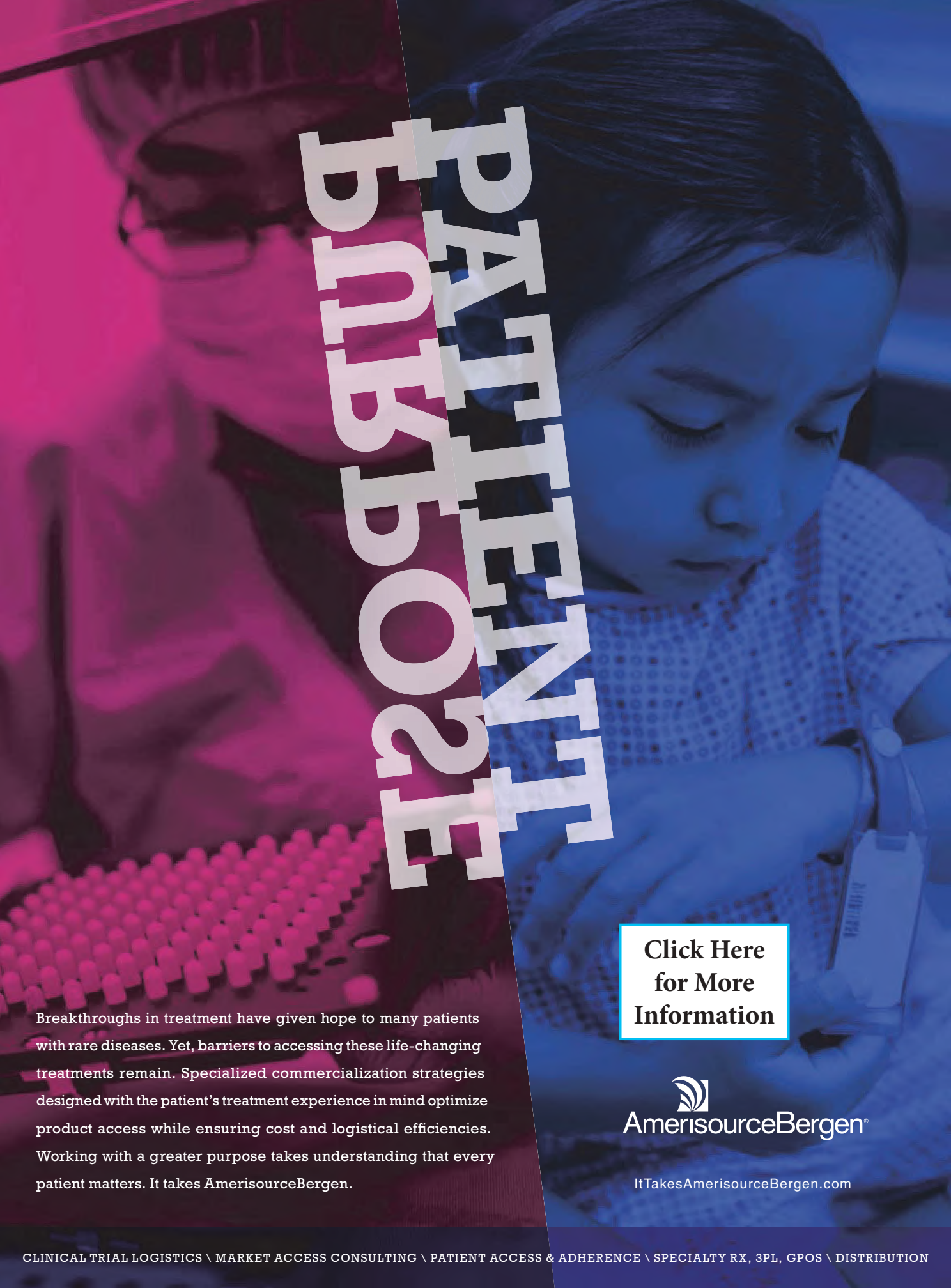
EBOOK FROM THE EDITORS OF

Pharmaceutical Executive

Bright Skies, Big Challenges:

ORPHAN DRUGS AND RARE DISEASES

UBM



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ORPHAN DRUGS ARE RARE DISEASES

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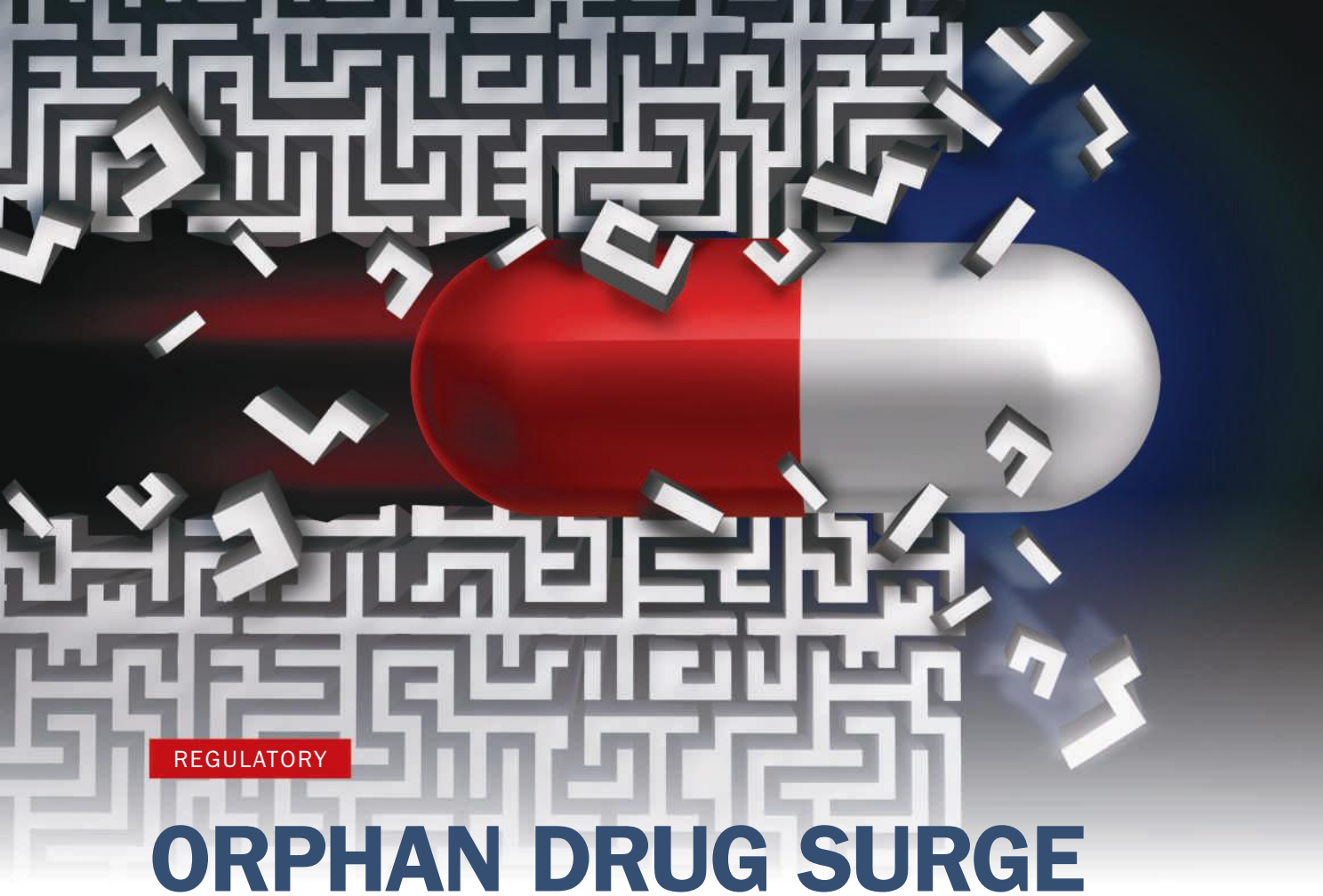

REGULATORY

ORPHAN DRUG SURGE RAISES REGULATORY & DEVELOPMENT STAKES

BY JILL WECHSLER

Treatments for rare conditions account for a large and growing proportion of new drugs and biotech therapies in the US, encouraged by FDA regulatory policies for developing, approving, and marketing promising therapies. Over 40% of new molecular entities in 2015 and 2016 were orphans, a level reflecting the success of the orphan drug designation program and expedited review pathways for breakthroughs and other innovative medicines.

