when the orphan disease patient speaks, listen.

the power of patient-centric digital approaches in orphan drug development and commercialization

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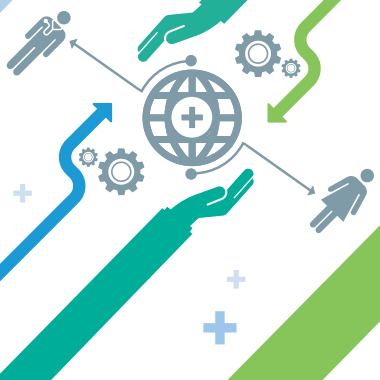

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executive summary

Since the early 1980s, orphan disease patients and their advocates have claimed abandonment by the Drug Development & Commercialization Complex (DDCC), and to a large extent there is evidence to support that assertion, both anecdotal and quantitative. However, that has been changing since the turn of the century when the DDCC began seeing the opportunity to engage its ample resources to investigate rare diseases.

The potential for scientific discovery and ground-breaking treatments has proven to be enormous given escalating advances in genetics, personalized medicine and access models. Assessment by the DDCC of available accommodating regulatory pathways, attractive pricing and research incentives, and other commercialization factors, has led to their conclusion that development opportunities outweigh the significant challenges when developing therapies for orphan diseases (including small patient populations, poor understanding of the patients' conditions, and mandated patient input on clinical trial design).

Patients and their oftentimes sophisticated advocates continue to voice their needs and wants; which mostly center around the obvious - research for treatments and cures. However, there is so much more for many of these complex multi-stakeholder populations including not only the patient, but their critical support systems of parents, caregivers, advocates, counselors, etc., that remain untapped and provide a way for the DDCC to engage more effectively.

"Patient-centricity" has been the watchword for pharma over the past few years, meaning expanding DDCC focus from product specific pre-market research, and inmarket sales & marketing, to include "beyond the pill" value-based patient-services. While some DDCC initiatives have surfaced, it seems that the DDCC has not completely embraced this movement.

We believe that drug development and commercialization in rare disease requires disease-specific services that benefit the patients, advocates and caregivers. The DDCC is best positioned to provide support, both financial and experiential, to change the outdated blockbuster paradigm associated with large population diseases. Critical to fostering this change in approach is for the DDCC to improve their listening skills, thereby allowing the DDCC to understand the concerns and ideas of patients and advocates in these smaller populations. Indeed, listening is a lynchpin to advancing research, increasing adherence and improving patient satisfaction.

Digital mediums, and expressly feature laden, "deep-knowledge" online patient communities, can provide a one-stop-shop, satisfying a myriad of patient needs (community, knowledge and clinical trials) and DDCC needs (data, feedback, access and recruitment) which will ultimately benefit the whole rare disease community.

pharma adopting orphans

"Despite the smaller patient pool for rare disease R&D, the economics of orphan drug development and potential for commercialization are attractive when compared to their nonorphan counterparts."

– Thomson Reuters. The Economic Power of Orphan Drugs. 2012.

One of the most robust – and most lucrative – areas of drug development today is in rare diseases. With more than 7,000 rare diseases worldwide affecting more than 250 million patients, an estimated five new rare diseases identified each week, and FDA-approved treatments available for just 5 percent of these diseases, the potential for pharmaceutical and biotech companies in this arena is tremendous.[1]

Pharmaceutical companies have taken notice. Today, orphan drugs account for one out of three drug approvals in the US, a rate that is expected to continue given the huge number of rare diseases and the increased use of genetics and personalized medicine to develop therapies.[2]

today, orphan drugs account for one out of three drug approvals in the US.

