

RARE DISEASES: The Patient as COLLABORATOR

In the rare disease market, working with patients and patient advocacy groups is critical for the success of new therapies.

The voice of the patient is critical in healthcare. Nowhere is this more true than in the area of rare diseases. It's critical to engage patients, industry experts say, to access the knowledge that patients and other stakeholders have about their disease. Early engagement with key opinion leaders and investigators leads to better protocols and trials that better meet the needs of patients, caregivers, and sponsors.

"The industry is gaining an appreciation for what the patient can bring to development," says Mary Cobb, president of PatientVue. "Patients need to be considered as partners and collaborators rather than just end users of treatment."

Because every rare disease community is unique, Wendy White, president of Siren Interactive, says there should be more involvement on the part of patients and caregivers in the decision-making process, all the way from the design of clinical trials to FDA evaluation.

"There is no one in a better position to judge the pros and cons of treatment and the impact of the disease than those who are actually living with it," she says.

The Food and Drug Administration, through the Prescription Drug User Fee Act (PDUFA) V, has initiated The Voice of the Patient program, which is addressing 20 disorders to gather and summarize the input provided by patients and patient representatives at public meetings. This initiative aims to more systematically gather patients' perspectives on their conditions and available therapies to treat their condition. As part of this

FAST FACT

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Source: Kalorama Information

commitment, the FDA is holding at least 20 meetings over the five years in which PDUFA V is in effect, each focused on a specific disease area. (See related box for more information.)

"There are several rare diseases included in the meetings the FDA has scheduled to gather the patient perspective as part of the 2014 Patient-Focused Drug Development initiative," Ms. White says. "It's exciting to see the FDA's commitment to patients."

Ellynn Szoke, VP of advocacy and outreach at the Cluster Headache Support group, says from a patient perspective the challenge has often been getting the attention of the pharmaceutical industry.

"In the past, pharmaceutical companies focused their attention on the blockbusters and orphan drugs weren't seen as economically feasible to develop and bring to market," she says. "If a rare disorder is not determined to be fatal, there can be a lack of true awareness on the part of pharma as to the importance of finding treatments. For example, my son has chronic cluster headaches. No medication has ever been developed for this disorder. Migraine drugs are given to these patients, but they

don't really help. Although cluster headaches are within the headache disorder spectrum, they manifest differently and need a different kind of drug than is currently on the market."

For many rare diseases, there is a lack of basic knowledge around the natural history of the disease, the cause, pathophysiology, and the availability of epidemiological data, says Kevin Lee, Ph.D., VP and chief scientific officer, rare disease research unit at Pfizer.

"Validated endpoints are often extremely limited or nonexistent," he says. "These are, in many cases, significant hurdles to diagnosing and treating such conditions."

Furthermore, Bert Bruce, VP, commercial development, rare diseases, at Pfizer, says fewer than 5% of all rare diseases currently have approved treatments, leaving tens of millions of patients around the world without therapies to address their disease.

"The encouraging news is that advances in science are unlocking a new understanding of many rare diseases," he says. "These new insights, coupled with the increasing empowerment and engagement of patient advocates and focused attention of governments and regulatory agencies, are helping to accelerate the potential development of new medicines to treat these conditions."

Pfizer has prioritized areas of focus for rare disease research in hematology, neuroscience, pulmonology, and oncology, Dr. Lee says.

"We have significant expertise and resources in these therapeutic areas, which provides us with an opportunity to potentially develop and deliver needed medicines to patients," he says. "While these are our areas of

focus within rare diseases, Pfizer is always open to considering other opportunities in rare disease research and development areas.”

Patients in Clinical Development

Reaching out to patients and patient groups is critical during the development process, and one of the biggest challenges in doing trials in rare disease indications is patient recruitment.

“Because rare diseases affect small groups of people who are often geographically dispersed, this tends to make it difficult to identify, reach, and interact with these patients about research efforts, clinical studies, or share emerging disease information with them,” Dr. Lee says.

Pfizer strives to collaborate with stakeholders across the rare disease community — including industry, academia, and advocacy organizations — to address patient recruitment in orphan drug trials.

