BY CYNTHIA BORDA

# Meeting the Needs of Patients with Rare Diseases

THE NATIONAL INSTITUTES OF HEALTH OFFICE OF RARE DISEASES (ORD) LISTS MORE THAN 6,000 RARE DISEASES AFFECTING AN ESTIMATED 25 MILLION PEOPLE IN THE UNITED STATES.

The goals of ORD are to stimulate and coordinate research on rare diseases and to support research to respond to the needs of patients who have any one of these rare diseases.

"More than 280 products have been approved since 1983 under the Orphan Drug Act (ODA)," says Marlene Haffner, M.D., MPH, director of the Office of Orphan Products Development (OOPD). "In the aggregate, those products have treated more than 14 million people in the United States. So the incentives provided by the ODA are working well. The downsides are that we do not know if the products developed for a particular rare disease will help everyone who has that disease and we are challenged to find all the patients and give them access to treatments."

In the last decade alone, 160 new medicines to treat orphan-designated diseases have been approved by the Food and Drug Administration, according to a new report by the Pharmaceutical Research and Manufacturers of America (PhRMA), National Organization for Rare Disorders (NORD), and the Genetic Alliance (GA).

The PhRMA report, A Decade of Innovation: Advances in the Treatment of Rare Diseases, highlights some of the many important drugs for rare diseases that have been approved in the last decade. For instance, a breakthrough treatment — Rilutek (riluzole) — was approved for treatment of amyotrophic lateral sclerosis, or ALS, in 1995. Rilutek is being marketed by Sanofi-Aventis. Another example is Genzyme Therapeutic's Fabrazyme (agalsidase beta), which was approved in 2003 as the first drug to attack Fabry's disease at its root rather than just ease its symptoms.

The ODA was signed Jan. 4, 1983, offering drug makers incentives such as tax credits, grants, seven-year marketing exclusivity, and a waiver of the Prescription Drug User Fee Act filing fee. The ODA also provides a regulatory framework for these products, which has enabled smaller companies to focus on the development of products to treat rare diseases.

A designated orphan drug is by definition a drug that is intended for a disease or condition that

Incentives designed to bring drugs to the market to treat rare diseases have been successful, **yielding 280 products,** but there are still many patients without adequate treatment.

affects fewer than 200,000 people in the United States, otherwise known as a rare disease or condition. Vaccines, diagnostic drugs, or preventive drugs can be classified as orphan status.

The OOPD also considers a compound eligible for orphan drug status if the disease or condition affects greater than 200,000 people, but the cost of drug development cannot be reasonably recovered by drug sales in the United States within seven years. Drug sponsors may also request orphan drug status if the product under development is for a subset of a disease or condition that is "medically plausible." The most requested application for this "medically plausible" subset is the pediatric population. In fact, for products already marketed without a pediatric indication the OOPD will consider an indication under orphan drug status if it meets the criteria described earlier.

"The OOPD not only accepts applications from companies and research institutes, but we also provide assistance to help find sponsors for a promising product and help to develop a pathway for getting a drug into a study," Dr. Haffner says.

## **Biotech** Leading the Way

The orphan drug market is steadily growing because of increased interest by biotechnology companies. Legislation in the United States and Europe has enabled biotechnology and specialty companies to focus on orphan drugs as a viable business model.

The ODA has been a driving force for biotechnology and smaller companies, says Joshua D. Schein, Ph.D., CEO and director of Lev Pharmaceuticals Inc.

"A disproportionate amount of orphan drugs are being developed by the biotechnology industry," he says. "There are many companies focused on developing drugs for orphan indications that couldn't compete with the large pharmaceutical companies were it not for the ODA."

Lev Pharmaceuticals' lead program is the development of C1-INH for the treatment of hereditary angioedema (HAE). HAE is a rare genetic disorder characterized by episodic attacks of swelling in various parts of the body, most seriously the airway passages. The disease is caused by a deficiency of C1-INH. It is estimated that about 6,000 people have HAE in the United States.

"The future for orphan drug development may be primarily in the biotechnology industry and among start-up companies," Dr. Schein says. "These are the companies that are best able to capitalize on the ODA and where an approval for a small indication can get a company going."

**Dr. Marlene Haffner**
Food and Drug Administration

Applications for orphan drugs have increased significantly. I believe this trend will continue as we learn more about genetic diseases and personalized medicine.