Yet, high prices on important new therapies and complaints about drugmakers exploiting loopholes in the Orphan Drug Act have led to push-back from policymakers and payers. A firestorm erupted following FDA's controversial approval in September 2016 of Sarepta's Exondys 51 for Duchenne muscular dystrophy (DMD), despite limited evidence of efficacy and a $300,000-a-year price tag for initial treatment. More recently, Biogen set a launch price of $750,000 for first-year treatment with its drug Spinraza for spinal muscular atrophy. And Marathon Pharmaceuticals raised eyebrows when it launched Emflaza for DMD at $89,000 a year, even though the drug was already available at low cost in Europe and the sponsor had to conduct only one fairly small study for US approval.

An analysis by Kaiser Health News cited biopharma companies for manipulating the rules to gain added exclusivity for drugs with mass market sales able to document an orphan indication. Congress is investigating whether sponsors develop some orphans with an eye to expanding use to much broader indications, or "evergreening" exclusivity. Leading senators want the Government Accountability Office (GAO) to examine whether the program is working as intended, while others back legislation that codifies such exclusivity extensions.

Meanwhile, orphan drugs will account for more than 21% of worldwide brand-name prescription drug sales in 2022, up from 6% in 2000, according to an analysis by EvaluatePharma. Sales reached $114 billion last year, but will grow to $209 billion in five years, as FDA's Office of Orphan Products Development processed nearly 600 designation requests in 2016 and granted more than half. Such promise has attracted pharma companies to the field, replacing small biotech firms that initially focused on developing these targeted therapies. And contract research organizations (CROs) are looking to tap the rare disease development business. In February, PPD formed a new center to oversee development programs for orphans and pediatric therapies.

President Trump highlighted the importance of "miracle" rare disease treatments in his address to Congress in February. Trump stated that the discovery of orphan drugs, as for Pompe disease, required significant reform of FDA's "slow and burdensome approval process….so more lives can be saved." The National Organization for Rare Disorders (NORD) fired back that FDA is doing a terrific job of speeding rare disease treatments through the approval process and of supporting flexible R&D approaches in evaluating those therapies.

Flexible studies

In fact, more than three-fourths of orphan drugs developed between 2008-2015 benefitted from "flexible development approaches," which consist of less than two well-controlled studies or novel endpoints, explained Richard Moscicki, deputy director for science operations at the Center for Drug Evaluation and Research (CDER), in a February address to the World Symposium on Science. He noted that it takes three years less to develop a drug with a breakthrough designation.

At the same time, Moscicki and others emphasize that randomized clinical trials often provide valuable evidence for developing rare disease drugs. At NORD's summit last October, Moscicki advised sponsors that including well-controlled studies in protocols can provide FDA with "good scientific information to make good regulatory decisions." Rigorous collection of natural history data can help researchers understand the disease, and qualification of important assays and biomarkers prior to use can support efficient development and avoid the waste of clinical specimens.

More collaboration on orphan drug designations and clinical trial design by FDA and the European Medicines Agency (EMA) also promises to streamline rare disease research and approvals. The regulators have formed a formal "cluster" for sharing information on orphan drug designation, exclusivity and regulatory flexibility. What is really needed to expedite orphan drug development, said NORD, is adequate FDA funding to expand rare disease office staff expertise.

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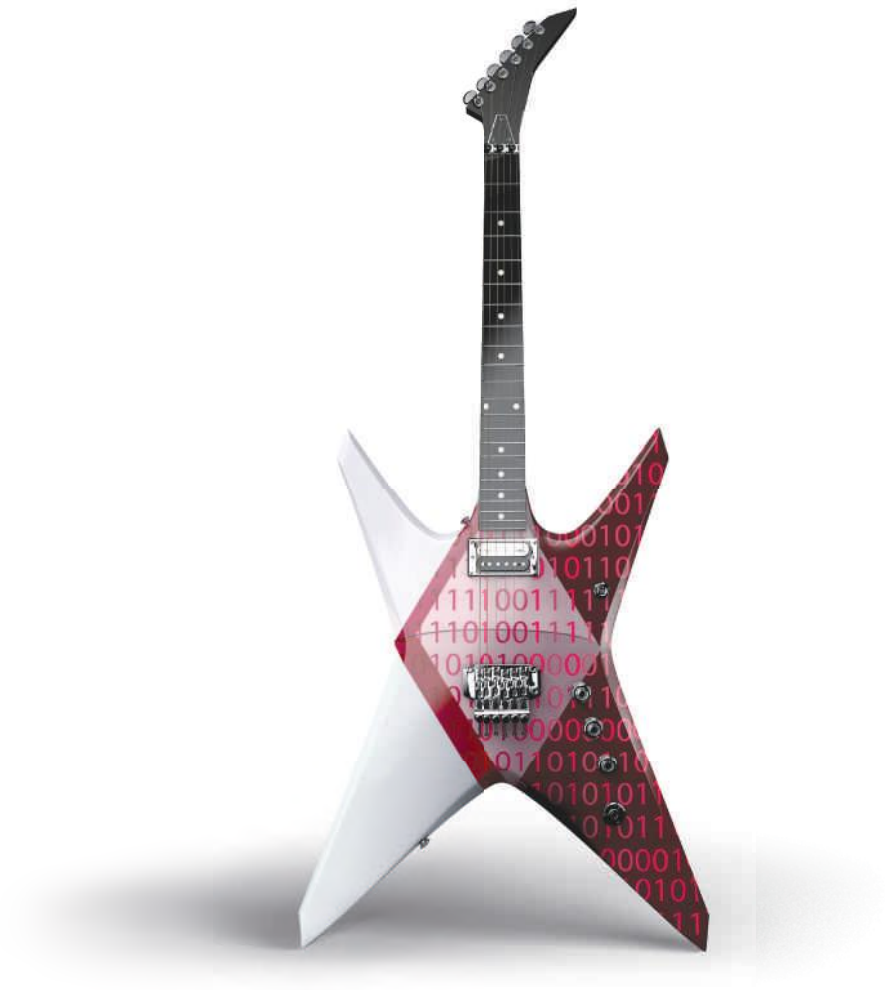

