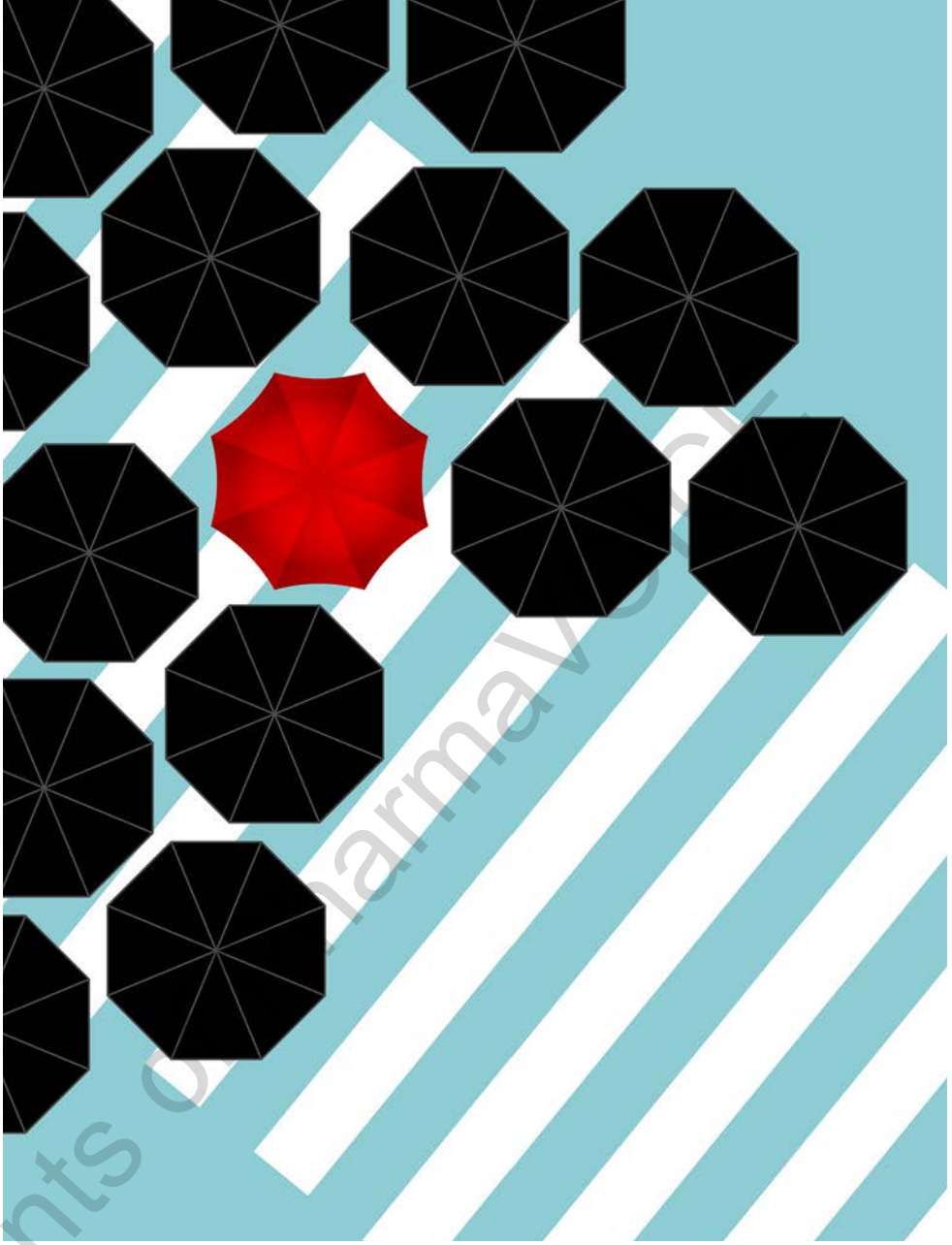

Focus on RARE DISEASES

With huge opportunities for patients and companies, collectively, rare diseases are receiving far more attention in terms of R&D, delivery, marketing, patient recruitment, etc., than ever before.

Rare diseases have been a focus of drug development for decades, and since the 1980s, there have been financial, legal, and legislative incentives, such as the Orphan Drug Act, that are drawing companies of all sizes to enter the market.

Rafal Kokolus, senior engagement manager, inVentiv Health Consulting, believes the rare disease market has passed a tipping point 34 years in the making.