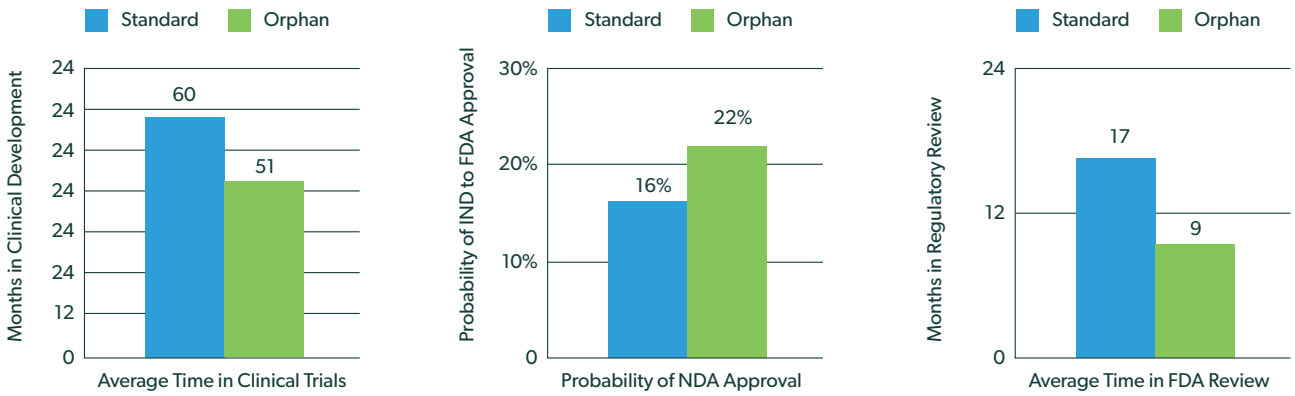
The reality is that although a rare disease affects fewer than 200,000 people in the US, drugs for these diseases carry a premium in the marketplace. In addition, there are numerous regulatory and commercial incentives designed to spur interest in orphan drug development by significantly reducing the cost of and time required to bring the drugs to market (Table 1; Figure 1).[3]

Table 1: Incentives for Rare Disease Development in the United States

Research Incentives	Commercial Incentives
50 % tax credit on R&D	Favorable pricing and reimbursement
R&D grants for clinical trials	Easier path to approval
FDA user fees waived	Longer exclusivity
Shorter development timeline	Lower marketing costs
Greater regulatory success	Faster uptake

Thomson Reuters. The Economic Power of Orphan Drugs 2012.