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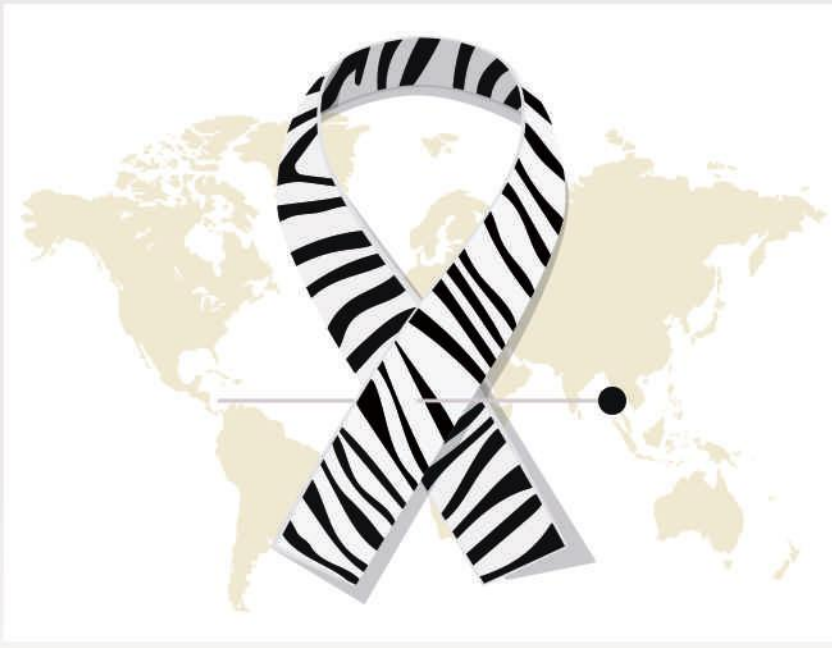

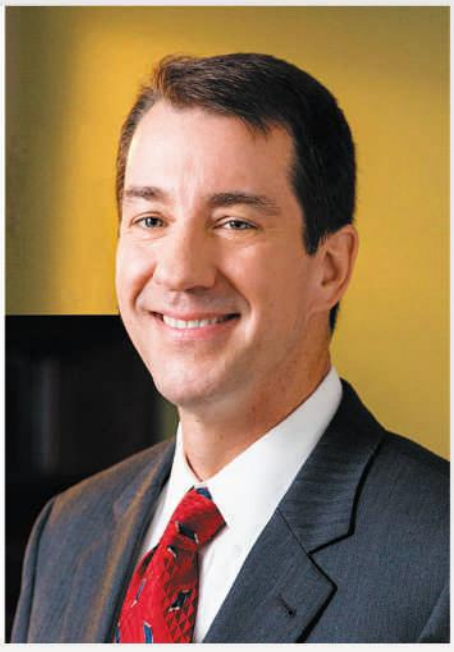

Christopher Austin, MD, chair of the IRDiRC Consortium Assembly

R&D

Advancing Rare Disease Research:

A MISSION UPDATE

BY JULIAN UPTON

The International Rare Diseases Research Consortium (IRDiRC) was launched in 2011 to facilitate cooperation and collaboration on a global scale among the many stakeholders active in rare diseases research, and to maximize the output of rare diseases R&D efforts around the world. *Pharm Exec* spoke to Dr. Christopher Austin, chair of the IRDiRC Consortium Assembly—who also serves as director of the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH)—about what IRDiRC is doing to realize its ambitious goals: to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by 2020.

PE: ***Can you outline the work IRDiRC is doing in order to realize its goals?***
AUSTIN: To guide its work, IRDiRC developed a set of policies and guidelines, which are the principles that IRDiRC members agree to follow, focused on the following areas: data sharing and standards, ontologies, diagnostics, biomarkers, patient registries, biobanks, natural history, therapeutics, models, publication and intellectual property, and communications about the Consortium. Coordination of efforts that address common roadblocks is key to maximizing the collective impact of global investments in rare diseases research and accelerating progress. To that end, barriers and gaps in rare diseases research were identified, and task forces were set

up to address some of these gaps through policy recommendation and/or technical solutions; the work has been guided by three scientific committees—diagnostics, interdisciplinary, and therapies—and three constituent committees—funders, companies, and patient advocacy—which also play important advisory role on the Consortium Assembly.

> "BARRIERS AND GAPS IN RARE DISEASES RESEARCH WERE IDENTIFIED, AND TASK FORCES WERE SET UP TO ADDRESS SOME OF THESE GAPS THROUGH POLICY RECOMMENDATION AND TECHNICAL SOLUTIONS"

PE: ***As we move closer to 2020, are the IRDiRC's two main objectives, to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by that time, still realistic?***
AUSTIN: Last year, the goal to deliver 200 new therapies was achieved, four years earlier than expected. The goal to deliver the means to diagnose most rare diseases has made significant strides, with over 3,600 tests available for the diagnosis of rare genetic diseases, compared to 2,200 in 2010. Overall, it is estimated that diagnostic possibilities increased from 10% to 30-50% in the last five years. Efforts are ongoing to deliver more diagnostic tests. In light of these successes, IRDiRC is currently setting new goals for the next decade that are expected to be even more ambitious, and will contribute to further diagnostic and therapeutic progress.

PE: ***What kind of success has IRDiRC had since its establishment six years ago?***
AUSTIN: IRDiRC has brought forth awareness to the importance of principles laid out in its policies and guidelines, and promotes the adherence of these principles in research projects funded by its members. The Therapies Scientific Committee further developed recommendations to guide policies and funding strategies so as to reach its goal of 200 new therapies by 2020, based on the IRDiRC Polices and Guidelines.

IRDiRC task forces have produced guidelines and recommendations for policy change in specific areas, including the guidelines for data mining and repurposing, patient-centered outcome measures, and small population clinical trials. IRDiRC also worked on developing standards for interoperability among databases for human phenotypes.

In collaboration with the Global Alliance for Genomics and Health, three task forces were set up, working on rare diseases gene discovery through a federated network of genotype and rare phenotype databases called Matchmaker Exchange, tackling the barrier of data sharing through interpretation of consent and condition of data use through Automatable Discovery and Access Matrix, and setting out the development of ethical, legal, and technical requirements of privacy-preserving participant identifiers in rare diseases research.

Additional task forces are due to commence shortly to address approaches for investigating unsolved diagnostic cases in non-coding genomic regions, bottlenecks and barriers to clinical data sharing, and best practices for patient engagement in rare disease research.

UK Orphan Drug Access Needs Boost

Equity and Access: Making the UK a Rare Disease Leader, a report commissioned and funded by Irish-headquartered Shire, brought together a steering group of experts from medical communities, patient advocacy, policymakers and healthcare to review a data analysis by OHE (Office of Health Economics) Consulting of access to orphan medicines across the UK, France Italy, Germany and Spain (EU5).

The data showed that, of the EU5 countries, Germany and France routinely provide both the quickest and the broadest access to orphan medicinal products (OMPs). The time taken for an OMP to receive funding in the English health system is "considerably slower" than in comparable countries. The average time to treatment being funded in England is 27.6 months—4.6 months slower than Spain, five months slower than Scotland, 6.6 months slower than France, 8.6 months slower than Italy, and over two years slower than Germany. Of the 143 medicines for rare diseases that were approved by the European Medicines Agency (EMA) in the last 15 years, 120 have a decision on use in England but only 68 are routinely funded, compared to 116 in France and 133 in Germany.

While the 2012 UK Strategy for Rare Diseases set out to "ensure no one gets left behind just because they have a rare disease," the Shire report highlights that the English health system "does not have a dedicated pathway to evaluate orphan medicines." To help achieve the UK government's commitment to investing in science, research and innovation, the steering group's recommendations include the following:

- An annual inter-governmental summit or steering group to drive forward the aspirations of the UK Rare Disease Strategy.
- A new national director for rare diseases to drive improvements and provide leadership to the rare disease community.
- Greater flexibility in accounting for investment in innovation.
- Adaptive and efficient processes to optimize the use of real-world data collected before and after an OMP value assessment.
- Collaboration between the National Institute for Health and Care Excellence (NICE), NHS England, the Department of Health, patient groups and industry to establish a fair process of appraisal for orphan medicines.

As the UK prepares to leave the European Union, the Shire report adds that the steering group recommendations "are particularly timely."

IRDiRC also created a quality label, "IRDiRC Recognized Resources," to highlight standards, guidelines, tools and platforms which, if more broadly used, would contribute toward IRDiRC goals—and encourage the research community to adopt interoperable data standards while promoting data sharing.

