



SHARING THE MISSION TO CONQUER RARE DISEASES

Closer collaboration between pharmaceutical companies and patient organizations will accelerate drug development

At an ever-quicken pace, biopharmaceutical companies and patient advocacy groups are banding together to hasten development of new drugs for rare diseases. Advocacy groups rely on their partners for financial and scientific support while providing access to repositories of patient data – the key to understanding rare diseases – as well as assistance with clinical trial enrollment. These relationships bring tremendous value to both sides but also present challenges. Increasingly, patient groups expect to be treated as equal partners. They want companies to consult with them earlier in the design of clinical trials, give them greater access to data generated in the studies, and make longer-term commitments to assist their patient communities. In this report, inVentiv Health looks at the dynamics reshaping collaboration in the rare disease space.



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INTRODUCTION

When Congress passed the Orphan Drug Act (ODA) in 1983, no one could guarantee that financial incentives in the law would spur development of life-saving drugs. But, the framework has proven highly effective. It provided tax credits, relief from regulatory fees, and other incentives for companies that develop treatments for some 7,000 rare conditions – those affecting fewer than 200,000 people.

In the three-plus decades since the law was signed, the FDA has approved more than 500 drugs for rare diseases and granted more than 3,000 orphan drug “designations.” Europe and Japan followed the US in drafting orphan drug laws, adding to a worldwide boom in drug development aimed at rare diseases. These medications have delivered immense health benefits to patients and opened up business opportunities at a time when pharma companies are grappling with patent cliffs and other hurdles. Global sales of orphan drugs have been growing nearly 12% per year and could reach \$178 billion in 2020, equal to one-fifth of annual prescription drug sales, excluding generics, according to consultancy EvaluatePharma.

Advocacy groups, working on behalf of patients and their families, contributed mightily to these medical and commercial success stories. Many drug companies have partnered with these organizations to better understand the natural course of diseases, identify patients who are eligible to participate in clinical trials, and present a compelling case to regulators and payers. Companies supported these organizations and, as a result, earned the privilege to get closer to patients, hear their voices first-hand, and then leverage what they learn to make better products. Up to a point, both sides are satisfied when partnerships contribute to the successful launch of life-altering medications. In the eyes of many advocacy groups, however, these relationships are still works in progress.



“I urge industry to work as early on as possible with advocacy. The benefits are truly amazing.”

- DEREK GAVIN, DIRECTOR OF DEVELOPMENT WITH NORD

In 2015, inVentiv Health PR Group interviewed 42 patient advocacy organizations to learn how these groups regard partnerships with drug companies. The result, a white paper titled, “The New Partnership Paradigm,” documented examples of ambitious collaboration between the two camps, but it also highlighted areas that needed improvement. Notably, the patient groups called on pharmaceutical companies to consult with them more effectively in the early stages of drug development and continue the relationship even when drugs go off patent. In the words of one patient advocate: “This should be a marriage, not a blind date.”

The advocacy groups we interviewed represented a broad sweep of diseases, from relatively common cancers to rare blood disorders. Toward the end of 2015, we went back to many of the organizations that focus on rare diseases to gain even a better understanding of partnerships in this closely watched space. This time, we also spoke with pharmaceutical companies

and outside experts specializing in rare diseases. Among the patient groups, we found heightened urgency around the need for lasting partnerships that could bring relief to patients and their families. We also heard concerns that the goals of advocacy groups and their pharma partners were sometimes misaligned.

For example, many drug companies working in rare diseases concentrate on developing disease-altering medicines known as new molecular or chemical entities, which take a decade or more to bring to market. While these novel drugs are the gold standard for pharma companies, they are also among the most challenging to develop, requiring the largest financial investment and longest time horizons. Parents of children with rare diseases support these efforts, but they may also have an urgent need for drugs that relieve a child's symptoms. Yet, such products may not receive priority status at a drug company, or at the FDA. “A parent may desperately need a

drug that will help her child sleep through the night,” says Christina Waters, founder of RARE Science, a research and advocacy alliance, who notes that children make up roughly half of the rare disease population (page 8).