“We look for unique and compelling partnerships, which may involve shared financial support and collaborative scientific oversight,” Dr. Lee says. “This can ultimately provide otherwise unattainable access to resourcing and clinical expertise that can optimize trial design and patient recruitment.”

Advocacy groups and medical networks play a substantial role in the clinical development of rare disease and orphan drug compounds, according to a survey last year of 50 biotech and pharmaceutical firms by Premier Research. In fact, advocacy groups were used by more than half (60%) of the respondents to assist with their site or patient recruitment. Just more than two-fifths (42%) indicated that the use of advocacy groups to meet patient recruitment goals was successful or vital to the program. Almost four in 10 respondents (38%) said advocacy groups were most helpful in increasing the awareness of studies.

“Some advocacy groups can help families come to large cities where there are clinical trial sites and assist with things such as child care,” Ms. White says. “Advocacy groups can provide a lot of support for families in these trials.”

She points out, though, that not every disease state has a patient advocacy group.

“Pharma companies need to fully use social media and understand where patients are gathering in order to do a better job of clinical trial recruitment,” she says. “Additionally, if there are incredibly empowered patients in the rare disease space, there is an opportunity to include those patients in the trial design.”

Much of the success in patient recruitment is based on finding the appropriate site for the small patient populations, the Premier Research survey found. Additionally, studies become even more difficult to manage when they are conducted outside of Western markets. An example of this was when Premier flew patients from the Middle East to a trial in the United Kingdom, which required oversight of countless details from arranging for transportation of patients and parents, to visa requirements, language issues, and ongoing follow up with patients upon their return home.

Another company developing therapies for orphan diseases is PTC Therapeutics. The company’s lead product is ataluren, an orally administered small-molecule compound designed to enable the production of a functioning protein in patients with genetic disorders due to a nonsense mutation. The product is in late-stage development for Duchenne muscular dystrophy and cystic fibrosis.

As part of the ongoing clinical development of ataluren, the company has collaborated with key opinion leaders and patient advocacy groups, as well as peer companies, to better understand the natural history of the disease, determine valid clinical endpoints and to enhance the dialogue with the regulatory authorities. By enabling patients to produce the protein that they are otherwise unable to make, ataluren has the potential to change the course of the disease for these patients.

“We have enlisted the support of the patient advocacy groups and key opinion leaders in the space to drive awareness of the disorder and potential therapies in development,” says Shane Kovacs, chief financial officer of PTC Therapeutics. “We are excited about the potential to bring this potentially disease-modifying therapy to boys who otherwise would suffer from this progressive and life-limiting disorder.”

Joseph Payne, founder, president, and CEO at Arcturus Therapeutics, says his company is working with key opinion leaders and clinicians who are leaders in the field to develop their key assets.

“We’ve also reached out to the three major hospital groups in San Diego and each of them have expressed the ability and willingness to identify patients for trials,” he says.

Arcturus, which was founded in 2013, is RNA drug delivery systems for the orphan disease market. The company uses a technology called LUNAR — lipid-enabled un-



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DR. KEVIN LEE / Pfizer



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SHANE KOVACS / PTC Therapeutics

blocked nucleic acid modified RNA technology — to enable the silencing of aberrant gene expression.

“This is a platform technology that will enable many RNA medicines to be used to address multiple diseases,” Mr. Payne says.

Addressing Development Challenges

Ms. Cobb says there is a need for communication with patients much earlier in the development process, even at the preclinical trial



“We are talking to the key leaders in rare diseases. Patient recruitment can proceed more readily because they know other leaders in the field.”

JOSEPH PAYNE / Arcturus Therapeutics

phase, because input from patients on their disease journey may inform clinical trial protocols.

