ing or evaluating the work of so many volunteers.

Some organizations conduct internal evaluations, and they tend to agree with experienced volunteers on some guidelines for effective overseas missions. It is best, they say, to send an advance team so that requirements such as lodging, an adequate electrical supply, clinic space, and surgical facilities can be anticipated. Many stress the importance of developing strong relationships with local physicians on the basis of respect for their skills, knowledge, and traditions and, whenever possible, using locally available medications. Surgeons recommend a conservative approach to choosing patients and operations to perform. Finally, says Migliori, "don't operate the day before you leave."

An interview with Dr. Mark Migliori can be heard at www.nejm.org.

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FOCUS ON RESEARCH

Adopting Orphan Drugs — Two Dozen Years of Treating Rare Diseases

Marlene E. Haffner, M.D., M.P.H.

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In 1982, when the Orphan Drug Act was passed as an amendment to the Federal Food, Drug, and Cosmetic Act,[1] few suspected the extent to which this law would alleviate the plight of patients with rare diseases. The law defines an orphan drug as one with efficacy against a disease affecting fewer than 200,000 people in the United States or one that scientists and economists at the Food and Drug Administration (FDA) determine will not be profitable for seven years after FDA approval.[2] In the 24 years since this law was passed, 282 such drugs and biologic products, providing treatment for more than 14 million patients in the United States, have come to market under its aegis. In the 8 to 10 years before 1982, by contrast, only 10 treatments for rare diseases had been approved by the FDA and brought to market.

Much has been learned about rare diseases in the United States since the passage of the law. Of the orphan drugs that have been approved, 56 percent are for chronic diseases. Examples include ovine digoxin immune Fab (Digibind) for the treatment of life-threatening digitalis intoxication; ceramide trihexosidase–α-galactosidase A (Fabrazyme) for the treatment of Fabry's disease, a lipid-storage disorder; and nitisinone (Orfadin) for the treatment of type 1 tyrosinemia, a metabolic disorder caused by the lack of the enzyme fumarylacetoacetate hydrolyase, which, if left untreated, results in hepatic carcinoma, often before four years of age.

Many rare diseases have a genetic component, and the patients who have them require treatment throughout their lives. Many cancers are also quite rare, and a number of drugs for cancer have been developed under the Orphan Drug Act (see graph) — for example, imatinib (Gleevec) for chronic myelogenous leukemia and gastrointestinal stromal tumors, tretinoin (Vesanoid) for acute promyelocytic leukemia, and ifosfamide (Ifex) for testicular cancer. A substantial proportion of the drugs in development are for use in children; for example, somatrem for injection (Protropin) has been developed to treat congenital growth hormone deficiency. Although most rare diseases are chronic, a number — such as infant botulism, discussed by Arnon et al. in this issue of the *Journal* (pages 462–471) — are acute.

Whether a disease is rare or common, however, the discovery, development, and clinical testing of a drug that can treat it represent a long, arduous, and expensive process. Drug companies are therefore loath to invest in a product for a disease that affects relatively few people unless they can be assured of a return on their investment. The Orphan Drug Act created government incentives to encourage academic researchers to participate in research on drugs for the treatment of rare diseases and to encourage the pharmaceutical industry to invest in the development and marketing of such drugs. Under this law, a

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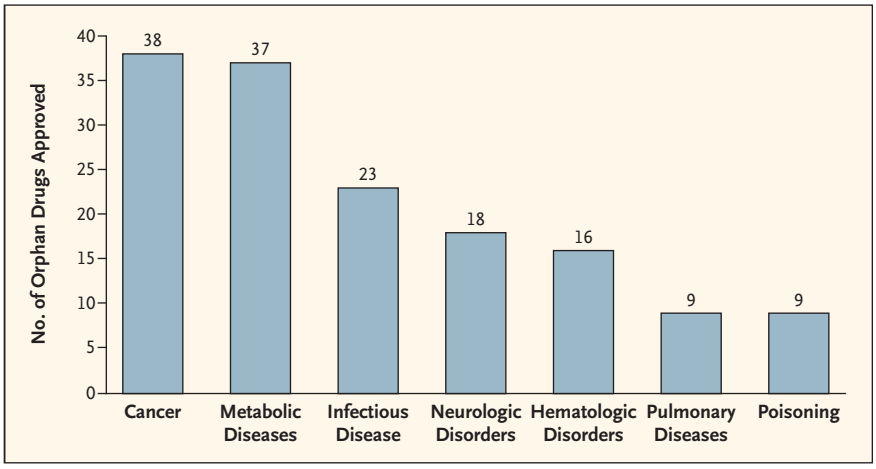
company or a researcher applies to the FDA's Office of Orphan Products Development to have the drug they wish to study designated as an orphan drug. After scientific review of an adequately documented submission, drugs that are so designated qualify their researchers and developers for benefits that include tax credits for clinical development, seven years of exclusive marketing for the specified indication after FDA approval, and development assistance from the Orphan Products Office. In addition, academic researchers and pharmaceutical firms may apply for FDA grant support to assist in the clinical development of the product.

