

BY DENISE MYSHKO

# ORPHAN DRUGS

## Opportunity in Rare Diseases

*The development of orphan drugs is becoming a strategy being pursued by companies large and small as the new era of nichebusters continues to evolve.*

### QUICK FACT

The global market for orphan drugs reached \$84.9 billion in 2009, up from \$80.3 billion in 2008. The market is expected to grow 5.7% CAGR to reach \$112.1 billion by 2014.

**BCC RESEARCH**

*We are developing a taskforce to work with the FDA and NIH to make sure we do everything we can to smooth out the drug development process for drugs for rare diseases.*

**PETER SALTONSTALL**  
National Organization for Rare Disorders



*We saw an opportunity for our company to develop needed drugs for rare diseases. There are large, grossly underserved groups of patients with uncommon diseases.*

**DR. ED MASCIOLI**  
Pfizer



**R**are diseases could be big business for the bio/pharmaceutical industry. A changing landscape in the healthcare and pharmaceutical industries is facilitating efforts to enhance the incentives for pursuing research and development for rare diseases.

The development of orphan drugs traditionally was pursued by small biotechnology companies, but that is beginning to shift. The blockbuster model is eroding, many best-selling products are facing patent expiration, and companies are trying to diversify. One area being explored is the development of orphan drugs for rare diseases.

The marketplace is going to continue to

change, especially as healthcare in the United States continues to evolve, says Vincent Milano, president and CEO of ViroPharma.

“The rare disease space and addressing unmet needs will be the centerpiece of future development,” he says. “The United States has created an advantageous model for companies pursuing orphan drugs; companies receive a reasonable period of exclusivity to enjoy the benefits of success, which hopefully allows them to apply good return to shareholders. The orphan drug platform works because it starts with the patient and moves all the way through to the shareholder. Small companies, like ours, have developed a solid business model around this concept; no doubt the bigger companies will also realize there is a tremendous amount of value in connecting the patient to the shareholder.”

Jean-Jacques Bienaime, CEO at BioMarin Pharmaceutical, says the Orphan Drug Act has been a positive for the development of drugs to treat rare diseases.

“It clearly made it easier for small companies, such as BioMarin, to get started, and the law created incentives to invest resources in R&D, especially when there is no guarantee of intellectual property protection at the end,” he says. “The issue with human proteins, which is our focus, is that they cannot be patented. Without the Orphan Drug Act, BioMarin would have had difficulty attracting investors.”

While executives say the Orphan Drug Act has been successful in bringing some therapies to those with rare diseases, more needs to be done. The FDA has granted market approval



*Large pharma companies have to diversify. At the same time, I think they would be surprised to see how specialized they need to be to understand all of the challenges involved with developing orphan drugs.*

**DR. SYLVIE GRÉGOIRE**  
Shire Human Genetic Therapies



*Bigger companies are realizing that there is a tremendous amount of value to be realized in connecting patients to shareholders.*

**VINCENT MILANO**  
ViroPharma

to 350 drugs and biologicals with an orphan designation; there are an estimated 6,000 to 7,000 rare diseases.

There is a great deal of conversation going on among the various stakeholders to determine how to encourage additional research in this area. In fact, U.S. regulatory officials, working with industry leaders, are trying to address some of the gaps in development for products for rare diseases. (Editor's Note: See the digital edition for more on the changing regulatory environment for orphan drugs.)

"We are in the early stages of putting committees together and are starting to develop the agendas where a number of the gaps and inconsistencies lie," says Peter Saltonstall, president and CEO of the National Organization for Rare Disorders (NORD). "NORD is developing a taskforce working with the FDA and the NIH

## QUICK FACT

There are 583 orphan drugs in active development; cancer is the leading indication, with more than 100 products in active development in the United States alone.

### BUSINESS INSIGHTS

to make sure that we do everything we can to smooth out the drug development process. At the same time, we want to make sure that there are consistent rules for everyone and the rules are clear. We are doing a lot of work to determine what we can do to encourage additional growth in the space by looking at how to make sure the process works efficiently."

Regulatory agency officials recognize the challenges sponsors face, and their goal is to work with them.