Figure 1: Development Time: Standard vs Orphan Drug

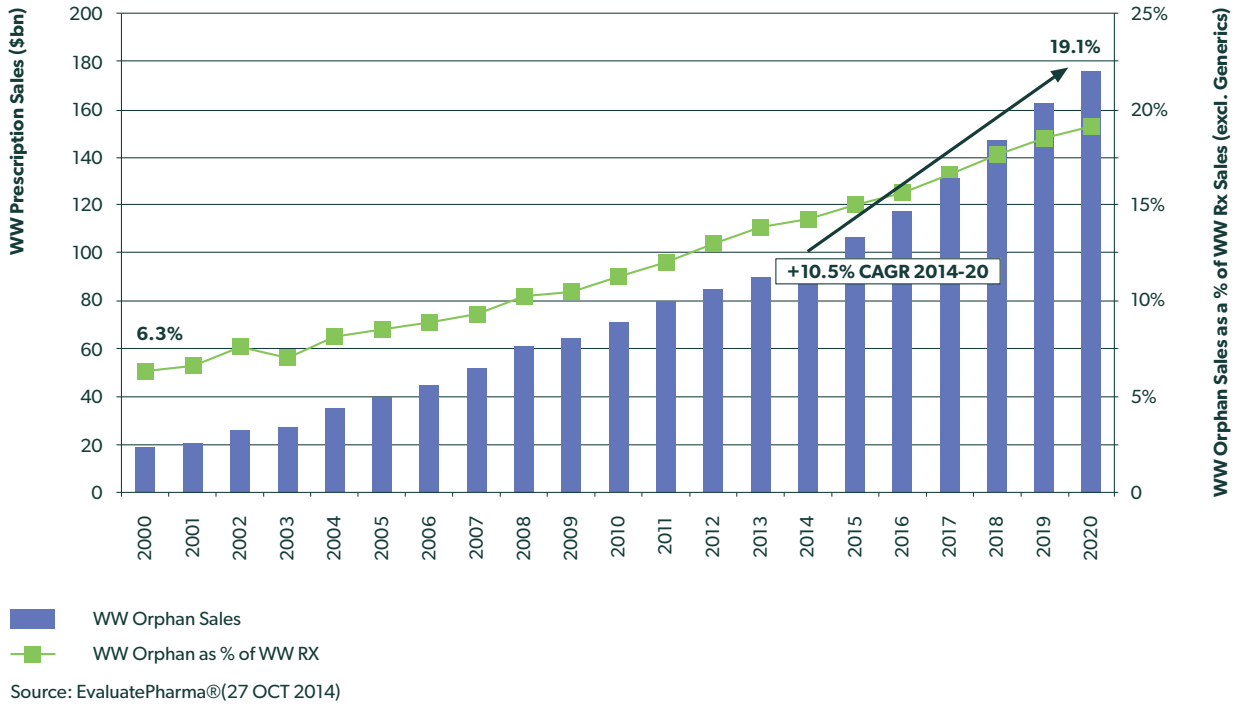


Premier Research. Orphan Drug & Rare Disease Development: Understanding the U.S. and European Regulatory Landscape. 2015.

While it is clear that orphan drug development offers a tremendous opportunity to the biopharmaceutical community, it also carries with it significant challenges, particularly in terms of clinical trial design and implementation. And on the other end of the spectrum, it offers a unique opportunity to re-write the drug commercialization playbook.

A recent report by Thomson Reuters found that orphan drugs are replacing the blockbuster drugs of previous decades, with potential lifetime revenue far greater than that of drugs developed for more common health conditions. Of 86 orphan drugs approved since 1990, a third were blockbusters with sales greater than $1 billion.[3] Another report, this one from Evaluate Pharma, predicted that global sales of orphan drugs would rise about 11 percent a year between 2014 and 2020, reaching $176 billion by decade's end (Figure 2).[4]

Figure 2: Worldwide Orphan & Prescription Drug Sales: historical and projected to 2020



Source: EvaluatePharma®(27 OCT 2014)

This high return comes from the ability to demand a "commercially attractive" pricing structure given the huge unmet need the drugs address.[3] It also comes as the drugs receive additional indications. For instance, Gleevec™ (imatinib), which was originally approved for chronic myeloid leukemia, now has multiple orphan indications and grossed sales of $4.7 billion in 2015.[5] Rituxan™ (rituximab), first developed as an orphan drug for B-cell non-Hodgkin's lymphoma, is now one of the most profitable drugs in the world. Indeed, of the top 10 selling orphan drugs in 2012, six had more than one rare disease indication.[4]

While it is clear that orphan drug development offers a tremendous opportunity to the biopharmaceutical community, it also carries with it significant challenges, particularly in terms of clinical trial design and implementation. Overcoming those challenges, as this paper highlights, requires engaging with the rare disease patient community in unique ways to partner with them in the development of these drugs and to harness their insights and provide the kind of targeted marketing and education that leads to commercial success.

living with a rare disease: the patient's perspective

"One of the biggest things about a rare disease is that you feel really isolated. You are literally one in a million."

Dakota Fisher-Vance, 27. Diagnosed with familial adenomatosis polyposis (FAP) at age 22.

Lack of online community

Patients have been gathering online for years. But while patients with more common chronic diseases typically have patient advocacy and support organizations with robust web sites, just 15 percent of the more than 7,000 identified rare diseases have dedicated patient organizations.[6]