In short, both drug companies and patient advocacy groups in rare diseases are enthusiastic about the promise of partnerships to develop new drugs and genomics-based diagnostics. But, the priorities that drive collaboration are not the same for each side. The collaborative model itself is changing. In some cases, patient groups have achieved elevated status as co-funders of research with their own scientific and data resources, and a passion for quickly placing research data in the public domain. However these mismatches in priorities are resolved, advocacy organizations we spoke with hope partnerships will keep evolving in ways that amplify the patient's voice and place their well-being at the heart of every medical and drug-development conversation.

PARTNERING IN RARE DISEASES:

A Guide for Pharmaceutical Companies

01 Build – and live – a patient-centric reputation that is welcoming to advocacy groups in this space. Engage early and often to infuse the patient voice into the entire drug and diagnostics development continuum.

02 Create a consensual framework for engaging with patients that brings together all relevant parties in the company (medical affairs, legal, regulatory, clinical, commercial, etc.)

03 Identify and build meaningful partnerships with global stakeholders, key opinion leaders and educational centers that are trusted by advocacy groups, caregivers and patients.

04 Organize and lead patient forums with support from advocacy organizations. Speaking directly with patients is the best way to ensure that your clinical trial protocols embody their point of view.

05 Conduct outreach initiatives that deepen the bonds between your staff and patients treated with your products. Disease awareness campaigns and write-ups in consumer health media can burnish your reputation, but they can't replace authentic interactions with patients.

06 Encourage collaboration among advocacy groups. Many rare disease advocates recognize that a single, focused group of patients speaking with one voice is more effective than a phalanx of smaller groups.

07 Develop a messaging platform that respects the knowledge and resources of the rare disease community. Mission and vision statements should showcase what patients bring to the relationship. Instead of professing, show that you have learned.

08 Design clinical trials, diagnostics and patient identification efforts with advocacy groups' input and support. The objective is to align the company's R&D and commercial goals with patient priorities, which often include symptom relief and speed to market.

THE PATIENT'S VOICE

When regulators around the world started passing orphan drug laws, they set the stage for deeper ties among drug makers and patient advocacy organizations. Armed with business incentives and hoping to better serve patients, drug companies turned to these groups for help identifying hard-to-reach patient populations and physicians who understood rare illnesses. The relationships proved valuable in clinical trial enrollment. And, most importantly, they created opportunities for corporate partners to hear – and heed – the patients' own voices. Those that embraced this approach were better able to define primary and secondary endpoints in clinical trials. Understanding the patient burden, they could design more effective trials.

It's now clear that partnerships formed early in the drug development process can give the drug company access to valuable knowledge assets, including data repositories known as "patient registries." Developed and groomed by the advocacy groups, these registries are comprehensive, long-term health records in which patients, as well as families, caregivers and medical staff, log every detail of daily life bearing on the patient's illness. The repositories, spanning long stretches of time, can be analyzed to create "natural histories" of the disease – an essential tool for pharma companies developing new medicines. "I urge industry to work as early on as possible with advocacy," says Derek Gavin, Director of Development with the National Organization for Rare Disorders (NORD). "The benefits are truly amazing. You reap what you sow."

In some cases, the advocacy groups finance their own research projects, making use of the knowledge assets they have in hand. For many others, registries are tools that help their pharma partners accelerate the clinical trial process. "Having a registry has allowed us to be more efficient and effective at recruiting and enrolling in clinical trials" for companies, says Jennifer Farmer, Executive Director of Friedreich's Ataxia Research Alliance (FARA), a research group seeking a cure for an inherited disease of the nervous system. On behalf of its partners, FARA can mine the registry for patients who meet inclusion criteria and send them notices about an upcoming trial – sometimes filling the recruiting requirements in a matter of hours. "All companies have to do is supply us with the recruitment flyer or notice and give us the go-ahead and we will engage the community and fill the trial with qualified subjects," she says.