The major biotech players — based on sales from drugs with orphan drug status — include Amgen, Biogen Idec, and Genzyme, according Decision Resources. There are also a number of emerging players within this market.

"Amgen, Biogen, and Genzyme are three of the large companies, with Amgen having huge returns on some of its earlier products, such as Epogen and Neupogen; Genzyme probably has the largest orphan drug pipeline," says Peter Norman, Ph.D., of Norman Consulting. "But for the most part, the market is fragmented, with orphan products being developed by small companies, biotechnology companies, and specialty companies dedicated to only rare diseases. It is not currently a strategic initiative among big pharma companies to develop orphan products."

Two up-and-coming pharmaceutical companies dedicated to the treatment of rare diseases are BioMarin Pharmaceutical Inc. and Sigma-Tau Pharmaceuticals Inc.

BioMarin is focused on the development and commercialization of biopharmaceuticals for serious diseases and medical conditions. The orphan product portfolio for the eight-year-old company includes Naglazyme (galsulfase) for treating mucopolysaccharidosis VI (MPS VI) and Aldurazyme (laronidase) for treating mucopolysaccharidosis I (MPS I). Aldurazyme is being marketed as part of a joint venture with Genzyme.

BioMarin also has two investigational product candidates, which include Phenoptin (sapropterin hydrochloride), a Phase III product candidate for the treatment of phenylketonuria (PKU), and 6R-BH4, which is in Phase I trials for the treatment of vascular dysfunction.

Sigma-Tau, which is solely dedicated to rare diseases, began operations in 1989, and its portfolio includes Carnitor (levocarnitine), for treating primary and dialysis-related carnitine deficiency, and Matulane (procarbazine), for treating advanced Hodgkin's disease. Matulane also is being investigated as a potential treatment for a rare form of brain tumors.

Other products in development at the company include Cystoran (cysteamine hydrochloride), a product to aid in the reduction of the corneal cystine crystal accumulation in the eye, which is a complication of lysosomal storage disease, and defibrotide for the treatment of severe hepatic venous occlusive disease (VOD). Hepatic VOD is a potentially devastating complication of both allogeneic and autologous stem-cell transplantation. Both Cystoran and defibrotide are in Phase III trials.

## **The Current** Market

In 2003, the total worldwide orphan drug market — United States, Europe, Japan, and Australia — was $28 billion based on market analysis by Decision Resources. Expectations are that this market will experience a steady period of growth for the foreseeable future, and it is estimated that the market will reach $45 billion by 2009, according to the July 2005 report. The United States will remain the primary source of growth.

In 2004, nine products with orphan drug status generated annual sales in excess of $1 billion, according to Decision Resources.

There will be an increasing number of high-value products reaching the market for orphan and nonorphan indications. Newly launched and later-stage development of recombinant products will be key drivers of growth in the near future.

In 2000, the European adoption of orphan drug legislation provided additional impetus for companies to pursue orphan drug development.

Decision Resources estimates the European orphan drug market will generate sales of at least $5 billion by 2009. With a 10-year

**Dr. Emil Kakkis**
BioMarin Pharmaceutical

There are some diseases that I call the 'ultra orphans' — those that affect fewer than 5,000 patients. We need legislation that helps define ways for companies to develop products for these diseases at a lower cost.

market exclusivity period allowed in Europe, analysts expect that growth should be sustained through 2014.

The orphan drug market spans many indications; but according to industry experts, it can be grouped into three general therapeutic categories: genetic diseases, including cystic fibrosis; autoimmune disorders, including multiple sclerosis; and cancer.

Genetic disorders make up the majority of rare diseases; but because so many of the patients die prematurely, the development of products is not commercially viable, even with the added incentives from the ODA.

There are several autoimmune disorders that qualify for orphan drug status, but most of the other diseases in the category are too prevelant to be applicable.

According to market analysts from Decision Resources, oncology drugs account for the majority of current orphan drug designations.

**Dr. Peter Norman**
Norman Consulting

There will probably be more orphan drugs approved, particularly in Europe where there have been so few to this point.

## Market Incentives

Before the enactment of the ODA, the small patient populations did not provide enough of an incentive to recoup development costs.

"There are obvious incentives associated with the ODA," says Gregg Lapointe, chief operating officer of Sigma-Tau. "The tax credits for research and development, potential fast-track review with the FDA, and the seven-year exclusivity are all quite positive. But there is still a long way to go to address more than 6,000 rare diseases. As a company, we are focused and passionate about developing products for these patients. We have found a sustainable economic model that does not rely on charity and allows us to re-invest 50% of the U.S. revenue back into research and development."