"Today, we have a much clearer understanding of what rare diseases are, an increasingly friendly regulatory environment, incentive systems to encourage their development, and several success stories," he explains. "Those clinical and business success stories have raised the profile of rare disease and generated the needed intellectual and financial capital to sustain pipeline growth. The rare disease growth story is incredible: starting with fewer than 10 assets pre-Orphan Drug Act to almost 500 drugs currently approved in more than 440 separate indications, and more than 400 additional drugs in development."

The rare disease market is growing faster than that for traditional drugs. According to a new report from Scalar Market Research, the global orphan drugs market is expected to grow at a steady CAGR of 11.43% from 2016 to 2022. At the estimated growth rate, the orphan drugs market is expected to grow from $111.87 billion in 2016 to $214.14 billion by 2022.

The potential size of this market has not gone unnoticed by biopharmaceutical companies of all sizes, which are leveraging cutting-edge technologies and capitalizing on the growing scientific understanding of many rare diseases to develop groundbreaking therapies.

According to Julianne Dunphy, Ph.D., director, medical strategy at Cambridge BioMarketing, recently innovative biotech companies that invest in developing therapies for rare disease have become increasingly attractive to big pharma.

"These enterprises are looking to develop a presence in the space not only because of the great unmet need and market potential, but also to soften the blow of the patent cliff," she says.

In the past decade, more than 230 new orphan drugs were approved by the U.S. Food and Drug Administration. In 2015 alone, nearly half — 47% — of novel new drug approvals were for rare diseases, including therapies for cancer, cystic fibrosis, difficult-to-treat high cholesterol, and several enzyme deficiency disorders. Many of the new medicines provide treatment options for patients where there were few or none previously available.

According to PhRMA, 30 million Americans, or 10% of the population, have one of the 7,000 known rare diseases, of which 80% are genetic in origin. Half of those affected worldwide are children.

Scheduled for 2017 — Rare Disease Focus Topics

January — R&D
February — Rare Disease Day
March — Marketing
May — Patient Recruitment
June — Supply Chain
September — Patient Communities
October — Regulatory Environment
November/December — Market recap

Streamlining trials for a rare disease product takes a specialty logistics partner with worldwide infrastructure and local expertise. Additionally, an effective market access strategy, combined with a high-touch approach to reimbursement and clinical support creates the treatment lifeline. Designing a commercialization strategy, including distribution and third party logistics services, with the patient's comprehensive experience in mind takes a partner who understands that every patient matters. It takes AmerisourceBergen.

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Observations

JUDITH NG-CASHIN, M.D.
Chief Scientific Officer, INC Research

Our Rare Diseases Consortium pulls together all our experts and staff with experience in rare disease trials to better leverage our collective insights and experience toward each rare disease program. The biggest lesson we've learned is that we are in a position to drive collaboration between the various stakeholders. We include patient advocacy groups in our protocol program and study development process to ensure the voice of the patient and his or her caregivers are reflected in the protocol. We develop intimate relationships with the investigator sites and support them through the complexity of the study. Connecting these groups with the sponsors and driving collaboration is how we can accelerate product development in these areas of great medical need.

JAMES RADKE
VP of Editorial, Rare Disease Communications

Scientific breakthroughs have caught up with our understanding of many rare diseases. Unlike more common diseases like cancer and diabetes, rare diseases often have a simpler pathophysiology that makes it easier to use new techniques such as gene therapy to treat them. There is also the philanthropic nature of rare diseases. The people in this community are special. Facing incredible challenges, they are often the most optimistic, driven, and strongest people you will ever meet. That is contagious and many people have invested their money, time, and efforts to help them succeed.

A disease is generally defined as "rare" when, by itself, it affects fewer than 200,000 people in the United States. However, many rare diseases impact significantly smaller groups of patients, sometimes as small as a few hundred.

"Scientific advances are leading to a greater understanding of diseases, and how to better treat those diseases with engineered and targeted therapy," says John Boland, VP of product development at Atlantic Research Group. "These advances have enabled sponsor companies to be able to identify patient populations and develop potential treatment options that may help them live fuller lives. This is a thrilling time to be in rare disease research, and it is very exciting to see science, technology, and regulatory dynamisms come together to help more patients in the underserved rare disease community."

Scott Schliebner, VP, scientific affairs, rare diseases, at PRA Health agrees that the convergence of regulatory flexibility, innovative trial designs, and patient involvement is shortening clinical development timelines and resulting in higher drug approval rates, and as a result small emerging biotech firms, established pharmaceutical companies, and big pharma are all taking notice.

