

# RARE DISEASES: RESEARCH, DEVELOPMENT, AND COMMERCIALIZATION

notional use.  
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By Denise Myshko

In the past few years, significant progress has been made in rare diseases; in 2014, orphan drugs constituted 17 of the 41 new molecular entities approved by the Food and Drug Administration. An average of 140 drugs have been designated as orphan drugs by the FDA each year over the past decade, compared with 64 in the previous 10 years, according to the Pharmaceutical Research and Manufacturers of America.

The Orphan Drug Act, passed in 1983, was designed to provide incentives to manufacturers to research and develop drugs for rare diseases, defined as diseases that affect fewer than 200,000 people in the United States. The law has helped bring more than 450 new drugs to the market. During the decade before 1983, only 10 new treatments were developed for rare diseases. Since 1983, more than 3,000 products have been designated orphan drugs.

Driving recent approvals of rare diseases is the addition of the FDA's breakthrough designation, says Maria Whitman, managing principal, at ZS.

"The breakthrough designation within the FDA in particular played a role in oncology where biomarkers have enabled targeting of an increasing number of subpopulations of patients even in larger cancers where therapies can target diseases at a more personalized level," she says.

Robert Ryan, Ph.D., CEO at Scioderm, says the breakthrough designation provides a different level of engagement with regulators.

"We received a breakthrough designation in March 2013 when we were raising our Series A funding," he says. "The breakthrough designation had a tremendous impact on our ability to sit down with the agency in a larger forum. It made a huge difference to be able to get everybody into the same room to discuss our IND."

Scioderm's lead product, Zorblisa, is in Phase III trials for treating skin effects associated with all subtypes of epidermolysis bullosa, a genetic connective tissue disorder.

Currently, America's biopharmaceutical research companies are developing 452 med-

Rare diseases are receiving increased interest and investment from many stakeholders in healthcare, including biopharma companies, regulators, physicians, payers, and even Congress.

icines and vaccines to treat rare diseases, according to PhRMA. In particular, researchers are focusing on rare cancers, genetic disorders, neurological conditions, infectious diseases, and autoimmune disorders.

But despite these efforts, there is a huge unmet need in rare disease. In fact, about 95% of the estimated 6,000 to 7,000 rare diseases do not have a single FDA-approved drug treatment. At the current rate of approval, it will take more than 100 years to have therapies for all rare diseases, says Steve Smith, senior director, patient value, at Medidata.

The biggest unmet need in rare diseases — in addition to the inherent unmet medical need in most rare disease indications — has been the lack of multi-stakeholder alignment and collaboration, says Scott Schliebner, VP, scientific affairs, rare diseases, federal programs, at PRA Health Sciences.

"To make significant strides in these disease areas, we need stronger partnerships between industry and nonprofit patient advocacy groups; between regulators, payers, and drug developers; and between patients, families, and caregivers," he says.

This, however, is beginning to change. An initiative that began last year within the U.S. Congress is aiming to understand how to advance innovative medical research and to accelerate the development of safe, effective medical treatments and cures, particularly for patients with unmet medical needs.

## 21st Century Cures Initiative

Many leaders in the rare disease space say while the Orphan Drug Act has been successful, enhancements and changes are needed to solve some of the challenges related to conducting trials in small patient populations.

"The Orphan Drug Act provided incentives for corporations to develop therapies, which many people have said is very effective," says Wendy White, senior VP, for rare diseases, at Dohmen Life Science Services. "Now we need a more coordinated effort and more directed support to move products to the market faster."

That effort, the 21st Century Cures — an initiative within the House of Representatives — seeks to understand how to advance innovative medical research and to accelerate the development of safe, effective medical treatments and cures, particularly for patients with unmet medical needs.



In May, leaders from the Energy and Commerce Committee released a discussion draft of the 21st Century Cures initiative. The bipartisan initiative, led by Reps. Fred Upton (R-Mich.) and Diana DeGette (D-Colo.), began in April 2014 to look at ways to accelerate the pace of medical breakthroughs in the United States. The committee has held eight hearings, issued a number of white papers, and committee members have hosted more than two dozen roundtables across the country to generate ideas for this initiative.

John Crowley, CEO of Amicus Therapeutics, says the 21st Century Cures Initiative will go a long way to addressing the gaps in the Orphan Drug Act.

“It is the most patient-centered piece of legislation that I’ve seen proposed in Congress,” he says. “It addresses a really important point: how do we develop medicines in the most patient-focused way,” he says. “The 21st Century Cure Initiative takes a pro-patient view, but it is also pro-science. It doesn’t put patients first at the expense of rigorous scientific evaluation of data. But it does approach the science in a much more flexible, responsive, and appropriate way.”