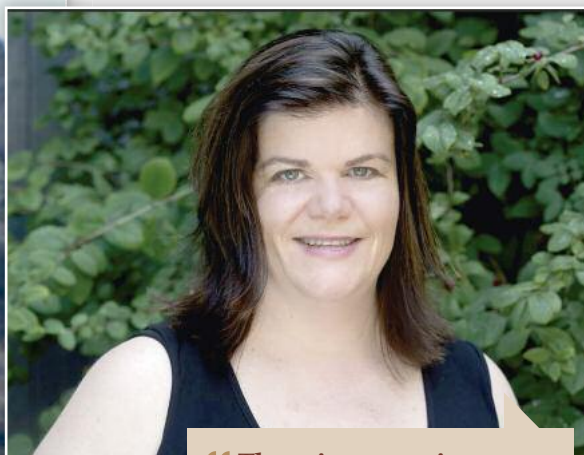
Karen Kaucic, M.D., VP, global head, at PPD Consulting, says the main challenge in developing orphan drugs is that developers continue to underestimate the challenges.

“Developers are still getting in their own way in a sense as they too often continue to take a common disease approach to the development of programs and protocols for rare diseases,” she says. “We need to devote adequate time to proactively planning those development programs with an eye toward their feasibility and executability.”

Dr. Kaucic says developers have to work with and across stakeholders from the very beginning of the trial design process.

“There needs to be early engagement with the investigators who are going to be executing these trials, along with key opinion leaders, clients, and CROs,” she says. “And there needs to be early engagement of patients and patient advocacy groups to include their perspective in the trial design process.”

Dr. Kaucic says modeling tools are impor-



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WENDY WHITE / Siren Interactive

tant to assess and determine implications of protocol complexity.

“There are data around operational feasibility of trial designs that already exist that we can bring to bear on the development of orphan programs,” she says. “Unfortunately, we often find that the work required to fully address the executability of a protocol isn’t completed before interactions with regulators. And, we still see situations where protocol designs have been presented to regulatory authorities before they have been optimized to execute to the time and costs the client has planned.”

Accessing Therapies

Ms. Cobb says one critical issue associated with rare diseases is patient access to therapy.

“Because rare disease therapies can be costly, patients need to be given information about how to get access to therapies, including the type of patient-assistance programs that are available,” she says.

Patient information is critical especially because of the uncertainty about what will happen as the Affordable Care Act goes forward.

“In rare diseases particularly, we recognize that we are a small part of a much larger community, and that a collaborative approach is critical, not only to speed delivery of approved medicines to treat rare diseases, but also in many cases to have the opportunity for successful drug development in the first place,” Mr. Bruce says.

FAST FACT

ORPHAN DRUGS ARE SET TO CONTRIBUTE 15.9% TO THE OVERALL PRESCRIPTION DRUG MARKET IN 2018, EXCLUDING GENERICS, UP FROM 5.1% IN 1998.

Source: EvaluatePharma

“We are engaged with healthcare stakeholders and the communities we serve in a dialogue to help create solutions that may provide increased access to treatments for patients in need,” Mr. Bruce continues. “Availability of and access to orphan medicines should be informed by, but not driven solely by, cost-effectiveness analyses. The fundamental nature of these diseases, both in the course of progression and relative paucity of patients, biases them in traditional cost-effectiveness models.

“Attributes and considerations, including the seriousness of the disease, the lack of readily-available treatment options, and the impact of the illness to patients and society if the medicine is not made readily available should also be considered,” he continues. “The length of time between regulatory approval and product reimbursement is a gap that needs to be closed. The positive news is that this is a broadly recognized issue, and that alignment is always the first step to achieving positive change.”

Joy Morrell, president of The Morrell Group, says pharmaceutical companies need to think differently about the support they offer patients with rare diseases.

“The chronicity of the disease is not always a factor in determining the behaviors of patients; it’s the patients themselves, their own behavior, and often the culture that they know,” she says. “Patients with severe diseases will take their drugs, but they sometimes will want to take drug holidays. They don’t understand the consequences of this decision.”

Ms. Morrell says deploying a team of clinical nurse educators who are disease state experts to work with patients can make the difference between a compliant patient and one who is not.