"The advances in genetic testing, along with leveraging new technologies like wearables, allow us to bring clinical trials directly to patients and make participation easier for families, caregivers, and parents of those affected with a rare disease," he says. "The rare disease market is somewhat of an 'innovation lab' right now, showing how creative collaborations and new approaches can bring therapies to patients faster. It is an exciting time filled with much progress, but at the same time we need to move faster and find ways to continually improve how we develop new treatments; patients can't wait."

Dr. Dunphy says there is no doubt that rare diseases are indeed getting more widespread attention.

Our future success in rare diseases will come down to how well we can come together in the spirit of open innovation as a true community of academics, rare disease companies, patient groups, and physicians to effectively collaborate on transformational R&D approaches.

RAFAL KOKOLUS
inVentiv Health Consulting

To launch an orphan drug, a manufacturer must overcome unique commercialization challenges, while navigating critical product access scenarios that exist most acutely for small patient populations.

TOMMY BRAMLEY
Xcenda

"New rare diseases are constantly being identified, and only a tiny minority of the diseases have targeted therapies," she says. "This means that the already substantial unmet need in this space continues to grow. The enormous scope of the challenge is impossible to ignore. Furthermore, the rare disease market is one with a level of patient involvement and advocacy unmatched by most other areas of medicine. It's always been true, but now, the ubiquity of digital connectivity has invigorated rare disease communities, amplifying the voices and elevating the needs of those affected."

Social media has indeed provided a forum for patients, but Tommy Bramley, Ph.D., R.Ph., president of Xcenda, says manufacturers need to be prepared to do the heavy lifting or find a partner that can help them do so in terms of communicating the unique value prop of these special products.

"Companies should keep in mind that the value story of their orphan products will be generated by real patients and they should develop a patient experience that will generate a value to support their products during and post-launch," Dr. Bramley says. "Patients with rare diseases often have few places to find support, and this should compel manufacturers to provide a high number of wraparound services."

For example, he says site of care is an important component when considering the patient journey. As some payers cover orphan drugs under the pharmacy benefit and others put them under the medical benefit, manufacturers want to be sure that they are positioned to support both types of coverage as well as the sites of care that manage drug purchasing.

"Manufacturers need to ensure a successful launch, where patient financial hurdles are swiftly overcome, supply chain and order management works smoothly and the product arrives safely to the point of care," he says. "All of these challenges present an opportunity for orphan drug manufacturers – often small to mid-sized in the market – to look to partners that can provide wrap-around, 360-degree services to successfully bring their product to market."

The increased focus on developing drugs for rare diseases is multi-faceted. BBK Worldwide CEO and Founding Principal Joan Bachenheimer contends that there are three main influences.

"The end of the blockbuster drug era made way for R&D to shift spend and innovation toward boutique conditions and niche drugs based on personalized medicine," she explains. "Smaller, more nimble biologic start-ups began to pursue treatments based on breakthrough science, and financial communities have been increasingly willing to invest in these ventures. These shifts are thanks in part to a much broader understanding about the need to study the genetic factors affecting disease and disease management, which are also most easily studied in smaller populations and families.

"Third, and perhaps most importantly, the growing influence of patients and advocacy groups — and having their voices amplified

The rare disease market is one with a level of patient involvement and advocacy unmatched by most other areas of medicine.

DR. JULIANNE DUNPHY
Cambridge BioMarketing

Rare Disease Medicines in Development: From Hope to Cures

30 Million Americans — about 1 in 10 — are living with a rare disease

Approximately **7,000** rare diseases are known to exist today

FDA approved more than **500** orphan drugs since the passage of the Orphan Drug Act