PE: ***Have you seen any advance in combating the lengthy diagnosis time associated with rare diseases?***

AUSTIN: According to patient surveys conducted in Western Australia, Canada, and Europe, the average time of diagnosis for a rare disease is five to six years. It is thought that this time will be decreased to two to three years if a patient has access to new diagnostics methods such as next-generation sequencing, but this has yet to be confirmed by systematic surveys. IRDiRC is planning to collect data on this, as decreasing diagnosis time for rare diseases is integral to progress and the aim is to enable all patients living with a rare disease to receive diagnosis within one year of coming to medical attention.

PE: ***Can you outline what involvement IRDiRC has with the pharma/biotech community and how you work together?***

AUSTIN: A dozen or so companies that meet membership criteria—investment of at least 10 million US dollars over five years on rare diseases research—are IRDiRC members, and participate in the Companies Constituent Committee to identify common roadblocks to efficient execution of research in the industry space that IRDiRC should address.

They also nominate experts to task forces who share their experience and knowledge, and, unsurprisingly, in the spirit of collaborative work, some members have also teamed up in their research and development efforts.

PE: ***We recently had Rare Disease Day. How has the evolution of this event advanced the thinking around issues of rare disease?***

AUSTIN: Worldwide Rare Disease Day events have helped create more awareness of and support for research collaborations that are bringing hope to patients. For more information, contact Rare Diseases Europe-EURORDIS, the US National Organization of Rare Diseases (NORD), and the US National Institutes of Health, National Center for Advancing Translational Sciences.

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Accelerating Rare Disease & Orphan Drug Development

Opportunities for Biomarkers, Diagnostics, & Patient Engagement

Leone Atkinson
MD, PhD

Rare diseases affect more than 350 million people worldwide, but patients often face limited options for approved therapies. As a result, many patients have joined advocacy groups first and foremost to connect with others struggling with their rare disease, but also to promote research, unite multiple stakeholders and stimulate new possibilities in the therapeutic pipeline. Research and orphan drug development efforts are starting to follow suit by increasingly incorporating patients' needs and examining potential outcomes.

Addressing clinical challenges in rare disease and orphan drug development

With government-driven financial incentives, advances in genomic technology to identify promising targets for drug development, increasingly organized patient communities, and above average regulatory approval rates, drug developers are motivated to address rare diseases. While these trends are promising for patients with urgent unmet medical needs, orphan drug development still faces many challenges. The very nature of rare disease places pressure on identifying and accessing a sufficient number of patients for clinical trials.

Given that 80% of rare diseases are genetically defined, patient registries and databases with genetic information can help ease the burden of patient recruitment. Patient advocacy groups further expand the source of potential participants with strong interest in advancing rare disease studies.

Patient-centric approaches

Beyond recruitment and participation in clinical trials, patients can be recognized in a therapy's entire lifecycle through a process called patient-centered outcomes research. Ideally, this process holistically examines a wide variety of patients' needs to facilitate better communication between caregivers and patients and drive more informed healthcare decision making.

This focus on patients' perspectives is not new, but it has been rapidly expanding and gaining more attention. Patients are becoming more engaged in taking an active role in their healthcare and the pharmaceutical industry is already moving toward more targeted, personalized healthcare.

In the rare disease space, this patient-centric approach also resonates with development efforts by obtaining as much data from a patient as possible, given the scarcity of subjects within sparse populations.

Building greater inclusion

As the voice of the patients and their involvement grows, the pharmaceutical industry must determine how to best incorporate appropriate interactions with patients and advocacy groups to facilitate open communication, in an inclusive manner, across all participating countries and regions.

One key to effective communication is striking a balance between the potential benefits and risks of the treatment while not overpromising or creating the impression of a breakthrough, miracle drug in advance of clinical evidence—a very real issue when addressing rare diseases.

Organizations like the Center for Information and Study on Clinical Research Participation (CISCRP) and Patient-Centered Outcomes Research Institute (PCORI) are actively studying these critical issues to improve knowledge about clinical research and integrate patient and stakeholder perspectives into the overall process.

Contract research organizations (CROs) also play a valuable role as an unbiased third-party intermediary by working between patients and sponsors and delivering informative and accurate communications about a treatment's potential in a clinical trial.

Supporting translational science

Patient engagement can also be incorporated into diagnostics research, especially during early stage development. Sample acquisition is key to identifying the genetic basis of a disease and potential biomarkers to measure target engagement and potential treatment effects. It also offers an opportunity to identify potential biomarkers that can be used to enhance early translational science and better inform clinical trial design and implementation.

As genomic technologies continue to mature and offer more powerful, faster identification of genetic aberrations, our industry's ability to leverage these targets will also improve. With LabCorp, Covance has already established well-known clinical diagnostics but is exploring the possibilities beyond clinical trials to enhance translational research. Building a solution won't happen overnight, but it will involve refining and enhancing biomarker and diagnostic capabilities so they better align with patient-centric approaches and make a difference for people in need.

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Rare Diseases:

MEETING THE UNIQUE CHALLENGES OF ORPHAN DRUG DEVELOPMENT

BY MICHAEL F. MURPHY, MD, PhD

While individually rare, orphan diseases are actually collectively common, with an estimated 350 million sufferers worldwide. Since the introduction of the US Orphan Drug Act more than 30 years ago, the number of orphan designations has skyrocketed and experts are predicting worldwide sales of these drugs will reach $176 billion by the end of 2020.[1] With the cost of developing orphan drugs comparatively less than non-orphan products, appreciable regulatory support for innovative program design, and with the possibility of demonstrating significant intellectual property value, interest and investment in orphan disease development programs has been explosive.

Creating a pharmaceutical development program for the treatment of a rare disease can, however, prove to be a monumental task. Poor understanding of the natural history of the proposed indication due to few observational studies studying disease progression, heterogeneous patient populations with variable phenotypes and clinical courses, geographic dispersion of patients and investigators, regulatory uncertainties, and lack of prior clinical studies to establish a template

for study execution, can all prove challenging. In addition, small patient populations isolated in a few tertiary care centers go against traditional methods of study operation. With at least 7,000 rare diseases, each exhibiting diverse symptomatology, the key differentiator for CRO engagement frequently is expertise in problem-solving, and passion for clinical development rather than disease-specific experience.

The importance of the patient

In an orphan drug trial, clinical management of individual patients can be difficult. Understanding the burden of disease and managing patient and family experience within a study is key. Patients with a rare disease frequently arrive at a diagnosis through a lengthy process of evaluations and may be experiencing a reduced quality of life and, in some cases, limited life expectancy. In rare disease trials, the need to recruit and retain patients while adhering to exceptional standards of care influences every decision. The protocol must account for the vulnerability of the patient population and address ethical considerations, particularly if the study design mandates discontinuation of ongoing therapy considered essential for patient support. Eligibility criteria always influence the number of available subjects, and if artificially constrained, reduce the likelihood of establishing a clinical trials database from which evidence of efficacy and safety can be extrapolated to a larger network of representative patients with the same disorder.

It is well-documented that rare diseases exert a substantial physical, emotional, and financial impact on patients and loved ones. Many rare diseases are fatal in infancy or childhood and children who do survive to adulthood face difficulties transitioning from pediatric to adolescent to adult care, and frequently the clinical presentation will evolve. Furthermore, treatment often involves multiple specialties such as neurology, gastroenterology, psychiatry, endocrinology, cardiology and physical therapy because clinically important comorbidities are common. Assuring care coordination in the context of an interventional study is important. CRO partners will be able to assist sponsors in considering all these factors when creating the study plan, obtaining input from key opinion leaders (KOLs) on diagnostics, outcome measures and care processes that can help inform trial design and study metrics.