"Everybody recognizes that the collection of data on safety and efficacy for people with rare diseases is different," says Timothy Coté, M.D., director of the Office of Orphan Products Development at the FDA. "It's more difficult in many ways than the provision of data for more common diseases."

### The Market Opportunities

The global market for orphan drugs reached \$84.9 billion in 2009, up from \$80.3 billion in 2008. The market is expected to grow at a compound annual growth rate (CAGR) of 5.7% to reach \$112.1 billion by 2014, according to a report from BCC Research.

And some large pharma companies, including Johnson & Johnson, Merck, and Novartis, are already active in the orphan drug market. Recently, GlaxoSmithKline and Pfizer began to seriously address rare diseases. In February, GSK announced the formation of a new stand-alone unit specializing in the development and commercialization of medicines for rare diseases. The new unit aims to leverage existing capabilities and partnerships and establish further in-licensing opportunities. And in June, Pfizer announced the creation of a new research unit focused on rare diseases. Company executives say its creation within worldwide research and development represents a significant step in Pfizer's diversification strategy.

"Rare diseases are opportunities for our company," says Ed Mascioli, M.D., VP of orphan and genetic diseases research unit at Pfizer. "There are large, grossly underserved groups of patients."

Dr. Mascioli says the unit is in the process of hiring key people, as well as evaluating diseases to tackle and is considering different technology platforms.

"Pfizer has a strong presence in protein therapeutics and small molecules," Dr. Mascioli says. "Many rare diseases are amenable to protein therapeutics, and this is certainly a strength we'll apply to development in this arena. We have a broad mandate in terms of the types of assets that we will apply to some of these diseases."

Wendy White, founder and president of Siren Interactive, says the reason companies are now looking to bring orphan drugs to market is because of technology; there is now potential return for these products.

"Companies know the era of the blockbuster is over, and they are looking at ways to diversify," she says. "Solutions for niche patient populations are good areas to explore. Less than 10% of rare diseases have treatments available, and 80% of these diseases are genetic in origin. In many cases, the cause of the disease is known, the patients can be diagnosed with certainty, and molecular targets are clear. Clinical trials can be small with clear endpoints, and the recruitment for trials is facilitated by expert physicians and patient groups."

The number of orphan drug designations is increasing, reflecting this growing interest by pharmaceutical and biotech companies in developing products to treat orphan diseases, according to a study by the Tufts Center for the Study of Drug Development.

There are 583 orphan drugs in active development; cancer is the leading indication, with more than 100 products in active development in the United States alone, according to a report from Business Insights.

But executives whose companies are already in this space caution that developing drugs for rare diseases is a very specialized area with challenges of its own.

Sylvie Grégoire, Pharm.D., president of Shire Human Genetic Therapies, says development of orphan drugs is a tailored process.

"There are no standardized processes with a lot of these therapies," she says. "To compete with this business model, companies have to be flexible and nimble. They need to have skilled executives overseeing the work, people who are able to assess programs, make judgments, and use hands-on experience in operations."

Dr. Grégoire says these development programs are very close to the patient, and at the moment, the expertise for successful development for products for rare diseases resides with smaller, more specialized companies.

"Larger companies that want to compete in this space will have to be able to build these capabilities internally," she says.

Mr. Milano agrees, saying treatments for rare diseases require much more one-on-one interactions with physicians and patients.

"Larger companies have to be willing to think about development and marketing dif-



*Everybody recognizes that the collection of data on safety and efficacy for people with rare diseases is different and special.*

**DR. TIMOTHY COTÉ**  
Food and Drug Administration

ferently,” he says. “It is not about leveraging the existing infrastructure, which is what big companies typically try to do. With rare diseases, companies need to build a very specific team dedicated to the task of serving a discrete patient population. A large infrastructure isn’t necessarily going to be as useful in these disease states as it is for the more traditional primary-care market. There needs to be a different mind set and an allocation of resources that serves the objectives of the patient populations, which is not the same as in the large-volume primary-care market.”

For Shire, it’s a business strategy the company developed through acquisition.