Emil D. Kakkis, M.D., Ph.D., chief medical officer of BioMarin Pharmaceutical says for his company's business strategy the incentives are three-fold.

## GLOBAL ORPHAN DRUG LEGISLATION

| | UNITED STATES | EUROPEAN UNION | JAPAN |
|---|---|---|---|
| Legal Framework | Orphan Drug Act (1983) | Regulation on Orphan Medicinal Products (2000) | Orphan Drug Regulation (1993) |
| Regulatory authority | FDA, Office of Orphan Product Development | EMEA, Committee for Orphan Medicinal Products | MHLW, Pharmaceutical and Medical Safety Bureau, Evaluation and Licensing Division |
| Prevalence requirement | No more than 200,000 people | No more than 185,000 people | No more than 50,000 people |
| Marketing exclusivity | 7 years | 10 years (6 if prevalence changes) | Extension of the reexamination period from the convention 6 years to maximum of 10 years |
| Tax incentives | Tax credit for up to 50% of clinical-trial costs | Tax credits of varying amounts, decided by individual member states | Tax reductions of 6% for certain authorized R&D expenses and limited to 10% of corporate tax |
| Grants | Grants of $150,000 to $300,000 per year for up to 3 years | Limited funds available; member states may contribute | Grants available to subsidize development |

Source: Decision Resources Inc., Waltham, Mass. For more information, visit decisionresources.com.

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"First, all the patients are underserved," he says. "Second, many genetic disorders have a clear biology and have been understood for years, which gives us a greater insight to the disease and lowers the development risk. Finally, the development path is shorter and more efficient. Companies can go from an IND to approval in a little more than five years."

The FDA works with pharmaceutical companies to develop meaningful trials to show efficacy of the products to gain approval of a marketing application.

"Beyond the incentives within ODA, the OOPD offers assistance and support for all aspects of orphan drug development," Dr. Haffner says.

## Market Challenges

Even though the FDA makes it as easy as possible to move an orphan drug through the process, there are challenges to bringing products to market for rare diseases.

"For many diseases, there is no history related to product development, so we have to blaze a trail," Dr. Kakkis says. "The second challenge is that clinical studies need to be in widely ranging locations because of the rarity of the disease. A third difficulty is the lack of surrogate markers or biochemical endpoints, so we cannot use these endpoints for these studies."

According to Mr. Lapointe another unique challenge is that there are very few researchers and physicians who know about rare diseases.

"Many patients or their families have educated themselves on the disease; and as we get to know them, we learn from them," he says. "Understanding the issues from a patient's perspective adds to the cost and complexity of trials, but what is exciting is that this type of greater understanding ultimately brings treatments to these patients."

Legislation on a global basis may pose some challenges as well. Market analysis from Decisions Resources finds that the different criteria and incentives among countries can complicate companies' efforts to devise global-development strategies.

In addition, reimbursement issues may constrain sales. Third-party payers have expressed a number of concerns about the cost of orphan drugs and the impact of their use on reimbursement budgets.

"The ultimate problem is that there are more rare diseases than there is sufficient funding for development," Dr. Kakkis says. "In general, there is the need to figure out how to reduce the cost of development. The FDA is working on a Critical Path Initiative that might help streamline development."

## Moving Forward

Despite all the challenges, the orphan drug market is steadily increasing. Mr. Lapointe's hope is that more companies will consider developing products for rare diseases.

"Ours is a business model that allows us to recover costs and be a sustainable entity," he says. "From our perspective, it is encouraging