Despite these challenging circumstances, patients with rare diseases and their caregivers are typically well-informed about their condition. Thanks to the wealth of information available via the Internet and social media platforms, they have easy access to information regarding disease management and treatment options. They are also more engaged with not only their healthcare providers, but also with other patients with similar conditions, and use social media extensively as an exchange platform for emerging basic and clinical research data.

In order to enhance the clinical trial process for participants, as well as improve study outcomes, sponsors frequently utilize the experiences and knowledge of patients and caregivers in the process of trial design. By doing this, drug developers can gain valuable insight into experiences associated with a specific condition—after all, first-hand knowledge of what it is like to progress through site visits and procedures while managing an illness is not something that can come readily, or exclusively, from a professional point of view. This crucial input can

then be used to develop "patient-centric" trials that make participation as easy and informative as possible for the patient, while increasing efficiency and enhancing the sensitivity of study outcomes.

Unique challenges

There are some fundamental differences between conducting trials for non-orphan drugs and those for orphan drugs, which present unique opportunities.

First, finding and activating feasible study sites and qualified investigators can be difficult. Selection involves identifying countries with a sufficient number of suitable study participants, then determining whether these patients are accessible, and, finally, identifying centers of excellence with the therapeutic and operational capabilities to execute an observational or interventional trial requested. The nature of the indication emphasizes the importance of the medical, cultural and regulatory context as well as the standard of care and treatment pathways within each country of interest.

Smaller patient groups and, occasionally, a decreased likelihood of identifying and engaging patient advocacy groups, means identifying and locating participants can be extremely challenging, while retaining them for the full study duration is key, particularly when modification in longer-term outcomes influence approval. If there is no patient advocacy group, general registries such as the Global Rare Disease Patient Registry and Data Repository[a], entities such as the National Organization for Rare Disorders (NORD) and the European Organisation for Rare Diseases (EURORDIS); as well as resources such as Orphanet[b]—are invaluable as a first step in an algorithm leading to site identification and selection.

Once sites are selected, site-by-site recruitment, retention analysis and planning and specialized outreach, must be undertaken. When studying an orphan disease, every single patient's participation is vitally important given limitations in patient availability, and the exceptional impact the data from a limited number of patients may have on program development. Engaging sites, investigators, and patients to confirm acceptance of the study design is vital. Proactively engaging all stakeholders can foster a collaborative approach that facilitates recruitment, retention, and commercial value long-term.

To ensure high levels of participant retention, sponsors must make the patient experience as smooth as possible and, where practical, reduce the burden on the patient and caregiver regarding both visit frequency, and visit intensity (the number and complexity of assessments at a site). For example, in-home nurse visits cognizant of the need for good clinical practice (GCP) compliance could be offered when patient mobility is a problem, and financial and logistical assistance should be provided to aid any travel and lodging requirements.

Pediatric research

Approximately 50% of patients with rare diseases are children. Understandably, patient recruitment, retention, and management can present more challenges with a younger demographic. Participants' physical, intellectual, and emotional growth, developing attitudes and beliefs, as well as family dynamics, all have an influence on their participation. It is key to strike a

careful balance between reducing risk and discomfort, and obtaining meaningful data. To support engagement and compliance, sponsors frequently consider age-appropriate communication, particularly during the assent and/or consent process, and ensure that disruptions to family life and school activities are minimized.

Additionally, a pediatric rare disease study might only enroll one to three patients per year, per site and, therefore, creative and proactive site management planning is vital for those professionals and other support staff who will have responsibility for patient management. Mutually beneficial relationships include the establishment of a proactive publication strategy, opportunities for investigator sponsored investigations embedded into an overall program of clinical research, and assistance in the creation of physician and patient educational programs that would facilitate product adoption following approval.

An evolving regulatory climate

Although orphan drugs typically follow the same regulatory approval path as non-orphan products, securing approval for the trial designs often required in rare-disease studies can provide an exciting opportunity for innovation. The introduction of the Orphan Drug Act of 1982 has provided considerable impetus and, subsequently, there has been a significant rise in the number of orphan drugs being successfully brought to market, using a mosaic of different program designs.[3] In fact, before the Act's introduction there were just 38 approved orphan drugs, compared with more than 460 today.[2] Acknowledging its success, Japan and the European Union have since mirrored the US' incentives and introduced comparable legislation, which offers tax credits, user fee waivers, and marketing exclusivity, to those developing drugs to treat rare diseases.

In August 2015, the FDA released an updated draft guidance which is intended to offer sponsors further support when tackling the common issues encountered in the development of orphan drugs.[4] While the issues addressed are also present in non-orphan drug development, the FDA highlights that many of the challenges are accentuated given the rarity of the disease and the gravity of the unmet clinical need, and therefore require special attention.

Interestingly, the guidance highlights the need for sponsors to gain greater biological, clinical, and epidemiological knowledge about the specific rare diseases under investigation, and suggests conducting natural history studies, through various forms of observational research in a companion development program. By conducting these studies—which look at the progression of a disease from initial symptoms, formal diagnosis, through various clinical endpoints, the FDA suggests that companies will be able to design more efficient drug development programs. Additionally, as these studies also provide information regarding healthcare utilization in representative patients under standard of care settings, the data influence decisions for formulary placement and levels of reimbursements.

For sponsors, working with scientific and regulatory professionals who have experience interacting with authorities can offer significant benefits to advancing programs. For example, because of the breadth and depth of experience in other orphan indications, they can offer support in mitigating limitations that may be present in non-clinical data, provide a rationale for the use of

non-validated biomarkers that nevertheless are "fit for purpose" in early phase investigations, as well as recommend innovative trial designs for proof of principle studies.

Final thought

All challenges considered, current market trends and industry predictions would suggest an increasing emphasis in considering unique genotypic and phenotypic information within a variety of larger indications under an umbrella of 'personalized medicine'. An interest in developing either repurposed or novel products for orphan indications represents a natural extension of this activity. As a result, the number of drugs that are successfully brought to market for a variety of orphan indications is likely to rise. However, securing regulatory approval for the trial designs required in this area requires an exploration of innovation in study design, appreciation of evolving regulatory guidance, and incorporation of patient and family perspectives into the scope and detail of the drug development process. Additionally, successful commercialization efforts are predicated on demonstration of value during the course of clinical development, requiring different types of trials capable of evaluating changes in overall healthcare utilization following the introduction of innovative therapy; i.e., an effort which evaluates the impact of novel therapy on a 'system of care' in order to enable patient access. Given the unique technology represented by these products, educational programs for physicians and patients enhance informed adoption.

By working with strategic partners who have the expertise and experience in designing and delivering these trials, and the passion to address unmet clinical needs, sponsors can implement effective patient-centric trials which will meet the special demands of this underserved clinical population.

Michael F. Murphy, MD, PhD, is Chief Medical and Scientific Officer at Worldwide Clinical Trials.

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Registries & Organizations

[a]Launched in 2012 by US National Institutes of Health Office of Rare Diseases Research.
[b]Orphanet, led by a consortium of 40 countries, is a reference portal for information on rare diseases and orphan drugs, for all audiences.

Understanding Channel Strategy Misconception

By
Donna Gilbert,
Vice President Specialty and Branded Strategic Accounts, Global Sourcing and Manufacturer Relations, AmerisourceBergen

As pharmaceutical companies continue to launch new specialty products, the right channel strategy can mean the difference between a successful launch and not meeting forecast. But, common misconceptions about channel strategy can mislead even the most experienced manufacturers, resulting in reduced patient access and sub-optimal product performance. By understanding these misconceptions, manufacturers can ensure their products are reaching the right patients at the right times in the right sites of care.