Amicus is conducting two Phase III global studies of migalastat HCl monotherapy in Fabry disease and a late-stage preclinical study of AT-B200 for treating Pompe disease. Mr. Crowley’s two youngest children have Pompe disease, a lysosomal storage disease (LSD) that interferes with the body’s ability to break down molecules inside the lysosomes. He founded Novazyme Pharmaceuticals, a specialty biopharmaceutical company, to research enzyme replacement therapies for Pompe. Since then the company was sold to Genzyme.

(Editor’s Note: Mr. Crowley’s journey to find therapies for his children was profiled in PharmaVOICE in January 2009, as well as in a movie Extraordinary Measures.)

The 21st Century Cures draft includes provisions to: incorporate the patient perspective in the discovery, development, and delivery process, as well as increase funding for the National Institutes of Health, both through re-

authorization and \$10 billion over five years in mandatory funding, starting in fiscal year 2016. The draft also looks at how to break down barriers to increased collaboration and data sharing among patients, researchers, providers, and innovators, and help the development of personalized and precision medicines so the right patient can receive the right treatment at the right time.

“This initiative is charged with examining what is wrong with drug development,” Mr. Smith says. “We needed all stakeholders to have a consolidated discussion with Congress so Congress can pass new laws to change the FDA’s clinical trial process. This is historic; we haven’t had this sort of collaboration before.”

One of the biggest components of the draft, Mr. Smith says, is that it puts patients at the center of drug development.

“It will do this by compelling the FDA to take patients’ own assessment of risk and benefit into account and using risk vs. benefit in a methodological way,” he says. “It’s also important for clinical trial protocols that allow for small patient populations and allows us to use the data we do generate to prove whether the drug is working or not. This relates to endpoints and biomarkers. Using genetic biomarkers as an endpoint can bring us faster and better trials. The new legislation would mean that the FDA develops guidance so that biomarkers can be used more often.”

Another critical element of the draft is an increase in funding for both the NIH and the FDA.

“The 21st Century Cure legislation will restore America’s ability to lead in the 21st century of drug development,”

To make significant strides in the rare disease area, we need stronger partnerships between industry and nonprofit patient advocacy groups; between regulators, payers, and drug developers; and between patients, families, and caregivers.

**SCOTT SCHLIEBNER**  
PRA Health Sciences



The 21st Century Cure legislation will restore America’s ability to lead in the 21st century of drug development. We are a country that has traditionally led in medicine but our leadership is in danger of being eroded by the weakening of the NIH and, by inference, the weakening of the FDA.

**STEVE SMITH**  
Medidata

Mr. Smith says. “We are a country that has traditionally led in medicine, but our leadership is in danger of being eroded by the weakening of the NIH and by inference, the weakening of the FDA.”

Mark Rothera, chief commercial officer, PTC Therapeutics, says an analysis of the risk-benefit trade offs that patients and families are prepared to make in order to have access to an effective therapy is important for a better understanding of the patient and family perspective, especially in the regulatory process.

“The European Medicines Agency is willing to provide approvals based on a single trial where it believes that the evidence is sufficient in terms of efficacy and safety,” he says. “The agency is prepared to give early approval subject to a subsequent confirmatory trial. This is a compelling approach when dealing with progression and devastating disorders. It would be beneficial to patients if the FDA adopted a similar approach when looking at rapidly progressing and deadly diseases, because time is of the essence.”

In February 2015, the Senate’s Health Committee began its effort to look at how to improve biomed-





## Sound Bites

Industry leaders talk about the biggest trends in rare disease research.



**DOUG DONELAN**  
Executive VP, Executive  
Creative Director,  
Lawrence & Company

Because of limitations imposed by the very nature of a rare disease, the first challenge is finding a sufficient number of patients to put together a valid clinical study. Therefore, out of necessity, rare disease research has entered an age of greater collaboration between stakeholders.

Advocacy groups such as NORD are working with researchers from multiple companies and research centers to get the word out about available clinical trials. There's also a growing number of research partnerships between industry and data analytic companies, as well as academia. Some pharma companies are even seeking research alliances with other pharma companies.



**JEFF FARINA**  
Executive VP, Managing  
Partner, ghg Summit

Gene therapies are finally poised to achieve their potential as rare disease treatments. During the last decade, gene therapies achieved some remarkable results treating certain patients with rare immunodeficiency disorders, primarily due to improvements in the efficiency and safety of the modified viral vectors used to insert functioning gene copies into patients' cells. In 2012, the first rare disease gene therapy, Glybera for lipoprotein lipase deficiency, was approved in Europe. More than 1,000 gene therapy trials are ongoing. However, Glybera costs more than \$1 million per patient; the biggest challenge now is to reduce the extremely high manufacturing costs of these agents.

**TIM HOCTOR**  
VP, Elsevier R&D Solutions

As we continue to decipher the genetic code of living beings, masses of data accumulate. Within that data are thousands of ground-breaking insights to be uncovered. Analysis of this information could



lead to new ways of personalizing medicines and health-care, which is key to solving the biggest medical challenges of our time, including the discovery of new treatments for rare diseases.