## RECENTLY APPROVED ORPHAN DRUGS

| YEAR | PRODUCT | COMPANY | RARE DISEASE |
|---|---|---|---|
| 2005 | Arranon (nelarabine) | GlaxoSmithKline | T-cell lymphoblastic leukemia |
| 2005 | Exjade (deferasirox) | Novartis | Chronic iron overload |
| 2005 | Nexavar (sorafenib tosylate) | Bayer Pharmaceuticals | Advanced renal cell carcinoma |
| 2005 | Revlimid (lenalidomide) | Celgene | Myelodysplastic syndromes |
| 2005 | Naglazyme (galsulfase) | BioMarin Pharmaceutical | Mucopolysaccharidosis VI |
| 2005 | Increlex (mecasermin) | Tercica | Severe primary IGF-1 deficiency |
| 2005 | Temodar (temozolomide) | Schering-Plough | Glioblastoma multiforme |
| 2004 | Sensipar (cinacalcet) | Amgen | Secondary hyperparathyroidism |
| 2004 | Alimta (pemetrexed) | Eli Lilly | Malignant pleural mesothelioma |
| 2004 | Clolar (clofarabine) | Genzyme | Acute lymphoblastic leukemia |
| 2004 | Ventavis (iloprost) | CoTherix | Pulmonary arterial hypertension |
| 2003 | Bexxar (tositumomab) | Corixa and GlaxoSmithKline | CD20-positive follicular non-Hodgkin's lymphoma |
| 2003 | Fabrazyme (agalsidase beta) | Genzyme | Fabry's disease |
| 2003 | Zavesca (miglustat) | Actelion | Type 1 Gaucher disease |
| 2003 | Somavert (pegvisomant) | Pfizer | Acromegaly |
| 2002 | Orfadin (nitisinone) | Swedish Orphan | Hereditary tyosinemia type 1 |
| | | | Cryptoporidium parvum or Giardia lamblia |
| 2002 | Xyrem (sodium oxybate) | Jazz Pharmaceuticals | Cataplexy associated with narcolespsy |
| 2002 | Remodulin (treprostinil) | United Therapeutics | Pulmonary arterial hypertension |
| 2001 | Gleevec (imatinib mesylate) | Novartis | Chronic myeloid leukemia |
| 2001 | Tracleer (bosentan) | Actelion | Pulmonary arterial hypertension |
| 2000 | Trisenox (Arsenic trioxide) | Cell Therapeutics | Acute promyelocytic leukemia |
| 2000 | Mylotarg (gemtuzumab) | Wyeth | Acute myeloid leukemia |

Source: Pharmaceutical Research and Manufacturers of America, Washington, D.C. For more information, visit phrma.org.

**Dr. Joshua Schein**
Lev Pharmaceuticals

The future for orphan drug development may be primarily in the biotechnology industry and among the start-up companies. These are the companies that are best able to capitalize on the Orphan Drug Act.

to witness the increasing understanding of the human genome, and hopefully companies will be in better positions to develop more treatments for rare diseases."

Dr. Haffner says as more is learned about genetic diseases and personalized medicine, more and more products for these diseases are progressing along the pipeline.

Dr. Norman adds there will probably be more orphan drugs approved, particularly in Europe where there have been few to date.

"But the market will become more fragmented because of the segmented patient populations, which may make things more complicated," he says. "Therefore, I believe that no one company will stand out, but many will be become significant niche players." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

## ORPHAN DRUG **APPROVALS IN EUROPE LAG**

**Only 7% of drug applications for treating people with rare diseases were approved in Europe between 2000 and 2004.** Yet during the same period, more than 79% of the other drug applications submitted to the European Agency for the Evaluation of Medicinal Products (EMEA) were approved, according to research published in a recent issue of the *British Journal of Clinical Pharmacology*.

"It's difficult to find a balance between the urgent need for drugs for patients with rare diseases and guaranteeing their quality, efficacy, safety, and, where necessary, making comparisons with existing drugs," says coauthor Professor Silvio Garattini from the Mario Negri Institute for Pharmacological Research in Milan, Italy.

Between August 2000, when new legislation came into force, and December 2004, the EMEA's Committee on Orphan Medical Products reviewed 255 possible drugs for rare diseases that affect fewer than five people in 10,000. Only 18 orphan drugs were approved on the basis of epidemiological data, medical plausibility, and potential benefit.

During the same period, the EMEA received 193 marketing authorization applications for nonorphan drugs, and 153 of these were approved.

Rare diseases covered by the approved drugs included two rare forms of leukemia; Fabry's disease, which affects the body's ability to break down lipids; and Wilson's disease, in which copper build-up can damage vital organs.

"In the last 20 years, international efforts have been made to encourage companies to develop orphan drugs by providing incentives such as tax credits and research aids, simplifying marketing authorization procedures, and extending market exclusivity," says Dr. Jeffrey Aronson, chair of the journal's editorial board. "Only the last of these incentives is available in Europe. This study suggests that we need more incentives in Europe to develop orphan drugs and to develop them cost effectively, so as not to compromise our ability to manage other diseases."

Source: Blackwell Publishing, Oxford, United Kingdom. For more information, visit blackwellpublishing.com.

## Experts on this topic

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