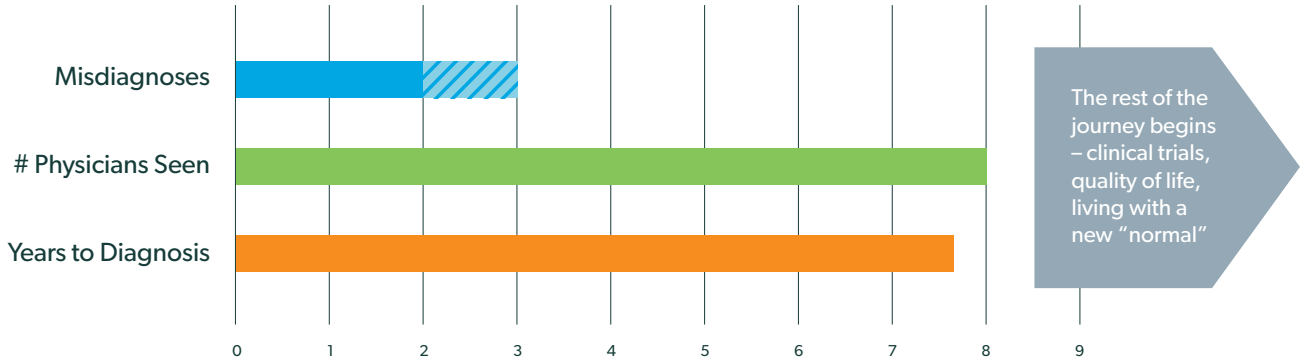
"The isolation of a rare disease is particularly difficult," says Dakota Fisher-Vance, 27, a patient and advocate who was diagnosed with familial adenomatosis polyposis (FAP) at age 22. "So finding others who share your condition, your story, and your journey is a huge comfort."

Lack of Information & Research Skills

One of the greatest challenges patients with rare diseases and their caregivers face is a lack of information. In one survey of 144 patients and 132 caregivers representing 178 rare diseases in the US, 60 percent said they received conflicting information from healthcare professionals about treatment and 67 percent had to provide their healthcare professional with information on their disease. The lack of information on their disease, patients report, contributes to high levels of anxiety, stress, and depression.[7]

"Information is so hard to find," says Fisher-Vance. "It's rarely in a centralized space. It might be out there in little pockets, but you have to be lucky to chance upon one of those pockets."

Figure 3: The Rare Disease Journey



Prolonged time to diagnosis

Patients and caregivers find that it takes an average of 7.6 years to get a diagnosis, which typically occurs after visiting eight physicians, four primary care and four specialists, and receiving two or three misdiagnoses (Figure 3a).[7] This journey only accounts for getting to the correct diagnosis. The next part of the journey deals with rare challenges like participation in clinical trials, the complex world of health insurance, seeking quality of life and living with a new "normal" life in the rare disease world.

Their healthcare professionals experience similar frustrations, with more than 90 percent of the 50 physicians surveyed saying it is more difficult to address the needs of a rare disease patient in a typical office visit and that more visits are required to diagnose and manage patients. In addition, 54 percent said they don't have enough opportunities to network with other physicians who treat rare diseases and 76 percent said they found it difficult to coordinate patient management with other physicians. [7]

Deep knowledge and community - a one-stop-shop

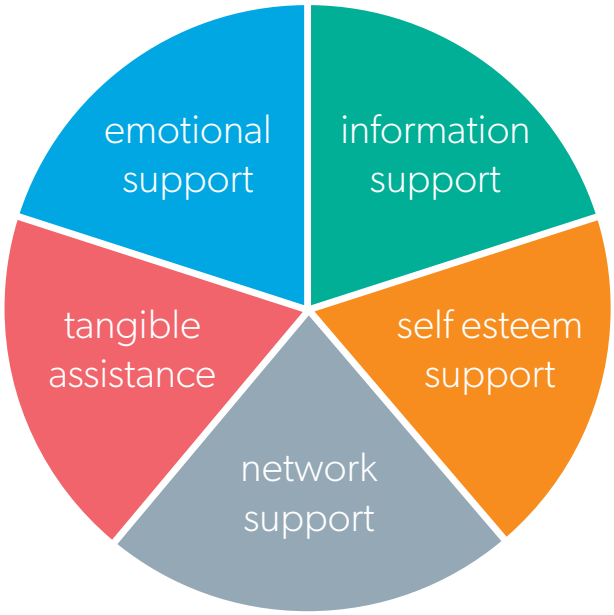
Patients want "one-stop-shopping," said Fisher-Vance, a centralized location where they can interact with other patients and healthcare professionals, share resources, and find reliable, vetted information.