The opportunity and the challenge when it comes to treating rare diseases is big data. An exhaustive amount of research and usable data are now readily accessible. With this data, it's possible that answers long sought to important queries could finally be within reach. In current drug studies, millions of genetic variations can be detected among participants in a single clinical trial.

Better characterization and categorization of data is what will allow scientists to find the targets to long-standing complex problems.



**DERENDA NICHOLS**  
Senior Director, Clinical  
Trial Management,  
Medpace

The largest challenge in conducting rare disease studies is finding and retaining the appropriate patients. The use of international patient registries to conduct studies will continue to demand resources.

Innovation in patient registry design for patient enrollment, as well as partnering models using patient advocacy groups, will continue to be of great value. Harnessing the power of these groups will enable researchers to design studies for improving therapies to combat rare diseases in the patient's lifetime.

**SANFORD PLACHTER**  
Marketing Manager, MonoSol Rx

The trend to watch for in rare disease research will be the use of the precision medicine initiative. Precision medicine, often called personalized medicine, will allow for access to huge databases of information regarding genetic diseases, which is often the cornerstone of rare diseases. Rare diseases and orphan diseases were once largely ignored by the



pharma industry due to the lack of financial incentives and clinical challenges. The combination of advanced research, greater clinical opportunities, and the ability to leverage rare disease treatments with payers will spark a new era in rare disease research and treatment.



**CHRISTOPHER TOBIAS, PH.D.**  
Executive VP, Managing  
Director, Dudnyk

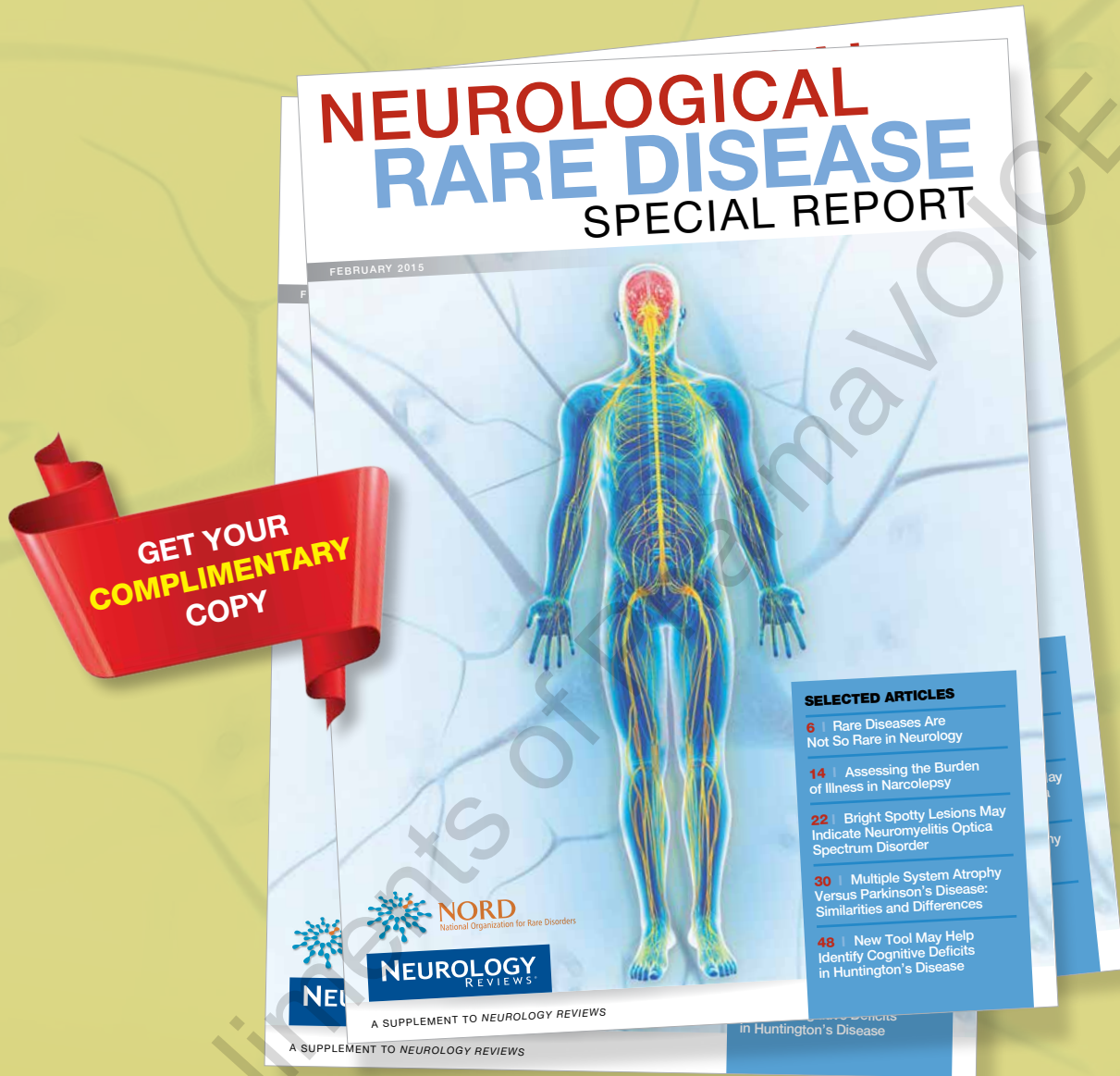
The newest genome editing technology, known as CRISPR, is composed of a guide RNA that is designed to recognize and target a specific site on the DNA and a bacterial enzyme that functions like "molecular scissors" to cut the DNA at the target site. CRISPR technology has corrected mutations that cause cystic fibrosis. The ease of genome editing may lead to the identification of new drugs to treat previously untreatable rare diseases.