For example, manufacturers of first-to-market products (or those with modified approaches to the market) may be tempted to disrupt the supply chain with distribution strategies that force providers away from their regular workflows to access these products. And while this approach may have providers and patients making an extra effort to access the product in the short term, it doesn't account for second or third market entrants with channel strategies that offer a superior customer experience. But even in the short term, clinical innovation alone does not necessarily ensure a product's success. One hospital customer had access to an innovative, new specialty product throughout clinical trials. Yet once the product launched commercially, the hospital's specialty pharmacy could no longer access the product because the manufacturer decided to create a restricted specialty pharmacy network. Such models, while often intended to protect the patient experience and gather data and insights, can make practical care delivery more complicated and compromise product performance.

Another common misconception that can hinder product performance is viewing the distributor as just a middleman and failing to recognize the full value of the distributor's role in the providers' customer experience. For example, health systems often order multiple products from a small set of sources per day. A few thousand transactions per day through distributors could fragment into millions of transactions between physician clinics and manufacturers. The transaction flow becomes even more complex when other customers – hospitals, retail, mail order, specialty pharmacies – are considered. In a direct model, the staffing and infrastructure requirements to order thousands of pharmaceutical products directly from multiple manufacturers would burden both the manufacturer and the health system in innumerable ways. Direct models are absent of the partnerships that can help manufacturers weigh the real-world impact of their decisions. It's the unseen services within the distributor's infrastructure, such as financial management, supply chain security, customer experience and more, that add value to manufacturer/distributor partnerships.

It is essential that a manufacturer evaluate their product's distribution and channel strategy against the needs of their product's attributes, their providers' preferences, and the unique needs of their patient population. Evaluating channel strategy through the lens of patient access and product success requires insight from a vested party who can positively impact commercialization curves. The bench strength and broad reach of a distributor lends itself to a deep understanding of all customers; resulting in insight that can guide channel strategy recommendations. By focusing on the patient first, manufacturers and distribution partners will reach their shared goals - bringing products to market and creating a healthier future for patients.

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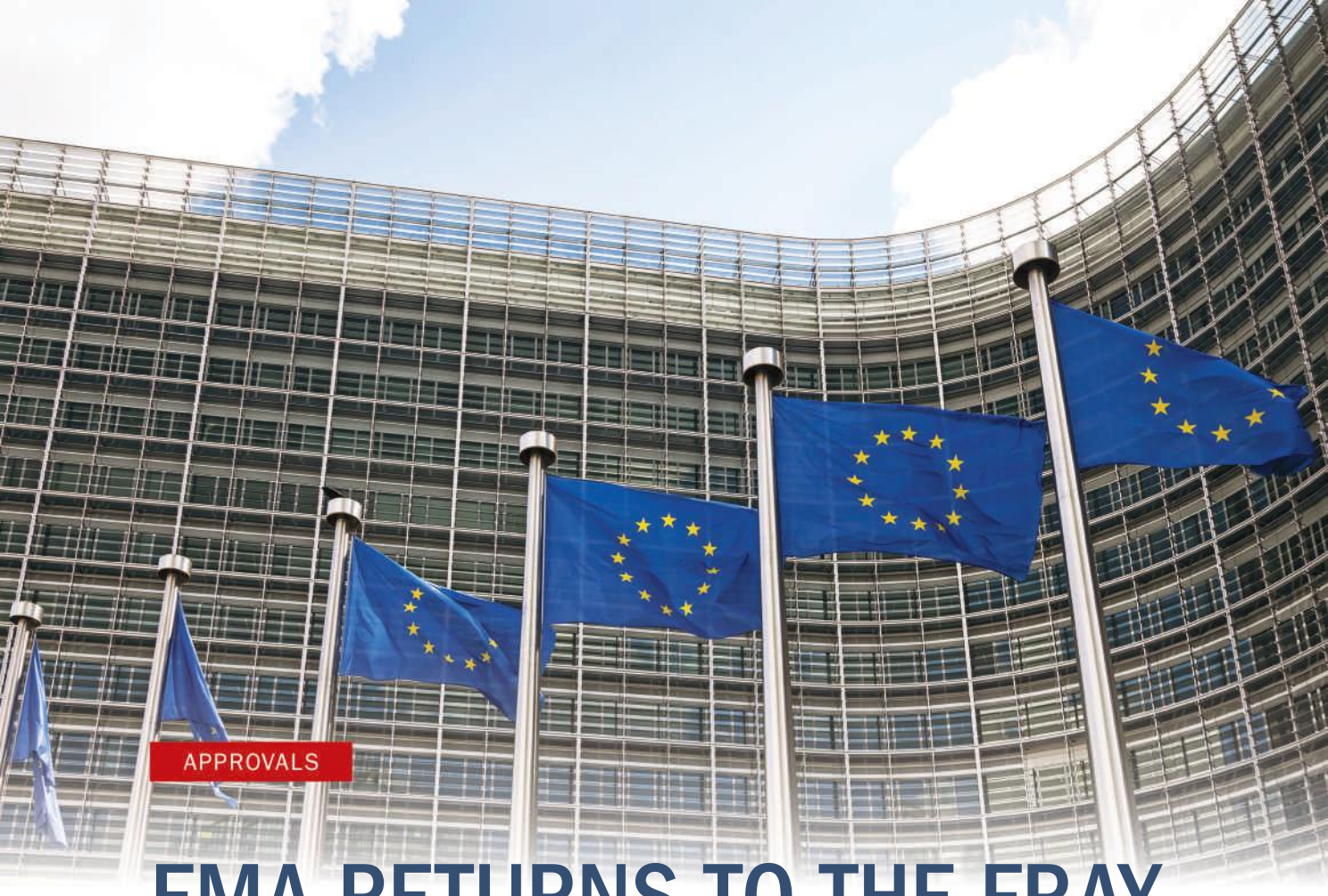

EMA RETURNS TO THE FRAY ON ADAPTIVE PATHWAYS

BY REFLECTOR

Undaunted in its determination to keep open all options on the future of drug approvals, the European Medicines Agency (EMA) pulled out all the stops in a crucial meeting held in early December last year. Not only did it bring many of Europe's leading thinkers on the subject to its London headquarters to reflect more closely on its adaptive pathways program—its plan to bring approval processes into line with 21st century medicine; it even issued participants with a lengthy "guide" to its views, and it asked everyone to absorb it before they turned up, so as—it says—"to support productive discussion."

EMA's careful preparation was based on its apprehensions that the European debate on new approaches to medicines assessment is spinning dangerously out of control. And its apprehensions were well-founded. As soon as the agency's senior officials raised questions five years ago over whether traditional approval procedures were still capable of meeting unmet medical need in a rapidly-evolving scientific environment, skeptical and conservative Europeans began to warn against any risky departure from gold-standard clinical trials. And in 2014, when the agency launched a pilot project to explore possible alternative approaches, the skepticism turned to outright hostility

from some civil society groups, scientific bodies, and national government advisers. So much so that by the time the pilot project came to an end earlier this year, there was a risk that the swelling opposition might kill off any chances of further exploration.

EMA was now looking to shore up the chances of continuing constructive technical discussion. It was aware that its options could soon be limited by widening negative perceptions of its initiative—or even foreclosed by policy decisions from hyper-cautious health ministers. There is a powerful "if it's not broken, don't try to fix it" school of thought that has been gaining sway over the agency's concerns that science is moving faster than regulatory systems are able to keep up with.

So to counter accusations of jeopardizing patient safety and public health budgets, or of mounting a centralized power grab, or of offering drug firms premature market access, the agency spelled out its progress and plans in unprecedented detail. It even presented examples—albeit anonymized—of the products that have been explored in the framework of its pilot, with outlines of the sort of regulatory and scientific questions that officials from the agency and health technology assessment bodies have confronted.