“Shire is a specialty pharma drug company, but in 2005, we wanted to diversify from the existing specialty business and add something that was clearly unique that could differentiate us from other specialty pharma companies,” Dr. Grégoire says. “TKT, which was acquired by Shire in 2005, was already working in rare diseases, and it had a human cell line enzyme replacement therapy. There is a lot of opportunity to grow this business model with the existing platform technology and provide a diversification of risk within Shire and for investors. This has allowed us to bring life-changing therapies to patients who have a high unmet need and to become global in nature. Shire didn’t have a worldwide presence previously. With the orphan drug business, we now have a presence in 28 countries.”

### Challenges of Developing Orphan Drugs

About \$2.5 billion was invested in R&D for neglected diseases in 2007. The major funders



*Often, the primary driver of diagnosis and treatment of a rare disorder is a patient or a caregiver, not the physician.*

**WENDY WHITE**  
Siren Interactive

were the National Institutes of Health and the Bill & Melinda Gates Foundation, according to a 2008 report from The George Institute. Almost 80% of the funding was directed toward three disease areas: HIV/AIDS, malaria, and tuberculosis. The next five disease areas, including pneumonia and diarrhea (No. 1 and No. 2 in terms of mortality), each receive from 1% to 5% of the total funds.

Industry experts say the small patient population of these diseases is often the biggest challenge for developing orphan drugs.

Dr. Grégoire says patients are often dispersed all over the globe, and they are not a homogeneous group.

“All patients have a different course of their disease,” she says. “To develop a drug in a reasonable amount of time, we have to refine the age group and inclusion criteria. For example, for the drug Elaprase, which is for Hunter’s syndrome, we had to conduct the trial in 17 countries, which lasted a year and a half. This included six months to recruit patients and then a year to do the trial.”

She says often patients have to travel — even to other countries — to be managed, diagnosed, or followed up with.

“Patients could receive their infusion where they lived but then had to travel to a larger site for assessment,” Dr. Grégoire says. “Assessments in 17 different countries would introduce variability that would go beyond the very small population.”

Mr. Milano says another challenge is that because there are no therapies available, clinical endpoints haven’t been established.

“Regulatory involvement is critical in helping to establish criteria and ways in which these studies can be conducted, which is often different from the 10th cardiovascular or the 12th anti-infective for the same bug,” he says.

### Orphan Product Designations More than Double

The number of orphan product designations in the United States more than doubled during the last decade, reflecting growing interest by pharmaceutical and biotech companies in developing products to treat orphan diseases, according to a study by the Tufts Center for the Study of Drug Development.

According to Tufts CSDD, orphan product designations increased from 208 in the 2000 to 2002 period to 425 in 2006 to 2008.

The Tufts report also found:

- During the 2000s, orphan products comprised 22% of all new molecular entities (NMEs) and 31% of all significant biologics receiving U.S. marketing approval.
- Orphan products receiving priority review status rose from 35% of all orphan NMEs in 2000 to 2002 to 50% in 2006 to 2008; during the same time the share of orphan significant biologics receiving priority review status rose from 17% to 67%.
- Sponsors engaged in clinical development funded through orphan grants reported that 22% of their programs led to approvals, which compares with a clinical approval success rate of 16% among mainstream drug developers.

Source: Tufts Center for the Study of Drug Development. For more information, visit [csdd.tufts.edu](http://csdd.tufts.edu).

“It takes more ingenuity and a balanced approach between sponsors and regulators.”

Another challenge, Mr. Milano says, is once a drug or therapy receives approval, by the very nature of these diseases, patients may not be diagnosed yet.

“One of the challenges that we all have is how meaningful is the business opportunity when there is no way to predict the numbers of

patients who have, or may develop, the disease,” he says.

Pharmaceutical companies also have to consider that orphan drugs may have special handling requirements, says Craig Kephart, president and CEO of Centric Health Resources.

“The typical product profile of these drugs involves infusion or injection, although we are starting to see more oral solids, and there may also be the need to comply with cold chain handling requirements,” he says. “Also, many of these drugs may have associated REMS mandates from the FDA, so this adds a layer of complexity. Because of these requirements, companies need to connect with and follow every patient.”

Mr. Kephart says servicing these patients, keeping them on a drug, and keeping them in a treatment program over time is challenging.