Health authorities understand the value in pharma-advocacy collaborations. In an era when all healthcare stakeholders pay homage to patient-centricity, regulators consider patients' personal experiences and voices as integral to a drug's value proposition. In rare diseases, they expect to see patient reported outcomes (PROs) in the product dossier.

What questions belong in the PRO survey? No one knows better than patients and their advocacy groups, and no one can better guarantee that patients participate in the surveys. In the end, PROs in the dossier shape official statements about the patient's quality of life, the drug's cost effectiveness, and, ultimately, the language on the label.

Patient centricity was similarly embedded in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) in 2012. That's when the FDA launched Patient-Focused Drug Development, a five-year initiative which aims to draw out patients' perspectives on their illnesses, the impact on daily life, and how drugs affect the picture.

Through Patient-Focused Drug Development and other frameworks, the FDA encourages drug companies to deepen ties with patient communities. Last summer, the agency issued guidance urging manufacturers to compile more comprehensive natural histories of rare diseases. The objective: to define the affected populations, understand disease manifestations and their causes, identify subtypes, find reliable biomarkers, and observe the full disease course from onset to end of life. Each of these elements in the guidance supports the aspirations of many advocacy groups: to engage patients and their families early in the clinical trial process and leverage their unique insights to create more effective medicines.

The type of analysis the FDA seeks in rare diseases would be inconceivable today without the trust and cooperation of patient organizations. "The whole conversation has changed in the past five years," says Louise Vetter, CEO of the Huntington's Disease Society of America. "Patients are finally being seen by the pharma industry and by the FDA as an essential resource."

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People afflicted with rare diseases face many hurdles, including a shortage of specialists who understand their conditions and limited treatment options. In 2016, however, patients and families are anything but silent. Digital and social media enhance the patient's voice. They also make it easier for individuals to investigate symptoms, track down relevant research, connect with experts and other patients, form communities, and leverage both the wisdom and political clout of crowds. In the words of Melissa Hogan, Founder and President of an advocacy group for people with Hunter syndrome: "Not only do patients connect with one another, they connect with the pharma companies that serve them, with the FDA, and with service providers – and they also connect researchers to pharma companies and patients to clinical trials. It's a very interesting kind of spoke-and-wheel dynamic."

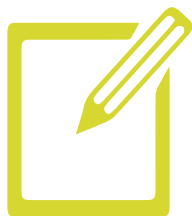
Hogan exemplifies the multifaceted, grassroots character of patient advocacy. Until 2009, she was a healthcare lawyer and strategy consultant. Then her son was diagnosed with Hunter syndrome, a genetic disease that causes loss of mental and physical abilities and a shortened life span, precipitating her shift to patient advocacy work. Now, in addition to running her organization, Saving Case and Friends, Hogan is a Patient Representative to the FDA and an advisor to the Mayo Clinic Social Media Network. Many other advocacy leaders have similar stories. Derek Gavin, NORD's Director of Development, is also a parent advocate who lost a child to a rare neurodegenerative disease. "My work is my mission," he explains.



THE GOALS OF PHARMA-ADVOCACY COLLABORATION



Understand the natural course of the particular rare disease



Define meaningful clinical trial endpoints, including use of patient reported outcomes (PROs)



Accelerate identification of patients and investigators to participate or assist in clinical trials



Build a case that's compelling to regulators and payers



Speed treatments to market to relieve suffering – even if cures aren't within reach



“We’re all trying to figure out how to do this. We’re on the cusp of change.”