The case that the agency made in its defense was that only new approaches can—and should be allowed to—reduce redundant/additional studies by optimizing the collection and use of clinical data, and cut the time-lag between regulatory approval and patient access. They can also make better use of real world data to boost understanding of how treatments actually perform in the daily clinical setting. And they can make the most of prospectively planned post-authorization activities.

If advantage is not taken of such new opportunities, the agency argued, reimbursement may be delayed, especially for products where current procedures do not provide sufficient information for authorities to make a decision—as in the case, EMA said, of new antimicrobials, Alzheimer's and other degenerative diseases, and rare cancers. In addition, emerging treatment options such as gene therapy will also be compromised, it said.

The workshop tackled the doubters head-on in the most sensitive areas of debate, including how patients and healthcare professionals feel about unmet need, how real world data can be better used, and how health technology assessors and drug budget payers can be more involved. The agency politely noted that "stakeholders' interest has been high," and added with fine ambiguity that feedback from civil society and researchers on the approaches "must be given the appropriate weight." At the same time, its workshop was designed "to explain aspects of the adaptive pathways concept."

One of those aspects the agency seized upon straight away, in a preemptive strike at one area of contention, was the legal framework. There is no question of changing the basic rules, said EMA. The completed pilot has shown, it said, that "the adaptive approach can take place within the existing regulatory tools and processes." Nor was the adaptive pathways approach intended to apply to all products: it focused on unmet needs. In other words, any fears that EMA was subverting current safeguards and opening the door to chaos are groundless.

Reassurance was also offered that the aim was not to create a system that will squeeze out dissenting or critical voices in the assessment process for potentially valuable medicine, the agency argued. On the contrary, it was to "increase the availability of relevant expertise from all stakeholders." But, the agency goes on to remark with striking candour, not everyone's views are

equally valid or relevant or adequate. One of the findings of its piloting of parallel discussions between EMA and HTA bodies on regulatory and scientific issues is that "not all stakeholders currently involved are competent to address these questions."

The preparations for the workshop also displayed EMA's desire to parry some ill-conceived attacks before they were launched. "Speakers at the workshop are encouraged to frame the discussion in light of the practical experience gained during the pilot," it said. In other words, "let's leave out all the idle speculation about what could conceivably go wrong, and stick to the concrete issues." This is why the briefing document presented anonymized cases of products submitted for the pilot where the conduct of randomized trials was difficult.

The agency was also keen to avoid accusations that it would be monopolizing discussion or imposing its view. People attending the meeting were encouraged, "if desired, to suggest potential alternative solutions." Again to paraphrase the agency's meaning: "We are aiming to offer regulatory mechanisms to help promising new medicines reach patients in a timely manner. So don't come here just to bitch about us. If you've got a better answer to the questions we pose, then let's hear it. If you haven't, then shut up and listen and learn."

Opportunities created by a disease-modifying drug for a well documented degenerative disease were missed under current procedures, according to the agency, by way of example. It would have taken a long time—too long—to start assessing whether the treatment could benefit pre-symptomatic patients. By contrast, in an adaptive pathways approach, scenarios could be discussed to define the conditions under which it may be possible to initiate trials earlier, and to design these trials to address the needs of all stakeholders—patients, healthcare professionals, researchers, regulators, and the authorities that pay for healthcare. This approach has the advantage of allowing preliminary discussion of potential scenarios, in advance of any commitment either from the authorities or from the company developing the treatment, and before the full protocols for the chosen pathway are developed.

Above all, the underlying fear in many criticisms of the EMA initiative is that earlier access to innovative medicines may send drug budgets spiralling out of control. EMA carefully sidestepped this issue in its preparatory guide. "Affordability… might be more of an issue for consumer bodies and payers rather than for patients and healthcare professionals," it says, with an assumption of Olympian detachment. EMA knows that prices and access are outside its mandate, so it meticulously avoided queering its own pitch by any ill-judged attempt to offer a solution to issues beyond its competence. But it is well aware that this is an aspect that will have to be resolved—and it made no secret of its expectations that the issue would come up at its workshop. "It may be raised at the workshop discussion by the competent stakeholders," EMA noted, primly. What it did not go on to say, but which was a clear implication of its stance, is that it is high time that "competent stakeholders"—that is, healthcare payers—get involved in these discussions and start coming up with answers.

The guide is available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/11/WC500216553.pdf

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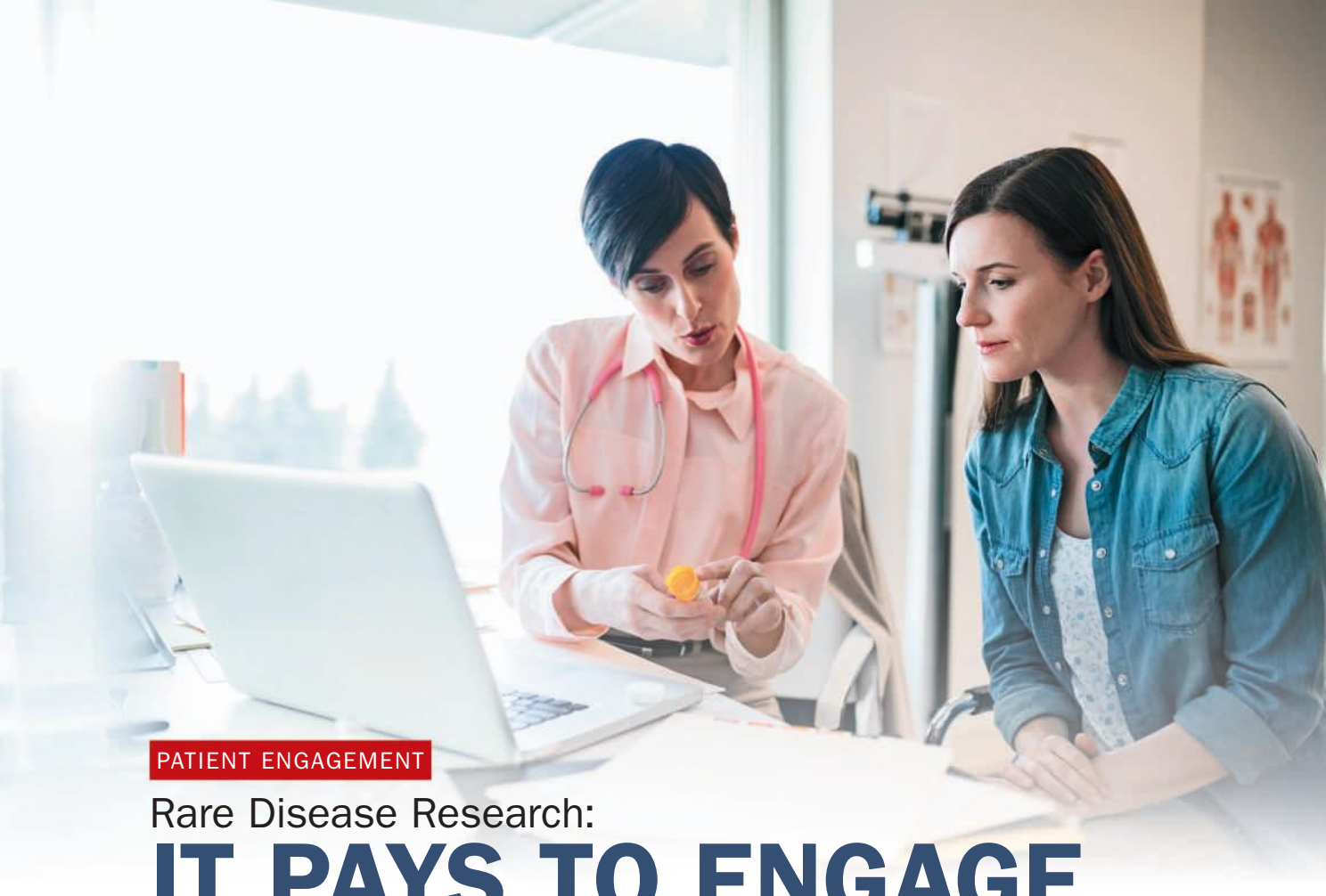

PATIENT ENGAGEMENT

Rare Disease Research:

IT PAYS TO ENGAGE

BY MICHAEL CHRISTEL

Behind the momentum of precision medicine programs such as Cancer Moonshot, coupled with the overall shift taking place toward ultra-targeted treatments—gene therapy, immunotherapy, biologics—the rare disease space seems to be joining the rarefied air of more common disease segments in biopharma business pursuits.