**JIM VITALE**  
Director, Product  
Management, Taconic  
Biosciences

Through access to inexpensive, high-throughput sequencing, scientists in rare disease research fields now have unprecedented genetic knowledge of specific rare diseases and can identify their genetic causes more quickly. These dedicated scientists can then leverage that knowledge to generate genetically engineered translational models that replicate human disease phenotypes. Such models are proving to be invaluable tools for a variety of studies, including efficacy testing of novel drug treatments. We anticipate that new, relevant translational models will continue to be generated for rare diseases, accelerating the drug discovery process and ultimately delivering new treatments.

The National Organization for Rare Disorders (NORD) and Frontline Medical Communications collaborate to develop innovative educational programs that improve awareness, understanding and diagnoses of rare diseases and promote optimal patient care.



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An analysis of the risk-benefit trade offs that patients and families are prepared to make in order to have access to an effective therapy is important for a better understanding of the patient and family perspective, especially in the regulatory process.

**MARK ROTHERA**  
PTC Therapeutics



The 21st Century Cure Initiative takes a pro-patient view but is also pro-science. It doesn't put patients first at the expense of rigorous scientific evaluation of data. But it does approach the science in a much more flexible, responsive, and appropriate way.

**JOHN CROWLEY**  
Amicus Therapeutics

"As this research then transitions into clinical and regulatory, we need to work very carefully with physicians to understand what biomarkers may be relevant to disease, and we need to engage with regulators early in the process to ensure that we are aligned on the appropriate biomarkers and clinical endpoints to focus on," he says.

Understanding the basic biology of disease is a challenge, Mr. Crowley agrees.

"But we are understanding more about the genetic mutations that lead to these diseases and how those result in different severities of disease, different onsets, different organ involvement, and different responses to various medicines and technologies that might be applicable to treat the disease," he says.

The challenges of developing drugs for rare diseases are often underestimated, says Kevin Lee, Ph.D., senior VP and chief scientific officer, Pfizer. He says partnering is the most effective way for drug discovery and the most rapid way in an area like rare disease. Pfizer's current pipeline includes clinical and preclinical programs in sickle cell disease, hemophilia, muscular dystrophies, spinal muscular atrophy, cystic fibrosis, and other rare diseases.

Scientific collaboration is crucial, says Eric Althoff, head of global media relations, Novartis. Novartis has nine marketed drugs that have been designated orphan drugs as well as a robust clinical pipeline, including more than 40 active preclinical and clinical research projects in the rare diseases area.

"Researchers must work together toward the goal of creating a global knowledge base, a necessary step to tackling the challenges of these diseases where basic knowledge is limited and the small patient populations are dispersed across the globe," he says. "Knowledge derived from the thorough analysis of a rare disease has high scientific and societal value, because insights into rare disorders may also provide scientists with a clear understanding of disease mechanisms that could be useful to treat more common disorders."

Industry experts identify numerous challenges specific to each particular disease state, including investigator cultivation and site identification; patient identification, recruitment, and retention; understanding the patient pathway and selection of endpoints; and engaging and including various stakeholders to the drug development process.

"There are strategic and tactical considerations that can be used to address and overcome the various challenges to rare disease drug development," Mr. Schliebner says. "We use an evidenced-based approach that leverages medical informatics to drive study design and trial positioning; natural history studies and registries can be developed to shed light

### Rare Disease Facts



▶ Rare diseases affect about **30 million Americans, or 1 in 10 people**



▶ It is estimated that **350 million people worldwide** suffer from rare diseases



▶ About **30% of children** with these debilitating diseases **will not live** to see their 5th birthday



▶ About **80%** of rare diseases are genetic



▶ Rare diseases **impact more people** than AIDS or cancer combined



▶ **95% of rare diseases** do not have a single FDA-approved drug treatment

Source: Global Genes

process for getting products to the market.