“Orphan drugs are expensive, and there is often a high reimbursement hurdle to overcome,” he says. “There are still a lot of challenges around patient copays and deductibles. When the cost of a drug is \$150,000 a year per patient, the way companies think about that patient has to change, including assumptions about the marketplace.”

## Best Practices for Development

Mr. Milano says the key success factors in the rare disease arena involve working with patient advocacy groups and key opinion leaders.

“Many people might say these are the keys to success in every field, but these two influential stakeholders are even more important for the success of products for rare diseases,” he says. “The numbers of patients are few, the distance between them is far, and the ability to be able to design a study that answers the question whether the drug has a benefit for these patients is that much more complicated.”

He says there are well-versed key opinion leaders in each rare disease state.

“The key is to find out who they are and spend time with them to understand what might be the best chance for success in designing a study,” he says.

Dr. Grégoire says, in addition, trials for rare diseases require more careful monitoring.

“For trials with larger populations, patient or trial site variability can be managed by volume,” she says. “A best practice for orphan drug development is constant monitoring. These trials are not always placebo controlled so there has to be feedback on the mechanism of action, more so than in other trials.”

Hari Nagaradona, Ph.D., director of regulatory affairs at Kendle, stresses the importance of working with regulators before beginning clinical research for an orphan drug.

“Many orphan drug developers are relatively small companies with relatively small financial support so planning ahead makes the process more efficient and saves companies time and energy in the long run,” he says. “It can be disastrous for a company to head off down the wrong path only to find that the FDA has different expectations. Companies might have to repeat trials that they couldn’t afford in the first place.”

Dr. Nagaradona says it’s important to be clear about regulatory expectations for the orphan drug development process.

“Sometimes there is a misunderstanding on the side of the sponsors,” he says. “Companies might assume that obtaining an orphan drug designation means going through the regulatory approval process very quickly. This is not quite true; orphan drug status helps, certainly, but the drug development and approval process is comparable to any investigational drug.”

Ms. White says drugs for rare diseases require a different marketing strategy as well.

“It makes no sense to push the message and do lots of advertising,” she says. “It’s all about providing value for patients and supporting them to find information and to connect with each other.”

She says frequently the primary driver of diagnosis and treatment in a rare disorder is a patient or a caregiver, not the physician.

“Often there is little information available for rare diseases, which means there is an opportunity for a brand to have a direct relationship with a patient,” Ms. White says. “But there is a distance problem, so most of what should be done to market a product for a rare disease should be online. This is where people are talking, this is where people are finding their information, and this is where they are connecting with each other. These are empowered patients looking for information. If companies listen to how patients talk to each other and about what their greatest unmet needs are, then brand managers can meet those needs through appropriate channels. And if brand managers can provide valuable information to them, patients will opt in for a relationship with the brand.”

Mr. Kephart says because the marketplace is moving aggressively toward value-based medicine, it’s not enough to show that a product has a therapeutic benefit.

“Companies have an opportunity in these small markets because they can work with a more limited distribution where they can touch the patients,” he says. “They have an opportunity to expand beyond just supporting a drug to supporting patients living with a rare disease.” ♦

## Experts on this topic

**JEAN-JACQUES BIENAIME**, CEO, BioMarin Pharmaceutical Inc., which develops and commercializes innovative biopharmaceuticals for serious diseases and medical conditions. For more information, visit [bmrn.com](http://bmrn.com).

**TIMOTHY COTÉ, M.D.** Director of the Office of Orphan Products Development, Food and Drug Administration, which is responsible for ensuring the safety of foods, cosmetics, human and veterinary drugs, biological products, and medical devices. For more information, visit [fda.gov](http://fda.gov).

**SYLVIE GRÉGOIRE, PHARM.D.** President, Shire Human Genetic Therapies (HGT), a biopharmaceutical company engaged in the research, development, and commercialization of therapeutics for genetic diseases caused by protein deficiencies. For more information, visit [shire.com](http://shire.com).

**CRAIG KEPHART**, President and CEO, Centric Health Resources, a patient-centered health management organization, serving patients with rare, orphan, ultra-orphan, and chronic genetic disorders. For more information, visit [centrichealthresources.com](http://centrichealthresources.com).

