

FDA'S ROLE IN THE APPROVAL OF DRUG PRODUCTS

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Patients with rare diseases encounter unique challenges, often beginning with the issue of diagnosis. As many of you are aware, it may take many months, if not years to receive an accurate diagnosis, only to be told that there are few, if any, drugs available to treat the disease. If a disease is an orphan disease – that is, it affects fewer than 200,000 patients in the U.S., pharmaceutical firms may be reluctant to invest in developing therapies for disease, since the return on investment may not be realized. What, then, is the role of the United States Food and Drug Administration (FDA) and the Office of Orphan Products Development (OPD) in helping patients receive therapy for their specific disease?

As a result of the obvious need to serve patients with rare diseases, the U.S. Congress, in 1982 passed the Orphan Drug Act (ODA), amending the Federal Food, Drug and Cosmetic Act. This law, which was signed by then President Reagan in 1983, created incentives for companies and academic researchers to develop products to treat rare diseases.

It is estimated that there are more than 6,000 rare diseases in the U.S., and the number of these diseases is constantly growing. In addition to aplastic anemia and myelodysplastic syndrome (MDS), other rare diseases include the childhood and adult leukemias, the inherited and inborn errors of metabolism like phenylketonuria (PKU), Lou Gehrig's Disease (Amyotrophic Lateral Sclerosis or ALS), Gaucher Disease, Severe Combined Immunodeficiency Syndrome and many, many more.

People with rare diseases are entitled to treatment for their disease that is safe and effective, just like patients with more common diseases. So, the ODA did not in any way change the standards for development, review and approval of a new drug. What the ODA did do is establish incentives that would create sufficient reward for pharmaceutical companies to be willing to invest in drugs for rare diseases.

Before talking about the incentives, I would first like to address, briefly, the process of drug development. How are new drugs developed? When a promising compound is described for a particular disease, the first step is to determine whether it is safe for people. The literature is replete with stories of disasters occurring when products were given to people without first establishing safety. The first step in safety is to look at the product in animals – both from a general safety/toxicity standpoint as well as from the standpoint of long-term use which might affect the offspring of the patient, or which might result in organ damage or cancer causation. When the product passes the safety threshold, it is time for the company to request an IND (Investigational New Drug Exemption) from the FDA Center for Drug Evaluation and Review (CDER), or the FDA Center for Biologic Evaluation and Review (CBER). Once the IND is approved, the company is then able to test the product in patients.

The first step in giving a previously untested product to patients is to give it to a small group of individuals – either normal volunteers or actual patients – to further evaluate safety parameters. If no problematic side effects appear during Stage I, we are ready to further evaluate the product as a treatment for the disease. Ideally, the next step would be Stage II: determining the best dosage of the product to be given. With rare diseases, this may or may not be easy to do. Often with very rare diseases – such as aplastic anemia and MDS, we do the best we can to ascertain proper dosage, but exact dosage establishment may not occur. And, finally,

the Stage III trial(s). This is the stage at which the efficacy of the product in this type of disease is actually evaluated. Ideally, this trial is conducted in a double blinded fashion, where some of the patients get the drug and some get a placebo. Neither the patients nor their physicians know what they are taking. Hence the term, "double blinded." After a predetermined period of time, the results are reviewed to determine if the individuals taking the product did significantly better than the individuals who received a placebo. Side effects are also reviewed. Usually two double-blinded trials are performed to be certain that the effects seen are real.

If the results of the trials are positive – that is to say, the patients on the real drug did better than the patients on the placebo – then the product data is ready to be presented to the FDA who will review the data and determine if significant efficacy and safety standards have been met. Needless to say, the above description is an over- simplification of the entire clinical trial process which actually takes a tremendous amount of time, and costs a significant amount of money.

How can the ODA assist in the process of development of treatments for rare diseases? As I previously mentioned, the ODA provides incentives to induce companies to develop products for rare diseases. The most important incentive is seven years exclusive marketing rights for that drug for that disease upon FDA market approval. No like product may be approved by the FDA to treat that disease for seven years. Marketing exclusivity provides assurance to the firm that their investment is safe from competition and erosion of their share of the market. There are also tax incentives which may be applied forward for 20 years and have a one year "fall back" provision as well. This incentive is particularly valuable for small and medium sized firms. The incentive is administered by the Internal Revenue Service (IRS) and not by the FDA. Once the product is designated as an orphan product, the company may seek advice and counsel from the OPD concerning the drug and its development. Staff from the OPD attend meetings with the company and the review divisions of the Center for Drug Evaluation and Research (CDER) and the Center for Biologic Evaluation and Research (CBER). At these meetings, the best way to study the drug is determined. The OPD serves as the ombudsman for the company and for the patients with the disease.

Another significant incentive of the ODA is the waiver of the PDUFA fee. PDUFA stands for Prescription Drug User Fee Act. That law permits FDA to charge a company for the review of the data leading up to the approval of a new drug. In 2006, the user fee for a new drug approval application is more than \$700,000. For small and medium sized firms, this is a significant cost. The waiver of this expenditure is very helpful in promoting the development of a product to treat a rare disease.

Grant dollars are also available to assist, mainly academic researchers, in the development of treatments for rare diseases. Often the awarding of an OPD grant will be the first time a particular product can be used in a patient. If the drug shows promise, a pharmaceutical firm will be more likely to be interested in the product.

Over the past 22 years, the ODA has proven to be VERY successful. There are 270 drugs and biological products that have been FDA approved to treat rare/orphan diseases. In the aggregate these products treat more than 13 million patients in the U.S. In addition, there are more than 1400 drugs and biological products that have been designated as orphan drugs by the OPD. Many of them will become FDA approved products to treat orphan diseases.

Most orphan diseases are serious and life-threatening diseases. FDA has always viewed these diseases as requiring more attention and faster review times. The OPD staff work diligently with the staffs at CDER and CBER to be certain that necessary products to treat serious orphan diseases are approved as quickly as possible.

Clearly, more needs to be done. While 270 is an impressive number of new drug approvals, with more than 6,000 diseases, we have just begun to scratch the surface.

For more information:

- ◆ Call the U.S. Food and Drug Administration at 800-300-7469
- ◆ U.S. Food and Drug Administration, Center for Drug Evaluation and Research
<http://www.fda.gov/cder/>
- ◆ From Test Tube to Patient
http://www.fda.gov/fdac/special/newdrug/ndd_toc.html
- ◆ Consumer Education: What You Should Know About Buying and Using Drug Products
<http://www.fda.gov/cder/consumerinfo/DPAdefault.htm>
- ◆ New Drug Approval Process (*chart*)
<http://www.fda.gov/cder/handbook/develop.htm>
- ◆ Investigational New Drug (IND) Review Process (*chart*)
<http://www.fda.gov/cder/handbook/ind.htm>
- ◆ New Drug Application (NDA) Review Process (*chart*)
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