. In other words, no other company could advertise or market zinc for Wilson's disease during this period.

An important outcome of the Act was to call attention to the need for treatment development for orphan