- CHRISTINA WATERS

RARE SCIENCE: POOLING KNOWLEDGE TO HELP KIDS

The organization is building a shared computational platform to speed therapeutic advances

When a child is in pain, adults who know about it do everything they can to help. It’s a powerful human instinct. And if it can be harnessed, it may hold the secret for speeding up discovery of drugs to treat rare diseases.

This is the core idea behind RARE Science, a not-for-profit research organization founded last year by Christina Waters in Encinitas, CA. The 50-year-old geneticist says there are barriers that separate communities of clinicians and researchers from one another and from parents of children with rare diseases. This obstructs the kinds of innovations kids and their families are counting on. Her organization has built a computational platform Waters calls “the rare hub.” It’s an environment where parents, researchers and medical teams can share clinical results, computational tools and other services to catalyze breakthroughs (conceptual or biochemical) that can have an immediate impact.

About half of an estimated 7,000 rare diseases begin in childhood, according to research funded by the National Institutes of Health. The conditions affect as many as 350 million children and adults globally and are responsible for 35% of deaths in the first year of life. Some 30% of children with these conditions will not live to see their fifth birthday, Waters says. She points to studies showing that it takes, on average, 14 years and \$2 billion to develop new drugs, of which 95% fail in clinical trials. “For kids that can’t wait 14 years, we need a completely different approach,” Waters says. “That includes repurposing older drugs and inventing new technologies in parallel with traditional drug

development.”

People who study or are afflicted with rare diseases face unusual challenges. Patient communities are small and scattered, and the conditions are often difficult to diagnose. In addition, Waters says, research and clinical groups tackling these diseases in academia and in industry sometimes operate at cross-purposes, with career incentives rooted in competition for intellectual property rights, publications and funding.

Drug repurposing is one case in point. Waters and other patient advocates believe some drugs on the market today could be combined or repurposed to help sick children. But such projects may not become a priority for drug companies until we have new and different economic models. “The misaligned incentives are detrimental,” Waters says. “Efforts should be coordinated internationally. To bring hope

to kids in their lifetime, we need more sharing of data and ideas that advance our knowledge of the underlying biology.”

Waters understands the constraints in academia and in corporate science. A geneticist with a PhD from the University of California, Davis, she was a postdoctoral scholar at Caltech and also earned an MBA from UCLA. Later, she spent years running programs at small and large biopharmaceutical companies, including Novartis. “I come from that world, and I know the challenges,” Waters says. But, she envisions a world where healthy competition and “open” science can coexist. “We’re all trying to figure out how to do this,” she says. “We’re on the cusp of change.”





FUTURE OF COLLABORATION

As advocacy groups seek more control in the partnerships they form with pharmaceutical and diagnostics companies, some groups are playing much larger roles in drug development. In the past, advocacy groups mainly turned to their industry partners to support their activities. In the new paradigm, sometimes labeled “venture philanthropy,” an advocacy group with strong patient backing and fundraising capabilities can transform itself into an organization that sponsors drug research, engages pharma partners as peers, and reaps commercial profits that can quickly be plowed back into research and development.

A good example is the Cystic Fibrosis Foundation, which began providing research grants to Vertex Pharmaceuticals in 1999. Over the next 15 years, the Foundation’s commitment swelled to \$150 million, helping to support the first two drugs that treat the underlying causes of CF: Kalydeco and Orkambi. In 2014, the foundation received \$3.3 billion by selling its rights to future royalties on drugs that were developed with its support.

The foundation’s dive into commercial transactions has drawn criticism in some quarters. But, the Foundation’s board was able to make a persuasive case for selling the royalty rights. The organization

has told the news media it will invest its immense cash hoard in projects to develop the next generation of cystic fibrosis treatments. Similarly, other patient advocacy organizations are pouring capital they raise into commercial and academic research ventures.

Another research powerhouse is the Multiple Myeloma Research Foundation (MMRF), which has raised \$275 million since its founding and directs nearly 90% of its total budget to research and related programming. Like commercial pharma companies, MMRF supports promising new investigational treatments that are up for review by the FDA. But it has a broader agenda: to use precision medicine’s powerful genomic and Big Data toolkits to analyze the interplay of an individual patient’s unique biology and his or her molecular subtype of multiple myeloma.