### Researching Rare Diseases

Phil Vickers, Ph.D., global head of R&D, Shire, says the research of rare diseases is different from more common diseases.

"With rare diseases we are not following a well-trodden path; we're making the path," he says. "There is usually no effective standard of care and no drug has gone through the regulatory process."

Shire has been active in the rare disease space since the acquisition of Transkaryotic Therapies (TKT) in 2005 and most recently established a three-year research agreement with the Cincinnati Children's Hospital Medical Center for rare diseases. In February 2015, the company also acquired NPS Pharma, a company focused on rare diseases.

Dr. Vickers says rare diseases are not fully understood and so companies in rare disease research often have to do natural history studies. They have to work closely with key opinion leaders to try to understand the disease.

cal innovation. Led by Sens. Lamar Alexander (R-Tenn.) and Patty Murray (D-Wash.), the committee is holding hearings to examine the

have to do natural history studies. They have to work closely with key opinion leaders to try to understand the disease.



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**DR. PHIL VICKERS**  
Shire



a clinical study to drive statistical significance. Partnering with advocacy organizations can go a long way to helping pharmaceutical companies reach patients.

"Patientricity is becoming a buzz word and is especially relevant to the rare disease arena," Mr. Schliebner says. "We are also seeing bigger industry players begin to enter the rare disease space, make acquisitions, and broaden their focus on orphan drug development. There are more agents in development and more awareness. This will continue."

Dr. Vickers agrees that having strong links with patient associations is particularly important in the rare disease space.

"We are working in areas where there is no effective standard of care and in many cases, there have been no drugs that have gone through the regulatory path," he says. "In fact, there is little published on some of the rare diseases that we work on, so just defining what are the appropriate factors to measure in clinical studies is something we spend a lot of time on."

Yuval Cohen, Ph.D., CEO of Corbus Pharmaceuticals, says patient groups are important partners in helping companies develop and execute trials in the best possible way. Corbus

on the disease state and the optimal selection of endpoints; early and transparent engagement with patient advocacy groups can help to build trust and collaboration to accelerate rare disease drug development."

Rare disease studies are often restricted by the number of patients available. And while patient recruitment continues to be a challenge for all trials, it is even more so for trials of rare diseases. Every patient counts in

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## Funding Innovation



- ▶ 78% of U.S. venture investment for therapeutics went toward novel drug R&D, suggesting innovation is a core priority for venture investors
- ▶ Total venture funding of drug R&D dropped 21%, from \$21.5 billion to \$16.7 billion, comparing five-year periods before and after the recent financial crisis (2004-2008 vs. 2009-2013)
- ▶ Disease areas affecting large populations — diabetes, psychiatry, gastrointestinal, respiratory, cardiovascular — have seen a decline in novel drug R&D venture funding
- ▶ Rare disease funding has seen a large increase over the past decade in terms of both dollars raised and number of companies funded
- ▶ There are fewer first-time Series A financings in recent years, down 30% from a peak in 2006, but higher dollar amounts for novel drug R&D venture funding

Source: Biotechnology Industry Organization

is working with the Cystic Fibrosis Foundation Therapeutics Development Network on a Phase II trial for Resunab, which is being investigated for the treatment of cystic fibrosis. They are also launching a Phase II clinical trial in diffuse systemic sclerosis.

Dr. Vickers says working closely with patient advocacy groups is essential to understand the patient's and caregiver's perspectives on the most significant unmet needs and the most devastating effects or consequences of these diseases on their daily lives in order to design studies to best meet patients' needs.

In many rare diseases, however, there is no patient advocacy organization. In this case, biopharmaceutical companies are working on their own to reach patients.

One such company is Catalyst Pharmaceuticals. The company's lead program is Firdapse. An NDA for this product is expected to be submitted to the FDA in the third quarter of 2015 to treat patients with Lambert-Eaton Myasthenic Syndrome (LEMS). LEMS is a rare autoimmune disorder with the primary symptoms of debilitating muscle weakness. While this disease would fall under the Muscular Dystrophy Association, no specific LEMS



In the rare disease ecosystem, the stakeholders tend to be more connected and they tend to be communicating with each other more.

**KRISTIN KELLER**  
Discovery USA

organization exists. Catalyst recently worked with the National Organization for Rare Disorders (NORD) to set up a patient meeting this spring in Orlando for patients and caregivers and their physicians.

"This meeting gave us an opportunity to better understand the patient's journey," says Pat McEnany, CEO of Catalyst. He says this was the company's first patient meeting and others are planned around the country for continued patient outreach.

Patient-to-patient connection is a powerful means of communications, says Dan Bobear, principal, managing director at The Patient Experience Project.