**ED MASCIOLI, M.D.** VP of Orphan and Genetic Diseases Research Unit, Pfizer Inc., which has a diversified global healthcare portfolio that includes human and animal biologic and small molecule medicines and vaccines. For more information, visit [pfizer.com](http://pfizer.com).

**VINCENT J. MILANO**, President and CEO, ViroPharma Inc., an international biopharmaceutical company committed to developing and commercializing products for patients with serious diseases. For more information, visit [viropharma.com](http://viropharma.com).

**HARI NAGARADONA, PH.D.** Director, Regulatory Affairs, Kendle, a global full-service clinical research organization. For more information, visit [kendle.com](http://kendle.com).

**PETER SALTONSTALL**, President and CEO, National Organization for Rare Disorders, which is dedicated to helping people with rare orphan diseases. For more information, visit [rarediseases.org](http://rarediseases.org).

**WINIFRED (WENDY) WHITE**, Founder and President, Siren Interactive Corp., a firm focused on relationship marketing for rare disorder therapies. For more information, visit [sireninteractive.com](http://sireninteractive.com).

DENISE MYSHKO

# The Changing Regulatory Environment for **ORPHAN DRUGS**

*While executives say the Orphan Drug Act has been successful in bringing some therapies to those with rare diseases, more needs to be done.*

**T**here are an estimated 6,000 to 7,000 rare diseases, and so far the FDA has granted market approval to 350 drugs and biologics with an orphan designation.

There is a great deal of conversation going on among the various stakeholders to determine how to encourage additional research in this area. And U.S. regulatory officials are working with industry leaders to address some of the development gaps for products for rare diseases.

The Patient Protection and Affordable Care Act enacted in March 2010 provides 12 years of data exclusivity for manufacturers of biologics. Although this isn't specific to orphan diseases, experts say this is likely to benefit research in this area because traditionally the development of orphan drugs has been done by small biotechnology companies.

Another feature of the healthcare reform act that could benefit research of rare diseases is the Therapeutic Discovery Project Program, which provides tax credits or grants to small companies that show significant potential to produce new and cost-saving therapies. The credit covers up to 50% of the cost of qualifying biomedical research, up to a maximum credit of \$5 million per firm and \$1 billion overall and is only available to firms with fewer than 250 employees.

Specifically, the FDA is also trying to help sponsors develop orphan drugs. The FDA's Priority Review Voucher program, which was part of the 2007 FDA Amendments Act, incentivizes companies to work on neglected diseases. Companies that receive an approval for a drug that treats a neglected disease receive a voucher for a priority review for any other future drug, and that voucher is not limited to neglected diseases. So far, one voucher has been issued. On April 7, 2009, the FDA issued the first priority review voucher to Novartis for the antimalarial drug Coartem.

Currently, the FDA holds workshops where sponsors and regulators can meet to discuss an application for an orphan drug designation. The agency also is working on a guidance document for the development of orphan drugs, with a draft expected to be released for comment in September 2011.

The Orphan Drug Act, which was estab-

lished in 1983, provided companies that develop a drug for a disorder affecting less than 200,000 people in the United States seven years of market exclusivity, as well as a tax credit for clinical trial expenses.

The act has been hugely successful, says Peter Saltonstall, president and CEO of the National Organization for Rare Disorders (NORD).

"We don't want to reduce the effectiveness

*There is no official policy for orphan drugs. Products for the treatment of rare diseases don't go into one special track or review because they involve all different organ systems and pathologies. They go to the relevant review divisions.*

**DR. TIMOTHY COTÉ**  
FDA



*We don't want to reduce the effectiveness of the Orphan Drug Act in any way, but we may want to think about creative ways to build additional incentives and take into consideration the changes in the marketplace from 1983.*

**PETER SALTONSTALL**  
NORD

## Rare Disease Research Efforts

PharmaVOICE spoke with several companies that are researching and developing drugs for rare diseases. Here is a look at some of their efforts.