Such online communities can help patients take a more active role in their disease with their healthcare providers; accelerate the dissemination of information about treatments and clinical trials; alleviate the sense of isolation as users discover others with their disease; and provide broader access to medical professionals.[8]

A study evaluating messages on a Huntington's Disease message board found five main categories in the discussions: information support, such as referring to experts, organizations, or websites; self esteem support, such as praise for how one is handling the disease; network support, such as encouraging people to post to the group and seek help; tangible assistance, such as communicating off line; and emotional support – offering love and friendship and affection (Illustration 1).[9]

Illustration 1: Rare disease discussion topics in Huntington's Disease

5 main support needs



In addition, the fractured nature of rare disease knowledge and treatment means that physicians also need a forum in which to exchange information not only with each other, but with patients, in order to learn best practices and better understand the disease state.

While there are a few high-quality web sites and disease portals for certain rare diseases, as well as hundreds of Facebook groups, most patients have little access to robust and curated information, creating significant hardships for them and their families during a time in which they desperately need this support. Sites that are available, whether web sites or disparate groups on Facebook, tend to be poorly managed with dated information and limited resources.[8]

"Ideally," says Fisher-Vance, "we need a community of not just other patients, but doctors and caregivers and the pharmaceutical industry that converges in one location. That's the way we're going to start getting things done and making progress." Such a site, she said, would collate all aspects of social media into one easy-to-navigate, dynamic, reliable, and trustworthy platform, providing real-time information from a variety of channels, including Facebook, Twitter, YouTube, the news media, and medical journals, and integrating physician and researcher forums with the patient experience.

The biopharmaceutical industry is well positioned to "adopt" orphan communities by partnering with advocacy groups, medical centers, and technology developers to build patient-centric services that provide reliable, quality information as well as emotional support.

clinical trials for orphan drugs: consulting the patient groups

"In an environment where scientists are many and trial participants are scarce, patient groups are starting to organize their own clinical trial networks and offer them to scientists because they realize their registries, their tissue banks, their biobanks, and their experience are the key resources."

– *Weisfeld W, English RA, Clairborne AB. Public Engagement and Clinical Trials: New Models and Disruptive Technologies: Workshop Summary. Institute of Medicine. 2012.*

Patient groups, whether large charitable foundations or small parent groups, are essential resources for overcoming the challenges in rare disease clinical trials. Such groups are often well-versed in the epidemiology and natural history of the disease. Patient groups can be crucial to solving three primary challenges faced when developing orphan drugs:

1. Provide patient reported data, tissue samples, and natural histories;
2. Provide access to, and education for, constituents regarding clinical trial enrollment opportunities; and
3. Provide federally mandated patient guidance and input to clinical trial design.

To facilitate patient-centric clinical trial involvement, new, more sophisticated, online tools beyond static websites, discussion boards and facebook 'likes' need to be provided to patient groups to overcome not only these three primary challenges but many other obstacles including:

- **Small patient trial populations.** Patients are geographically dispersed throughout the world, requiring multicenter sites.

- **Diverse patient characteristics.**
  - Disabilities that prevent patients from traveling to often distant clinical centers
  - Difficulty diagnosing patients, so many cases go unrecognized
  - Diseases that primarily manifest in children, increasing the difficulty of trial design and implementation
  - The psychological and social burdens the disease place upon patients, which can lead to despair and lack of hope for therapy
  - Heterogeneity within the disease depending on the genetic mutation

- **Clinical trial design.**
  - Lack of standardized clinical trial design
  - Challenges with efficacy and outcome measures
  - Questions regarding the length of the trial given the chronic nature of the disease
  - Finding experienced investigators and vendors

Considering the wide organizational variance of patient groups and their demonstrated reliance on the internet to communicate and learn, a "one-stop-shop" for their community, information and clinical trial needs becomes a valuable opportunity to interact with them and understand their particular challenges.

patient experience: mandating patient-centered research

Patient-centered clinical research has been codified into the law over the past several years, with pharmaceutical and medical device companies now required to engage and involve patients in research (Table 2).