"In rare diseases, there is an interesting dynamic in that many patients have never, or rarely, spoken to someone else with the same condition," he says. "So when patients speak to, hear stories, or get advice from someone in the same situation it has deep meaning and the potential for connection and engagement is incredible."

Because the understanding around rare diseases is often limited, patient registries and postmarketing studies play an increasingly important role in research.

Fewer than 20% of rare diseases have patient registries, and most are operated by patients' organizations or academic researchers, according to the National Institutes of Health.

One such program is the Global Rare Diseases Patient Registry Data Repository/GRDR program from the NIH's National Center for Advancing Translational Sciences. This program aims to develop a Web-based



Communicating value to payers is becoming challenging with orphan and rare diseases as more products launch and budget impact goes up.

**MARIA WHITMAN**  
ZS

resource that aggregates, secures, and stores de-identified patient information from many different registries. NORD has been instrumental in helping set up a number of patient registries, the most recent is the Foundation for Prader-Willi Research, which launched in May. Prader-Willi is a rare genetic disorder that affects development and growth.

Patient registries are important to gather additional information about how a drug is performing in patients, says Stella Blackburn, VP of global risk management, in Quintiles' real world and late-phase research division.

"All the evidence before registration is from clinical trials," she says. "A lot of the patients who will get the drug will have more complex diseases and may be different age ranges or they may be taking other drugs as well. These registries aim to answer questions that couldn't be answered pre-authorization."

## Commercializing Drugs for Rare Diseases

Sales of drugs designated as orphans by regulators in the United States, Europe, or Japan will grow at an annual rate of almost 11% per year through 2020, compared with only about 4% for drugs treating larger populations, according to a 2014 report from EvaluatePharma. In fact, orphan drug sales will constitute 19% of the total share of prescription drug sales by 2020, totaling \$176 billion.

Launch strategies for products for rare dis-



eases need to be different from other product launches, says Kristin Keller, executive VP, client engagement, Discovery USA. She says in the rare disease ecosystem, the stakeholders tend to be more connected and they tend to be communicating with each other more. This means pharma companies have to make sure brands have a very holistic and innovative strategy at a brand, commercial, and communications level.

“Typically there is a heavy burden put on the patients both by the disease and by the dynamics of the treatment,” Ms. Keller says. “Patients may be dealing with more intensive treatment regimens, and are typically dealing with life-long chronic diseases. It’s important to provide as much support and value at a high level of service to the patient community.”

Ms. Keller says these services make sure that patients are at the center of the treatment and can include anything from reimbursement, patient support, or nurse counselors who come to the home; patient mentors; or wrap around services that are designed to address the unmet needs of the patient and their family.

Physicians are challenged in dealing with patients with rare diseases. Physicians — both primary care and specialists — have limited resources and information to properly diagnose/manage patients with rare diseases as compared with the more common diseases they see. Frontline Medical Communications conducted a survey of healthcare professionals, and found

that 88% of the HCPs surveyed agreed there is a need for professional content around rare diseases. HCPs have an average of 12 patients who have either been diagnosed with, are being treated for, or are suspected to have and remain undiagnosed with a rare disease.

“A survey of our readers found physicians know they lack understanding of rare diseases and want more information,” says Elizabeth Katz, publisher of *Neurology Reviews*, Frontline Medical Communications.

Unless patients are seeing a key opinion leader in the disease area, they may not be receiving the highest standard of care, Ms. White says.

“Primary care physicians just don’t have the time to learn about diseases they may never see in their practice,” she says. “They are doing exactly the same thing that patients and caregivers do when a patient presents with something they don’t recognize — they look it up on the Internet. If we, on behalf of manufacturers, can help them know that there is a treatment available and how to get to the right diagnosis and provide that in a timely way, then we can help physicians be more effective.”

Ms. White says it’s important to bring payers into the discussions about new therapies for rare diseases early on.

“Bringing payers in as a company is developing its clinical trial and thinking about what kind of proof is going to be needed to cover costs is critically important,” she says.

Ms. Whitman says pharma companies have not had a high burden to communicate value in rare diseases so far. Communicating value to payers is becoming challenging with orphan and rare diseases as more products launch and budget impact goes up. More companies are launching products into rare indications, and while there is a limited breadth of patients and data, many drugs will expand into broader indications.

Ms. Whitman recommends companies consider constructing a cohesive value story for payers, physicians, and patients. While each of these stakeholders is making different decisions in the patient journey, in rare diseases there is much more collaboration among the stakeholders across the journey of a patient.

“We haven’t gotten to a point yet in most rare diseases where there are multiple products to determine if certain endpoints outweigh others,” she says. “With more rare approvals and comparators emerging impact is harder to prove. The value will be in demonstrating differentiation in disease modification and how this is going to make a difference to the patient. A rare disease is one of the areas where we can still truly change the course of a patient’s life.” <sup>PV</sup>



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By Denise Myshko

# RARE DISEASES RESEARCH

Experts in pharma and biotech companies provide information about their research efforts.