Only **5%** of rare diseases have an approved treatment

Source: PhRMA

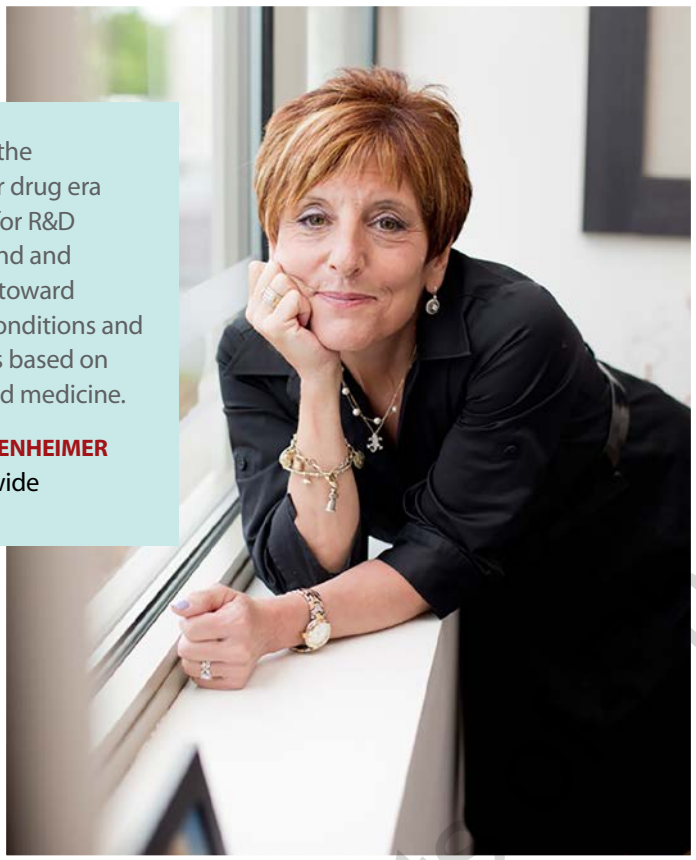
Observations

GUR ROSHWALB, M.D.
CEO, Akari Therapeutics

There are several factors at play as to why there is increased focus on the rare disease market — from legislation on orphan diseases that provides benefits to companies at the regulatory level, to the general advance in sciences, to the ability to price drugs higher in these markets making them more attractive. In essence, though, all these factors, especially the regulatory support, makes it much more achievable for a small company to advance a drug in these conditions. For example, an orphan program may entail as few as 40 to 50 patients, while a drug for heart diseases could require patients in the thousands.

TIM HOCTOR
VP, Life Science Solutions Services
Elsevier R&D Solutions

Until recently, finding new indications for existing drugs was a haphazard, often serendipitous process — an unintended consequence of a drug would emerge, and ultimately lead to a new indication. This is no longer the case, with increasing amounts of data and new technology available to drug researchers. With the right tools, R&D professionals have the ability to rapidly mine data from the literature, regulatory documents, clinical trial data, electronic health records and other patient-centric information to help identify repurposing candidates. This will mean that identifying a targeted therapeutic for a rare disease can be done with a higher degree of success from a smaller initial candidate set.



The end of the blockbuster drug era made way for R&D to shift spend and innovation toward boutique conditions and niche drugs based on personalized medicine.

JOAN BACHENHEIMER
BBK Worldwide

thanks to social media — on legislative support for rare disease research where few to no treatment options exist," Ms. Bachenheimer says.

In getting rare disease drugs into the hands of those who need them most, companies face additional challenges, Dr. Bramley says.

"To launch an orphan drug, a manufacturer must overcome unique commercialization challenges, while navigating critical product access scenarios that exist most acutely for small patient populations," he says. "Orphan drugs require a unique value story, bolstered by real-world evidence of a successful patient journey."

The Future is Bright

PhRMA noted in its recently released Medicines in Development for Rare Diseases that the biopharmaceutical industry is currently developing more than 560 medicines for patient with rare diseases. Of those 560 medicines, 151 are for rare cancers and 82 are for rare blood cancers; 468 are for generic disorders, including cystic fibrosis and spinal muscular atrophy; 38 for neurological disorders, including ALS and seizures; 31 for infectious diseases, including rare bacterial infections and hepatitis; and 25 for autoimmune diseases, including systemic sclerosis and juvenile arthritis.

Ms. Bachenheimer believes the focus on rare disease has not yet peaked and the current trends are far from reaching a saturation point.

"It's a promising time, but we must work better and faster and more collaboratively — for the industry, the science, and patients," Ms. Bachenheimer concludes.

Other contributing factors to the increased attention being paid to the rare disease market are more vocal patient advocacy groups, such as Global Genes and NORD (the National Organization for Rare Disease) as well as the specific rare disease groups, better education, and social media, which is connecting patients and caregivers.

Mr. Boland believes the trend of more products being designated with orphan drug status will continue.

"The mapping of the human genome has led to a greater understanding of diseases and

This is a thrilling time to be in rare disease research, and it is very exciting to see science, technology, and regulatory dynamisms come together to help more patients in the underserved rare disease community.

JOHN BOLAND
Atlantic Research Group

RARE in the SQUARE
GLOBAL GENES

Rare in the Square

Global Genes, a global advocacy organization for rare disease, is hosting Rare in the Square, an event for rare disease innovators, investors, and patients January 9-11, 2017, in San Francisco's Union Square to network. Rare in the Square coincides with the annual JP Morgan Healthcare Conference, Biotech Showcase, and other meetings, which draw more than 10,000 high-level participants.