In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) called for the agency to develop and implement strategies to solicit the views of patients during the medical product development process and to consider their perspectives during regulatory discussions.[11]

That same year, the fifth authorization of the Prescription Drug User Fee Act (PDUFA) also required that the agency and industry consider the patient perspective on disease severity or the unmet medical need in a therapeutic area to benefit the drug review process.[11]

Such requirements will likely be strengthened in the sixth PDUFA authorization now under development. Constituents, including the FDA, industry, and patient organizations, have identified "expanding patient perspectives in regulatory decision-making" as a top priority.

To prepare, in late March the Center for Drug Evaluation and Research (CDER) sponsored a public workshop: Navigating CDER: What You Should Know for Effective Engagement. The purpose was to help the public and patient advocacy groups gain a better understanding of how to effectively engage CDER.[12] The Center for Device and Radiological Health is implementing similar patient-centered approaches, and is also expected to strengthen requirements in the Medical Device User Fee Act (MDUFA) IV reauthorization.

In September 2015, the FDA announced the first Patient Engagement Advisory Committee (PEAC). The group will provide advice to the FDA Commissioner on a range of complex issues relating to medical devices, the regulation of devices, and their use by patients. It is designed to provide the agency with opportunities to obtain expertise on various patient-related topics, with the goal of improving communication of benefits and risks and increasing integration of patient perspectives into the regulatory process.[13]

Additional impetus for patient-centric research comes from the 21st Century Cures Act, which broadens the type of data that may be used for drug/device approvals from randomized clinical trial data alone to observational studies, registries and therapeutic use. The law passed the House in 2015 and is under consideration in the Senate.[14]

Table 2: Government Mandated Patient Centricity

Government Intervention in Rare Disease	Impact
PDUFA (Prescription Drug User Fee Act)	Expanded patient perspectives in regulatory decision-making
MDUFA (Medical Device User Fee Act)	Strengthened the patient voice in the medical device development and review process
PEAC (Patient Engagement Advisory Committee)	Increased integration of patient perspectives into the regulatory process
21st Century Cares Act (proposed)	Provided incentive to create safe and effective treatments for rare disease patients

patient engagement, rare diseases, and pharma

"[Patient engagement] is about truly engaging patients in a meaningful way so that patients can inform the work we are doing within the organization. Many people also think about this in terms of market research—but this is about so much more. ***It's about actively listening—not just around a product—but for what it is that patients need.*** It entails using social media; talking to individual patients; working with patient advocacy groups; and making sure that we gain patient input to understand their needs." (emphasis added)

– Anne Beal, MD. Chief Patient Office, Sanofi.[15]

Patient engagement has been called the "blockbuster drug" of the 21st century.[16] No longer content to be bystanders in their own medical journey, today's patients, particularly those with rare diseases, demand an interactive experience with the healthcare system and a voice in the development of management strategies as well as new treatments.[16-19]

Patients, especially in the rare disease community, crave this interaction with industry, says Fisher-Vance. "It means that pharma, which has a million other more common diseases to focus on, are taking an interest in us. They are acknowledging that we exist and are open to learning about our experiences and the nuances of this disease." Whether through research, patient education, or continuing education for healthcare professionals, she said, "it's the fact that they're showing interest in us" that is so important.

Industry recognizes that its approach to orphan-drug development differs from the development of drugs for larger populations. As one senior rare pharma industry executive noted: " . . . looking at the patient in a holistic 360 degree, 24/7 view to provide solutions not only with the disease but also access to drugs, transportation to trials, and genetic counseling are just a few examples of how industry can work better with the rare disease community."