John Crowley

## Amicus Therapeutics

Amicus Therapeutics is a biopharmaceutical company developing treatments for a broad range of human genetic diseases, with a focus on improving therapies for lysosomal storage diseases. Amicus is conducting two Phase III global studies of migalastat HCl monotherapy in males and females with Fabry disease who have -Gal mutations that are considered amenable to chaperone monotherapy based on a proprietary cell-based assay.

Regulatory authorities in the United States, the European Union, and Japan have granted orphan drug designation for the active ingredient in migalastat HCl.

“Traditionally, the way we’ve thought about Fabry disease is that the patient is missing an enzyme, and using a replacement therapy such as the Genzyme or Shire product, which are infused proteins, was the way to treat this disease,” says John Crowley, CEO of Amicus Therapeutics. “The more we learned about the genetics of Fabry disease the more we actually understood that the majority of patients do make the protein. They just don’t make it correctly so it misfolds and doesn’t work.”

The company’s lead product is a small molecule “chaperone” that binds to and stabilizes the patient’s own enzyme, which allows it to become transported to the lysosome where the enzyme needs to live and work.

Amicus also is conducting research in Pompe disease. The company’s preclinical studies aim to assess AT-B200 in combination with AT2220. Initial human proof-of-concept for the chaperone-ERT combination approach in Pompe disease was established in a Phase II study (Study 010). The results from this study demonstrated that co-administration of oral AT2220 just prior to infusing Myozyme/Lumizyme increased GAA enzyme activity in muscle tissue compared with ERTs alone.

The company also has a preclinical program in Parkinson’s disease. AT3375 is a next-generation, small molecule pharmacological chaperone that targets the GCase enzyme in the brain.

AT3375 was the lead compound selected from a series of chaperones designed by Amicus to improve upon the properties of AT2101, a first-generation chaperone previously developed as a monotherapy for Gaucher disease. AT3375 is currently in preclinical studies that are funded in part by a grant from the Michael J. Fox Foundation.



Pat McEnany

## Catalyst Pharmaceuticals

Catalyst Pharmaceutical Partners is a biopharmaceutical company focused on developing and commercializing innovative therapies for people with rare debilitating diseases.

For its lead program, Firdapse, the company is currently engaged in filing an NDA following the completion of a pivotal Phase III, global, multi-centered trial for the treatment of patients with Lambert - Eaton Myasthenic Syndrome (LEMS). LEMS is a rare autoimmune disorder with the primary symptoms of debilitating muscle weakness, where the immune system attacks the nerves that control the muscles.

The company is also studying the product for congenital myasthenic syndrome (CMS), a rare neuromuscular disease comprising a spectrum of genetic defects and is characterized by fatigable weakness of skeletal muscles with onset at or shortly after birth or early childhood.

Pat McEnany, CEO of Catalyst Pharmaceuticals, says the mechanism of action is unique. Firdapse blocks potassium channels, which prolongs the opening of the calcium channels and on nerve endings. The longer open time of the calcium channels results in

increased acetylcholine release, a neurotransmitter responsible for muscle contraction, which restores muscle strength that was lost due to LEMS.

The company is planning to begin a rolling NDA with the FDA beginning in the third quarter of this year.



Dr. Yuval Cohen

## Corbus Pharmaceuticals

Corbus Pharmaceuticals is focused on the development and commercialization of novel therapeutics to treat rare, life-threatening inflammatory and fibrotic diseases. The company’s lead product candidate, Resunab, is

a first-in-class, oral anti-inflammatory drug that acts to resolve inflammation through an endogenous pathway. Resunab is scheduled to begin two Phase II clinical trials in 2015 for the treatment of cystic fibrosis and diffuse systemic sclerosis. In both instances, inflammation contributes to disease progression and fibrosis is linked to high mortality rates. Resunab also has the potential to treat additional rare, inflammatory diseases.

Resunab targets both the inflammation and scarring that occurs in a tissue after it has been subjected to chronic inflammation, says Yuval Cohen, Ph.D., CEO of Corbus Pharmaceuticals.

“Resunab tackles inflammation and fibrosis in a novel manner,” he says. “A classic anti-inflammatory, for example, NSAIDs try to freeze or jam the inflammatory cascade. This approach often involves serious side effects and typically is not sufficiently potent or ap-



appropriate for many diseases. There is currently no approved therapy that addresses chronic inflammation in either cystic fibrosis or systemic sclerosis.”

Dr. Cohen says Resunab binds to a receptor found in the immune system called CB2. The receptor is found in all white blood cells and once bound, it activates a process known as inflammatory resolution.

In April, the company received a \$5 million developmental award to support its Phase II trial from the Cystic Fibrosis Foundation Therapeutics, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation.