### BioMarin Pharmaceutical

BioMarin Pharmaceutical's approved products include Naglazyme for mucopolysaccharidosis VI; Aldurazyme for mucopolysaccharidosis I (MPS I), a product that BioMarin developed through a 50/50 joint venture with Genzyme; and Kuvan Tablets, a product for the treatment of phenylketonuria (PKU), developed in partnership with Merck Serono.

The company's products in development include PEG-PAL, which is now in Phase II clinical development to treat patients who do not adequately respond to Kuvan. PEG-PAL (PEGylated recombinant phenylalanine ammonia lyase or PAL) is an investigational enzyme substitution therapy for the treatment PKU, an inherited metabolic disease caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH).

Another product in development is GALNS for MPS IVA (Morquio A Syndrome), an inherited, autosomal recessive disease caused by a deficiency of a particular lysosomal enzyme, GALNS. This can cause systemic skeletal dysplasia, short stature, and joint abnormalities, which limit mobility and endurance. The company expects to begin a Phase III trial in January 2011.

BioMarin also expects to initiate a Phase III trial for Firdapse by late 2010 or early 2011, file in the second half of 2011, and if successful, receive approval by the third quarter of 2012 for Lambert-Eaton myasthenic syndrome (LEMS), a rare autoimmune disease whose symptoms and origins are somewhat similar to those of Myasthenia Gravis.

Another product is BMN-195, which is in Phase I trials for Duchenne muscular dystrophy, a common cause of muscle disease in children. BioMarin's treatment for DMD is the use of a small molecule inducer of utrophin gene expression, a naturally occurring homologue gene of dystrophin that is normally only expressed in fetal muscle.

### Shire Human Genetic Therapies

Shire Human Genetic Therapies has expertise in enzyme replacement therapy and a focus on developing treatments for other rare diseases. Almost two dozen projects are in full development in Shire's HGT and specialty pharma pipeline and 30% of the company's revenue is derived from products launched within the last two years. The company's research is focused on Fabry disease, Hunter syndrome, Gaucher disease, hereditary angioedema, and metachromatic leukodystrophy.

The company has two products currently awaiting marketing approval, VPRIV and Replagal. VPRIV is awaiting approval in the EU for the treatment of Gaucher disease Type 1, an autosomal recessive disease and the most prevalent Lysosomal Storage Disorder. VPRIV was approved by the FDA in February 2010. Replagal is awaiting

approval in the United States for Fabry disease, an inherited disorder that results from the buildup of a particular type of fat in the body's cells.

Shire also has two products in development: Firazyr in Phase III trials in the United States for hereditary angioedema, which is caused by low levels or improper function of a protein called C1 inhibitor and can cause rapid swelling of the hands, feet, limbs, and face; and another product in Phase I/II for metachromatic leukodystrophy, a group of lethal genetic disorders that impair the growth or development of the myelin sheath, the fatty covering that acts as an insulator around nerve fibers.

### ViroPharma

In 2009, ViroPharma launched Cinryze in the United States. Cinryze is the only drug approved to prevent angioedema attacks in patients with hereditary angioedema (HAE), which is caused by low levels or improper function of a protein called C1 inhibitor and can cause rapid swelling of the hands, feet, limbs, and face. The company expects 2010 sales of between \$165 and \$175 million. The company is currently awaiting approval of Cinryze in the EU for both the prevention and treatment of acute attacks of HAE.

ViroPharma continues to study Cinryze and recently initiated Phase II study of subcutaneous administration of Cinryze. A study of the product in pediatric patients is ongoing.

ViroPharma also has completed a Phase I study of another product, VP20621, for non-toxicogenic C. difficile.

of the Orphan Drug Act in any way, but we may want to think about creative ways to build additional incentives and take into consideration the changes in the marketplace from 1983," he says. "Later this year, we will have some indication of areas that we need to start to drill down into further and work on to improve the process to make sure innovation is still viable."

In June, the FDA's Office of Orphan Products Development held a two-day public hearing on the development of products for rare diseases. Based on input given at this meeting, the agency is expected to provide Congress with a report on the meeting in March 2011, with a draft guidance expected in September 2011.

Much of the meeting revolved around the

question of the agency's flexibility, says Timothy Coté, M.D., director of the Office of Orphan Products Development at the Food and Drug Administration.