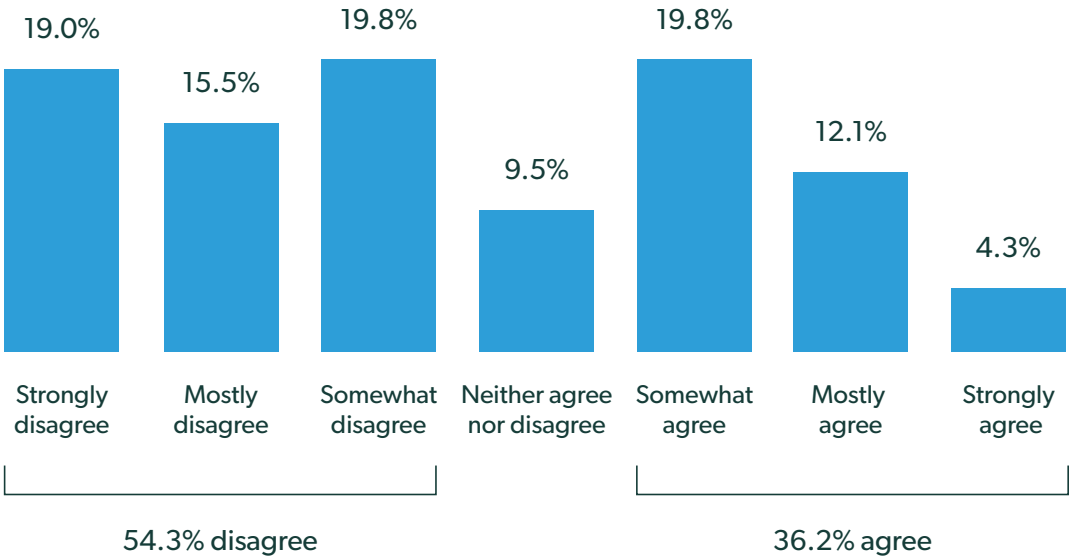
Engaging with the rare disease community also provides pharma with an opportunity to build trust with current and future patients. This is particularly important today when the industry has come under attack for a variety of issues, including drug pricing. Given that many orphan drugs carry high price tags, creating a community before a high-cost drug launches could mitigate potential backlash once the drug becomes available.

"As long as companies intensify their patient engagement efforts with transparency, authenticity and compassion, engaged patients will want to work with companies. Engaged patients will even forgive the occasional misstep. What they won't forgive, though, is not talking to them at all."

– Mahoney S. All grown up: Patient engagement comes of age. Medical Marketing & Media. June 2015.

Yet a 2015 survey of 116 patients, caregivers, and healthcare professionals found that less than 10 percent felt that pharmaceutical companies understood the needs of patients and did everything possible to address them. More than 50 percent felt that pharma was not working collaboratively with patients and patient leaders to improve patient engagement (Figure 4). One of the most effective ways to engage with patients, they told researchers, was to become active in an online community.[20]

Figure 4: Patients Want Collaboration with Pharma but don't feel Pharma is Engaged



WEGO Health. WEGO Health Patient Engagement Study. July 2015.

Patients appreciate the involvement. An international survey of 10,000 patients from the consulting firm Accenture found that about 60 percent would use whatever tools pharma provides. This, the researchers concluded, "provides an important opportunity for pharmaceutical companies to develop a trusting, respected relationship with patients."[21]

engaging patients through online platforms: the drug development ecosystem wins

"Our market is comprised of two main groups: key opinion leaders and patients. Having patients and clinicians residing in one place can be leveraged to assist in clinical trials, launch planning, marketing, and commercialization."

– Jeffrey Jacob, CEO and Chairman of the Board of Directors, Cancer Prevention Pharmaceuticals

Supporting patient-focused digital platforms has numerous advantages for pharmaceutical companies, particularly in the rare disease arena.

In one study, researchers created a survey to determine if social media could aid in research on including protein losing enteropathy (PLE) and plastic bronchitis (PB). They posted the survey on web for one year. They had 671 respondents, with 84 percent coming from social media sites. Basically, the survey went viral within that rare disease community.[22]

The researchers received a rich data set regarding patient disease history, risk factors, and therapy which, they noted, was not available anywhere else in the medical literature for these conditions.

the mayo clinic and rare disease research: a success story

One successful example that demonstrates the potential of an online community initiated study in rare disease comes from the Mayo Clinic, which used an online discussion board to recruit patients with a rare cardiac condition called spontaneous coronary artery dissection. Within a week of receiving IRB approval for the trial, 18 patients wanted to enroll, but the IRB approval limited enrollment to 12.