After all, by 2020, the rare and orphan drug market is forecast to grab 20.2% of worldwide prescription drug sales (excluding generics) and total $178 billion in annual revenue. In the US, the FDA granted nearly double the number of orphan drug designations in 2015 compared to 2010. The demographics are well documented: rare diseases affect fewer than 200,000 patients, but, in aggregate, afflict as many as 350 million people worldwide—more than the total for cancer and AIDS combined. Children are especially impacted; about 35% of deaths in the first year of life are reportedly caused by these conditions.

But despite greater financial and regulatory incentives to develop drugs for rare diseases, plenty of caution remains. The low prevalence of these conditions still results in various challenges in development, pricing, and reimbursement. And with treatments usually requiring large per-patient payments, this area won't be immune to the pricing scrutiny that continues to swarm the industry.

Juliet Moritz, executive director of strategic development in rare diseases for Premier Research, a CRO, has watched all these trends unfold with a close eye.

Involved in clinical research for 28 years, with experience in single-site studies as well as large, multinational trials, Moritz is particularly passionate about informed consent and the role of patient advocacy involvement in clinical research. *Pharmaceutical Executive* chatted with Moritz, where she discussed the challenges and opportunities unique to this specialty market—particularly related to growing focus areas such as patient engagement.

PE: ***What approaches are getting the most attention right now in rare disease research?***
MORITZ: We're seeing more interest in lysosomal storage disorders. But, in general, we're seeing a lot more focus on genetic conditions (80% of the estimated 7,000 rare diseases involve a genetic component). Now that the genome has been characterized, there's a lot of work going on that's relating a particular disease back to the genetics—the genotype and the phenotype. That brings us closer. Once we understand what the mutation is, we can then try to understand what's going wrong. Is it a protein being misshapen or is it a protein not being produced at all? We're finding conditions that are considered one condition but might have 10 or 12 different mutations that result in the same presentation of the disease.

We're also seeing enzyme replacement therapy—for patients in which their disease results in the deficit of an enzyme or the creation of an enzyme that can't cross the membrane. We're seeing a lot more therapies that can address that—either replace the enzyme or chaperone the protein across.

PE: ***What are some promising opportunities in patient recruitment for rare disease trials?***
MORITZ: To me, what's very exciting is the fact that the regulatory agencies are really now paying a lot of attention to patient engagement. We're seeing them go back to the pharma and biotech companies and specifically asking them, "what did you do in terms of patient engagement during your clinical development plan? Share that information with us." We've seen some legislative changes as well.

It's evolved, from when it used to be just putting a link about a study on a patient group's website. Now it's engaging in the protocol development, talking about meaningful endpoints and outcome measures. So that the protocols hopefully, over time, begin to reflect the day-to-day course of the disease and how it affects the patient, and in rare disease, often the family and caregivers.

PE: ***Do you think the targeted patient engagement approach has been more effective amid advances in digital information tools?***
MORITZ: I think so. There are companies in our space—niche vendors—that are trying to leverage technologies by creating online communities for these patients. I've been in the business 28 years. Twenty-eight years ago, we didn't have the Internet, we didn't have Facebook, we didn't have a place where a parent of a newly diagnosed child could go online and learn what resources are available. Now, if you look at almost every patient advocacy group, they're talking about research in their disease state. They're talking about clinical trials, and, in general, why people would want to participate in clinical trials. And depending on the therapeutic area and the target indication, they might even point people to specific trials.

The technology has been a significant boon. It doesn't completely eliminate the challenges in patient recruitment. It's still challenging because in some of these conditions you only have 1,000 or even just 2,000 people in the world that have them. You have to connect them to the places where the research is happening. But now it's less of a "let me reach out and try to find somebody." It's more of a combination—we're reaching out while they're also reaching out to try to find opportunities to participate in research.

PE: ***Are sponsors and CROs, in turn, more sensitive these days to the unique burden rare disease patients experience?***

MORITZ: That's a big part of protocol development—reaching out to the advocacy groups and evaluating the protocol and determining, well, this might answer all of the scientific questions, but is it so onerous that we're not going to be able to keep anybody in through the end?

As a CRO, we have to think what can we do to mitigate that burden so that we can enhance recruitment, but, more importantly, retention. Once someone's in the study, we need to make sure we're getting them through so that their effort turns out to be meaningful. It's incumbent on us to make sure that the protocol is scientifically rigorous but also operationally executable, and not just thinking about what makes sense for us and the sponsor but for the patients and their families.

PE: ***How do you go about including those considerations in the protocol?***

MORITZ: You build in as much as you can. Sometimes you only have a little bit of leeway depending on what the regulatory agencies want to see out of the protocol. But then you work around that to say, "alright, what can we do to support these patients and their families as they're participating in this experience?" Is it more timely reimbursement of expenses? is it working with the sites to make sure they can schedule these folks first thing in the morning if they've got a three-hour train ride, for example.

There's no magic bullet, there's no one answer. That's the nice thing about having been involved in rare disease research for so long. You build a tool box basically of strategies and things that you could do. Not all of them are appropriate for every study, but having that depth of experience allows you to make more informed decisions on what might work.

PE: ***Is the use of real-world data beneficial for trials in rare diseases? Is there enough data out there that could help?***

MORITZ: It's not as comfortable a transition as in more prevalent disease research, that's for sure. I think where big data might come into play is implementing strategies to try and identify lags in diagnoses. One of the challenges for a lot of people with rare diseases is that it could take quite a while to get a diagnosis. Are there other ways to characterize a patient's profile as they're going

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through their diagnostic arc? Is there any way we can shorten that up based on symptom and test information in medical records?

But right now I don't see a lot of that happening in rare disease research where it translates into impacts in clinical trials.

PE: ***What important caution would you advise companies interested in pursuing rare disease research?***

MORITZ: The regulatory pathways are compressed. You have a lot of what I call the slash studies: Phase I/II, Phase II/III. You have smaller patient populations; every single patient counts—and beyond that, every single data point counts. So the operational challenges are a little different. It's really important to understand and be able to anticipate that. Because otherwise you can take a small company that's got very limited resources, and if they go down the wrong path, they may not have an opportunity to reinvestigate that potential therapeutic.

PE: ***What about the economic challenges that still exist in developing drugs for rare disease?***

MORITZ: On average, the cost per patient to study a drug in rare disease is often higher, largely because of operational issues. The trials are often spread out and have a lot of assessments—and when you're bringing a patient to a clinic, you're often bringing their entire family. It's difficult to find control groups for some of these ultra-rare populations. So you have to be a little creative. Maybe you're doing crossover studies.

It's not as straightforward as Phase I, healthy volunteers; Phase II; Phase III; okay, we're going to market. It's not the same at all. It requires whomever you're working with to be nimble and know the regulatory environment.

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