"There is no official policy for orphan drugs," he says. "Products for the treatment of rare diseases don't go into one special track or review because they involve all different organ systems and pathologies. They go to the relevant review divisions. But there is considerable sense and sensibility throughout the agency. We are not asking sponsors to do clinical trials with 1,000 people if only 100 patients exist with the disease. Whether this process needs to be formalized is a question for the committee and the report to Congress."

He says the committee is looking at all of

the ways the agency reviews biologics, drugs, and devices for the treatment of rare diseases.

"We know that if we hold sponsors to certain rules, we might lock them out entirely and this would not be fair to patients in need nor would this approach be tolerated by the agency or the commissioner. But at the same time, we need to uphold the standards. When a drug is FDA approved, it means that it is safe and effective in the treatment of that disease."

Regulatory officials are committed to working with the industry to address special issues. In fact, the agency has begun holding orphan drug designation workshops to help sponsors prepare and submit applications for orphan designations.

"At these workshops, we meet the sponsors

and over the course of two days, review the application for submission,” Dr. Coté says. “There is a lot of misunderstanding out there on the part of sponsors. At the workshops, we demystify the process. We discuss with them the basic criteria they need to meet and how to meet them. If they have a product that is truly an orphan product, they should have no problem at all.”

Sylvie Grégoire, Pharm.D., president of Shire Human Genetic Therapies, says development of drugs for rare diseases needs to happen in concert with regulatory agencies.

“Rare diseases are often not well known,” she says. “Therefore, the rapport and interaction with regulators is important. But the difficulty for sponsors is that often one agency may ask something very different from another agency. We have to reconcile these queries because there can only be one development program. Over time, the agencies have developed mechanisms to speak to each other about these issues.”

Dr. Grégoire says another positive step would be for the FDA to have a special review division for orphan drugs.

“One of the things that we suggested is that the FDA develop a special committee that looks only at rare diseases,” she says. “Right

now each drug is reviewed in its provisional review division. But the regulators who are accustomed to reviewing drugs with established standards may not be the best people to deal with drugs with unknown outcomes or exceptions. We believe there should be one committee where all of the orphan drugs come under review. These regulators would become experts in managing rare diseases and the exceptions.”

Hari Nagaradona, Ph.D., director of regulatory affairs at Kendle, says another consideration for regulators would be to reconsider the definition of an orphan drug.

“The prevalence numbers that were defined in the law 25 years ago still apply, but the population has grown since then,” he says. “A disease may still be rare, but the prevalence may be a little bit more than 200,000 patients, and in these cases the product in development would no longer be considered an orphan drug.”

Mr. Nagaradona feels that the FDA should consider changing the definition of rare disease from an absolute number to a percentage of the population, similar to the approach used in Europe. He also suggests that the agency should consider developing guidance on how to define moderate and severe forms of diseases.

“Sometimes sponsors want to carve out a special population or a portion of the condition as an orphan indication and they are not clear about how they should go about it,” Dr. Nagaradona. “It would be nice to have some guidance from the agency about how to measure or define a moderate or moderate-to-severe or severe condition. Until the sponsors submit an application to the agency, they will not know whether the agency agrees or doesn’t agree with their definition.”

This is important because often companies want to expand beyond that orphan indication to cover larger, more profitable indications.

Jean-Jacques Bienaime, CEO at BioMarin Pharmaceutical, says healthcare reform efforts have changed some of the incentives for developing new biological products.

“All biologics, whether they are for orphan diseases or not, receive 12 years of marketing exclusivity now, which is a great incentive for biotech in general,” he says. “In a sense, the Orphan Drug Act has lost some of its value as it relates to biological products. It would be great if additional protection were provided to orphan molecules beyond the 12 years when they are also biologics.” ♦



Centric provides commercialization, distribution and Health Management services to the ultra-orphan and unique disorders marketplace. Centric's business model focuses on patient well-being and compliance, which drives positive outcomes and growth.

For more information, contact **Penny Bemus** at:  
Email: [pbemus@centrichealthresources.com](mailto:pbemus@centrichealthresources.com) or Phone: **636.519.2758**