Orphan drugs must go through the same development process as any other drug and must be shown to meet the same standards for effectiveness and safety as a drug for a common condition. Indeed, because of the small number of patients available to be enrolled in clinical trials of orphan drugs, these products must be even more effective than the average drug if a statistically significant benefit is to be established. As for safety, since 85 to 90 percent of known rare diseases are serious or life-threatening, patients and physicians may be willing to accept a slightly higher level of risk than they would from a treatment for a less serious disease. But the limited number of patients plays a role here as well: although there have been no reports of serious adverse reactions to any orphan drug thus far, when a product is tested in a very small population, our knowledge of the safety profile may not be as complete as it can be for a treatment for a more prevalent condition.

At the time the Orphan Drug Act was passed, it was thought that some products would not be approvable by the FDA because the population of patients would be too small to permit adequate, well-controlled trials. This has not turned out to be the case. The product that has been approved for the smallest population is bovine pegademase (Adagen) for the treatment of severe combined immunodeficiency syndrome (SCID) of the adenosine deaminase type. The clinical trial for that product involved 8 patients, and only 14 people in the United States had the disease at the time, but they benefited from the interest of a Ph.D. candidate who had used adenosine deaminase as a model in studying whether the attachment of polyethylene glycol to a product could facilitate its entry into a cell. A historical control was used in the trial, and the drug proved 100 percent effective. In the past, children with the syndrome would have died from infection before their sixth birthday, but today, affected children can lead normal lives, contracting the usual colds, chickenpox, and impetigo, as long as they continue to receive this medication.

A study sample of eight for a clinical trial is unusually small, even for an orphan drug. It is possible to study most orphan drugs in two separate clinical trials, both of which may be conducted in a double-blind fashion. However, because the patients are not only few, but also generally geographically dispersed, accrual of patients for studies of orphan drugs is often difficult. Indeed, the randomized, double-blind study reported by Arnon et al. had to be approved by 62 different institutional review boards representing 90 different hospitals in California, and the open-label study involved 155 California hospitals. In some instances, clinical trials of orphan drugs must include centers outside the United States in order to enroll a sufficient number of patients. In cases in which non–U.S. centers are used, the design of the trial and the methods followed, including the obtaining of informed consent, must be the same as those used in the United States if the data are to be acceptable for review and approval by the FDA.

The research and development encouraged by the Orphan Drug Act have brought needed thera-



Drugs Approved by the FDA for the Top Seven Types of Rare Diseases Addressed by Orphan Drugs.

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pies to millions of patients in the United States, but these products are not free from controversy. One criticism concerns the high cost of some orphan drugs — although other drugs developed by means of biotechnology are equally expensive. According to the *Wall Street Journal*, "the cost of specialty pharmaceuticals — biotechnology drugs and other expensive medicines prescribed by medical specialists — is growing twice as fast as [that of] traditional prescription drugs."[3] In the early 1990s, the Orphan Drug Act was credited with enhancing the development of the biotechnology industry by providing the incentive of seven years of exclusive marketing. Many biotechnology products were not eligible for patent protection, since they had been synthesized, and their structure published, before their medical use became known. But generic versions of such products do not currently exist, and the cost of production is high. In addition, in the genomic era, as personalized medicine becomes increasingly possible, developers will be able to make drugs that target a specific genetic profile. Such drugs may serve an even smaller population than most orphan drugs, and although they may be very effective, they may also be quite expensive. The affordability of all medications in the United States is clearly an issue that needs to be addressed.

By most measures, however, the Orphan Drug Act has been successful in enabling patients with rare diseases to receive treatments that would otherwise never have been developed. Moreover, orphan-drug legislation incorporating the basic tenets of the U.S. law has been enacted in the European Union, Australia, and Japan, and other countries have made some legal accommodation for the importation of products that treat rare diseases. Thus, the Orphan Drug Act has had not only domestic but also global benefits for patients with serious and rare diseases — benefits that will only expand as genomic medicine fuels more rapid progress in alleviating the effects of devastating diseases.

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1. Orphan Drug Act, Pub. L. No. 97-414 (1983).
2. Orphan Drug Act, Pub. L. No. 97-414 (1984 as amended).
3. Anand G. As biotech drug prices surge, U.S. is hunting for a solution. Wall Street Journal. December 28, 2005:A1.

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