The company is also investigating Resunab for the treatment of scleroderma.



Eric Althoff

### Novartis

Novartis has nine marketed drugs that have been designated orphan drugs as well as a robust clinical pipeline, including more than 40 active preclinical and clinical research projects in the rare diseases

area.

“Our drug discovery priorities are determined by patient need and sound science — not by the potential market size of a medicine,” says Eric Althoff, head of global media relations, Novartis. “We are committed to finding treatments for rare diseases where there is unmet need and where the scientific understanding is strongest.”

### Pfizer

Pfizer has 22 medicines approved worldwide that treat rare diseases in the areas of hematology, neuroscience, inherited metabolic disorders, pulmonology, and oncology. The company’s current pipeline includes clinical and preclinical programs in sickle cell disease, hemophilia, muscular dystrophies, spinal muscular atrophy, cystic fibrosis, and other rare diseases.

Two recent collaborations demonstrate Pfizer’s commitment to working with external partners. Pfizer has expanded its research partnership with Cystic Fibrosis Foundation Therapeutics (CFFT) that began with the company’s acquisition of FoldRx Pharmaceuticals in 2010. Under the new six-year preclinical research agreement, CFFT, the nonprofit drug discovery and development affiliate of the Cys-

tic Fibrosis Foundation, will invest up to \$58 million to speed the discovery and development of new treatments for the most common mutation of cystic fibrosis, Delta F508.

In another key partnership, Pfizer’s Centers for Therapeutic Innovation (CTI) worked with the Alliance for Lupus Research (ALR) to discover new therapeutic options for patients living with this chronic autoimmune disease. CTI and ALR co-funded translational research projects led by academic medical centers from within the CTI network.

“About 70% of our rare disease portfolio is partnered in one way or another,” says Kevin Lee, Ph.D., senior VP and chief scientific officer, Pfizer. “We have partnerships with biotech companies and with the academic community. We believe that is the most effective way for drug discovery and the most rapid way in an area like rare disease.”

### PTC Therapeutics

PTC Therapeutics is a global biopharmaceutical company focused on the discovery, development, and commercialization of orally administered, proprietary small molecule drugs targeting RNA biology. In August 2014, the company received marketing approval from the European Medicines Agency for Translarna, for the treatment of nonsense mutation Duchenne muscular dystrophy based on a commitment to complete a confirmatory ACT DMD trial. Translarna is a protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. A nonsense mutation is an alteration in the genetic code that is present in the messenger RNA and prematurely halts the synthesis of an essential protein. The resulting disorder is determined by which protein cannot be expressed in its entirety and is no longer functional, such as dystrophin in Duchenne muscular dystrophy.

This is the first product approved for Duchenne muscular dystrophy, says Mark Rothera, chief commercial officer, at PTC Therapeutics.

Some Duchene patients, Mr. Rothera says, have a mutation where the protein dystrophin is not produced because of a premature stop signal in the mRNA. What Translarna does is help bypass the premature stop signal and allow the production of the full length active protein dystrophin.

In December 2014, the company began a rolling NDA submission of Translarna as a

treatment for nmDMD, which it will complete following the availability of data from its Phase III clinical trial in nmDMD, which is expected in fourth quarter of 2015.

Translarna is also in Phase III trials to treat cystic fibrosis caused by a nonsense mutation, and the company plans to file a regulatory application in Europe in the second half of this year.

### Scioderm

Scioderm is a biopharmaceutical company focused on developing therapies for treating diseases with high unmet need, including orphan products. The company’s lead product, Zorblisa, is being developed for treatment of the skin effects associated with all subtypes of Epidermolysis Bullosa (EB), which is a rare genetic connective tissue disorder.

In March 2015, the company initiated a Phase III registration trial Zorblisa as a topical therapy for the treatment of blisters and lesions in patients with EB.

“We are doing a pivotal study that will support both U.S. and European registration if the study comes out as we anticipate,” says Robert Ryan, Ph.D., CEO, at Scioderm.



Dr. Phil Vickers

### Shire

Shire has been active in the rare disease space since the acquisition of Transkaryotic Therapies Inc. (TKT) in 2005, and Phil Vickers, Ph.D., global head of R&D, Shire, says the company is always looking for opportunities to address high unmet medical needs. Most recently the company established a three-year research agreement with the Cincinnati Children’s Hospital Medical Center for rare diseases. The company also has an ongoing partnership with Boston Children’s Hospital.

In February 2015 Shire acquired NPS Pharma, a biopharmaceutical company focused on rare diseases. The therapeutic focus of NPS is aligned with Shire’s expertise in their gastrointestinal and metabolic disease business unit. NPS received approval in January 2015 for NATPARA as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Hypoparathyroidism is a rare endocrine disorder characterized by insufficient levels of parathyroid hormone. NATPARA is a bioengineered form of human PTH. <sup>®</sup>