“We can help them understand what this means to their treatment regimen,” she says. “A larger percentage of patients will work to be more persistent in their lives if they understand the untoward side effects, how to manage their disease, how to pay for the treat-

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Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2015

2013

Chronic Fatigue Syndrome and Myalgic

Encephalomyelitis: April 25, 2013

Human Immunodeficiency Virus (HIV):

June 14, 2013

Lung cancer: June 28, 2013

Narcolepsy: Sept. 24, 2013

Fibromyalgia: Dec. 10, 2013

2014 AND 2015

Sickle cell disease: Feb. 7, 2014

Alpha-1 antitrypsin deficiency: TBD

Breast cancer: TBD

Chronic Chagas disease: TBD

Female sexual dysfunction: TBD

Hemophilia A, Hemophilia B,

von Willebrand disease, and other heritable bleeding disorders: TBD

Idiopathic pulmonary fibrosis: TBD

Irritable bowel syndrome, gastroparesis, and gastroesophageal reflux disease with persistent regurgitation symptoms on proton-pump inhibitors: TBD

Neurological manifestations of inborn errors of metabolism: TBD

Parkinson's disease and Huntington's disease: TBD

Pulmonary arterial hypertension: TBD

▼ For more information, visit <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm>

ments, and most important, what the overall health benefits are for them."

Ms. Szoke says when marketing products for rare diseases, pharma companies need to have a much closer connection to the patient groups.

"The people who suffer from rare diseases and their supporters live their lives trying to understand everything they can about the disease," she says. "They're probably the most knowledgeable patients there are because they live it every day. The more that companies tap into this valuable resource, the closer we will be to finding better treatment options."

The Orphan Drug Market

According to Kalorama Information, the

world orphan drug market was valued at \$61 billion in 2012 and is expected to increase at a rate of 11.5%, reaching a value of \$105.2 billion by 2017. Analysts say driving this growth is the increasing incidence of diseases affecting older people.

Orphan drugs are set to contribute 15.9% to the overall prescription drug market in 2018, excluding generics, up from 5.1% in 1998, according to EvaluatePharma.

Orphan drugs currently offer a greater return on investment than non-orphan medicines, according to a report last year by EvaluatePharma. This significantly better ROI is primarily due to the fact that orphan drugs require a median Phase III trial size of 528 patients versus 2,234 for nonorphan drugs.

Experts at EvaluatePharma estimate the average Phase III cost at \$85 million for orphan drugs versus \$186 million for the key Phase III trial for nonorphan drugs. When factoring in the potential 50% U.S. tax credit, this can reduce the cost of developing orphan drugs to \$43 million.

"There has been an increase in interest by large pharma companies over the last 10 years in developing therapies for orphan disorders," Mr. Kovacs says. "Previously, there were few leaders in the space, primarily Genzyme. Today, more large companies are shifting away from the primary-care model and moving into the specialist and orphan drug model."

Orphan diseases did not receive much attention from the pharmaceutical industry until the United States passed the first Orphan Drug Act in 1983. Other countries quickly began following suit with similar versions. In the United States, orphan diseases are those that affect fewer than 200,000 people; in the European Union, an orphan disease is one that affects fewer than 250,000 patients.

There are between 5,000 and 8,000 distinct rare diseases, affecting between 6% to 8% of the population. About 250 new rare diseases are identified each year, and 80% of these are genetic in origin and 50% affect children.

In the United States, since 1983 the program has successfully enabled the development and marketing of more than 400 drugs and biologic products for rare diseases, according to the FDA.

In contrast, fewer than 10 such products supported by the industry came to market between 1973 and 1983.

In 2012 alone, 13 orphan drugs were approved for rare diseases, including therapies for Cushing disease, cystic fibrosis, and Gaucher disease.

And, according to the Pharmaceutical Research and Manufacturers of America, more than 450 medicines are in development for rare diseases. **PV**



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MARY COBB / PatientVue



"We need to devote adequate time to proactively planning development programs for rare diseases with an eye toward their feasibility."

DR. KAREN KAUCIC / PPD Consulting



"Advances in science are unlocking a new understanding of many rare diseases. This has opened the door to potentially accelerate the development of new medicines to treat these conditions."

BERT BRUCE / Pfizer

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