"Rare disease has become an important area of investment in healthcare, with an annual growth rate nearly double the general drug market, some important treatments reaching the market just last year, and even more progress anticipated in 2017," says Nicole Boice, CEO and founder of Global Genes. "We are bringing rare disease companies, investors, and patient communities together to celebrate advances, and to foster new connections that will be the basis for future innovations for the thousands of other rare diseases in need of treatments."

To learn more about Rare in the Square and how to get involved, visit GlobalGenes.org/rareinthesquare.

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provides researchers with data to develop targeted therapies for rare diseases," he says. "We will continue to learn from this breakthrough and develop more treatment options."

PRA Health's Mr. Schliebner is optimistic that the momentum and progress in the rare disease market will continue.

"We're moving toward an era of personalized and precision medicine that I think will drive innovation across R&D efforts in other therapeutic areas and in more prevalent traditional diseases," he says. "Our current R&D process is quite archaic and unsustainable; we need to look at big shifts to move the needle and make drug development faster and less expensive. I believe we will see the innovations from the rare disease market begin to influence other markets for the better."

For many, including Dr. Dunphy, the future of the rare disease market is active and exciting.

"The fact that the majority of known rare diseases have an identifiable genetic underpinning means they are candidates for a potential gene-based therapy," she explains. "Indeed, with our increasing understanding of the human genome, technologies that are based on manipulation of genetic material are becoming a reality. Gene therapy, antisense RNA, and others already exist on the market for rare diseases, and other interesting approaches such as RNAi therapeutics and CRISPR hold a lot of promise. Immunotherapy has taken the oncology world by storm, including rare tumors, and that is unlikely to let up anytime soon. Additionally, what's new in rare disease is oftentimes an old treatment previously used for another condition. Thus, the more we know about the mechanism of disease, we'll also be able to continue cross-purposing existing therapies more and more. There are hundreds of therapies in clinical development for rare diseases already. I suspect that will only grow in light of the demand and as drug developers continue to identify and validate new technologies."

Excited by the promise of the R&D pipeline for rare disease patients and their families, Mr. Kokolus says however, realization of this promise will depend squarely on the energy, ideas, and people involved in the discovery process.

"I think the funding is there and the excitement is very real with R&D entrepreneurial leaders bootstrapping creative solutions," he notes. "I expect this community to continue pioneering the use of a mashup of transformative technologies across genomics, disease modeling, diagnostics, trial design, advanced data analytics, machine learning, healthcare IoT, and more to drive R&D innovation.

"Most importantly there is growing collaborative intrapreneurship," Mr. Kokolus continues. "Our future success in rare diseases will come down to how well we can come together in the spirit of open innovation as a true community of academics, rare disease companies, patient groups, and physicians to effectively collaborate on transformational R&D approaches." PV

2015: Banner Year for Rare Disease

47% of new drug approvals were for rare diseases

8 first-in-class treatments, representing entirely new ways for treating disease

5 new medicines for pediatric patients

11 new cancer therapies

New treatments for cystic fibrosis, difficult-to-treat high cholesterol, and several enzyme deficiency disorders

Source: PhRMA

The rare disease market is somewhat of an 'innovation lab' right now, showing how creative collaborations and new approaches can bring therapies to patients faster.

SCOTT SCHLIEBNER
PRA Health

Missed Opportunity

In December, Congress passed the 21st Century Cures Act, with the exclusion of the Orphan Products Extensions (Open Act: HR971/S 1421) from the new bill. The ultimate impact this will have on future development of drugs for rare disease indications is still unclear, but Rafal Kokolus, senior engagement manager, inVentiv Health Consulting, says excluding Open Act eliminates an industry-funded pathway that had potential to increase therapeutic options and lower costs by enabling repurposing of existing drugs, while increasing funding for rare disease R&D centers that would create new U.S.-based jobs and advance knowledge of rare diseases and associated treatment pathways.

"This is a disappointing development with negative consequences," he says. "Rare disease sufferers and their doctors will have fewer choices and will not benefit from the improvements in understanding rare disease pathways, their diagnosis, and management that would have been a natural by-product of the research required to bring existing therapies to market for rare diseases. Society will lose the cost benefits of using existing therapies for rare diseases and the creation of new high value R&D jobs."

Furthermore, he believes the missed opportunity is very real, especially when we look at the positive impact BPCE/PREA, which the Open Act was modeled after, has had on children.

"BPCE/PREA reduced harm and improved care; reducing use of drugs without established pediatric safety and efficacy by nearly 40%, contributing to improvements in survival of serious childhood disorders," he says.

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