The goal is to figure out which combination of drugs, commercial or experimental, will be most effective for the individual. MMRF places all of its data in the public domain, with “gateways” that allow scientists to query the data for answers relevant to their research. This open approach is bearing fruit. In a \$40 million research initiative called CoMMpass, MMRF is looking at data from 1,000 patients on individual or combination treatments that include Velcade, Revlimid, Thalomid, Kyprolis and others.

RESOLVING CONFLICTS

The emerging venture philanthropy model goes a long way toward leveling the playing field in pharma-advocacy partnerships. But, it doesn't address every incident of frustration or discord. To cite just one example, RARE Science's founder Christina Waters says she is seeing frequent disagreements over the use of data in commercial or product registries. To the pharma companies supporting advocacy groups that assemble this valuable information, patient data is an asset, like intellectual property, that provides a competitive edge. In contrast, many patient organizations believe the information should be accessible to all researchers striving to develop treatments. "Parents must have the ability to own and share this information, given the urgency of their children's needs," says Waters. In the near future, she expects that some form of open sharing of data and crowd/research-sourced analysis might start to compete with the current model based on proprietary patient registries.

Many advocacy groups interviewed by inVentiv Health say they understand the constraints under which companies do business, but they continue to push for change. "It's easy for people in pharma to think about the work in front of them and forget about the patient who has a name and face," says Lindsay B. Groff, Executive Director of the Barth Syndrome Foundation. Her organization supports research and raises awareness of Barth Syndrome, which strikes small children and can lead to weakened musculature, impaired immune responses, growth delay and other problems. Through conferences connecting patients, scientists and physicians, "we try and humanize the end result of the work they're doing. Real people are suffering. It makes clinicians and researchers more empathetic."



The FDA is looking to promote patient engagement in research and also trying to show progress in the areas of social media, which advocacy groups try to leverage to a great extent. They're certainly making strides.

**- GAIL COHEN,
COMMUNICATIONS
DIRECTOR AT ACORDA
THERAPEUTICS**



It's important to remember that as a patient advocacy group, I'm in a different business than pharma. They're making a huge, upfront investment in a rare disease, and they need to be profitable. I'm in the business of going out of business.

**- JENNIFER FARMER,
EXECUTIVE DIRECTOR
OF FRIEDREICH'S ATAXIA
RESEARCH ALLIANCE**

FARA's Jennifer Farmer believes the first step in keeping relationships on course is to be honest and define the issues. "It's important to remember that as a patient advocacy group, I'm in a different business than pharma. They're making a huge, upfront investment in a rare disease, and they need to be profitable. I'm in the business of going out of business."

Among industry and advocacy groups that make up the rare disease research community, all sides acknowledge there are points of contention when it comes to registries and patient data. But, this landscape is evolving in important ways, says Jayne Gershkowitz, Senior VP and Chief Patient Advocate at Amicus Therapeutics, a biotech company developing advanced therapies to treat a range of devastating rare and orphan diseases. Particularly in rare diseases that do not yet have an approved treatment, Gershkowitz says advocacy groups are taking the lead in building registries to collect key information and advance drug development. These can complement the commercial or product registries that regulatory agencies require for tracking the longer-term safety and efficacy of approved treatments. "There is a growing preference, particularly in the patient advocacy community, toward hybrid registries," says Gershkowitz. "These could enable the collection of proprietary elements that satisfy regulators, but also allow patients, or their parents and physicians, to supply information."

For the most part, companies interviewed by inVentiv Health applaud regulatory changes that advance the patient's viewpoint. The FDA's Patient-Focused Drug Development initiative is an important step, says Gail Cohen, Communications Director at Acorda Therapeutics, a biopharmaceutical company with treatments for multiple sclerosis and other neurologic disorders. "The FDA is looking to promote patient engagement in research," she says, "and also trying to show progress in the areas of social media, which advocacy groups try to leverage to a great extent. They're certainly making strides."

CONCLUSION

Partnerships among stakeholders in rare diseases may never be perfectly harmonious, though progress has been swift and profound. We believe pharmaceutical and diagnostics companies will keep striving to accommodate requests from their advocacy partners. Just as surely, patient advocacy groups will continue to push for a more authentic patient-centric focus. "Companies need to understand the cost-benefit from the perspective of patients' families," says Jenn McNary, Director of Outreach and Advocacy at the Jett Foundation, which advocates on behalf of Duchenne muscular dystrophy patients. She wants partnerships to begin with early-stage drug development. When children are sick, companies should consult with parents in end-point selection and design of clinical trials. "What if they are creating a drug that the families don't want," she asks. "They need to understand what we are willing to accept from a risk perspective. What is ethically acceptable from the FDA or industry perspective may be unacceptable from the parents' point of view."

An even greater source of dismay, for some patient advocates, is the sense that they are being swept up in commercial jousts that aren't always driven by the patient's interests. "I wish some [drug makers] would be more careful in how they engage community advocacy," says Kimberly Haugstad, Executive Director of the Hemophilia Federation of America. "Don't use us to ensure drugs are paid for. It's a battle between the insurance companies and pharma, and sometimes patients get knocked around like ping pong balls."

What's striking is the speed with which drug companies, inspired by work with rare disease advocacy groups, are elevating executives into advocacy roles or "chief patient officers." From this perch, they often take up the advocacy group's refrain. "Companies are learning the intrinsic value of the patient perspective throughout the drug development process," says Jayne Gershkowitz, the chief patient advocate at Amicus. "This is key to a true partnership between patients and companies." Disagreements among groups may be inevitable, but they can't obscure the benefits that have flowed to both sides. As new models for pharma-advocacy collaboration shake up old ideas about research objectives, data sharing, capital allocation and the trajectory of precision medicine, patients and families struggling with rare diseases will see many more examples of the progress they seek.



ABOUT INVENTIV HEALTH PUBLIC RELATIONS GROUP

The global public relations group of inVentiv Health helps launch brands and build the reputations of companies working to improve human health. Integration with the advertising and medical communications agencies within inVentiv Health creates complete communications solutions that build corporate and brand value and to deliver on the bottom line.

inVentiv Health is a top-tier professional services organization that accelerates the clinical and commercial success of biopharmaceutical companies worldwide.

Our Advocacy Patient Engagement Solutions

inVentiv Health PR Group's advocacy hub is centered in our Washington, D.C. office with a network of experts throughout the US and UK. Our team brings decades of experience in advocacy consulting for pharmaceutical, biotech and device companies, and patient and advocacy organizations. As a result, our experts are adept at bridging the gap between patients and companies to find mutual solutions and in the support of new and existing treatments that improve patient care.

Traditionally, the patient voice has been limited to discrete points later in the development product lifecycle. inVentiv Health helps clients infuse the patient voice throughout clinical development and commercialization with input mechanisms providing a continual feedback loop.

INVENTIV HEALTH OFFERS:

- **Voice of the Patient Workshops** to better understand the patient mindset, needs and how to incorporate that information
- **Clinical Trial Recruitment**, including investigator engagement
- **Patient Advisory Boards**
- **Patient Lens Diagnostic Deep Dives** on a specific patient population/therapeutic category to support better clinical development activities
- **Behavioral Insights and Adherence Programs**
- **Patient and HCP Communications**
- **Comprehensive Patient Engagement Plans** for how companies/franchises/brands should infuse the patient voice into the clinical pathway
- **Medical Communications**
- **Social and Digital Activation**
- **Public Relations**
- **Advertising**



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