As the researchers wrote: "Our highly engaged and committed study participants, linked only via the internet, demonstrated levels of sophistication and specificity in their patient-initiated researcher questions that were on par with those developed by formally organized groups."[23]

In addition, support for online engagement provides industry with the opportunity to be involved in the patient journey early –before there is a product to sell. As Accenture noted in a report on patient engagement: "Pharmaceutical companies are missing a significant opportunity to provide services to patients prior to beginning treatment. This is when patients' greatest unmet need, and the opportunity for education and engagement, is highest."[21]

Other benefits for pharma companies that support online multi-stakeholder communities include:

Improved patient engagement. Pharmaceutical companies have the opportunity to engage directly with future and current patients in a safe, compliant, anonymous environment that encourages patients to share their experiences.

Improved adherence. Online communities provide an important avenue to improve patient adherence to therapy. Patients can share challenges in taking the drugs, receive advice and support, engage with interactive tools and smartphone apps, and identify opportunities to manage adverse effects.

Commercialization shift. The community may become the de facto sales force. Word of mouth improves sales more than any other form of marketing; patients trust others with their same disease more than they trust any direct-to-consumer ad. Patients want to share what they've learned about a treatment, thus "adding value" through dialogue.

In addition, there are always influencers within forums who, with just a single posting, can affect the action of numerous others. A study from Kantar Health and PharmaPhorum found 30 "citizen experts" in the areas of diabetes or cancer directly influenced 820,000 people every month through their online interactions.[24] Influencers can also bring in trial participants by describing their own experiences.

Competitive intelligence. Patients enrolled in online forums share information about adverse and beneficial effects of treatment, providing an additional data set on patient experiences as well as information to assess the potential of new drugs.

Market research. An online forum provides an important opportunity for pharma to understand what patients view as most valuable with treatments and integrate those insights into their future research and marketing plans. They can also identify real patient language to use in marketing materials.[25]

"As a small company with an orphan drug in development, robust patient platforms provide an opportunity to commercialize the drug without having 100 sales people…Plus, I can communicate directly with the market – patients and clinicians. In addition, patients are already educated because they've been part of the process. I believe that can enable faster uptake after regulatory agencies approve a medication."

– Jeffrey Jacob, CEO and Chairman of the Board of Directors, Cancer Prevention Pharmaceuticals

Return-on-investment (ROI) data. The ROI of an online rare disease community ranges from the information the community provides to the actual dollars saved on research, via faster recruitment and better designed trials, and earned through sales and improved adherence.

Information dissemination. Engaging directly with patients and caregivers in the rare disease community and building trust enables industry to share information and prevent misinformation.

gamification

Gamification is defined as the integration of game-related components (prizes, challenges) in a non-game setting designed to motivate behavior. In health care, it has been used to improve adherence, encourage lifestyle changes, or provide education.

Although it has one of the highest impacts on healthcare outcomes, it is one of the least-used digital tools for engaging patients.[26]

Gamification provides a unique opportunity to engage rare disease patients and their caregivers more fully in online communities. For instance, they could earn badges for posting in the public forum; completing surveys; sharing information.

pharma and patients online together: facing fears

"Patients are online sharing experiences, perspectives, and asking questions. For a pharmaceutical manufacturer that wants to be patient-engaged, it's difficult to do that if you're not somehow visible and present with social media."

– Murray Aitken, senior vice president of IMS Health. In: Hughes V. Social storm. Nature Biotech. 2015;33(1):14-17.

When it comes to online interactions with patients, pharmaceutical companies have two main concerns: complying with FDA requirements around user-generated content and adverse event reporting.

User-Generated Content (UGC). The pharmaceutical industry has come late to the social media world, citing concerns about regulatory issues and risk as part of their reluctance to interact directly with patients online.[27] The FDA's April 2, 2009 warning letters in the area combined with years of delayed social media guidance kept the industry from venturing into the space even for nonpromotional activities. Today, just half of the 50 largest pharmaceutical companies actively engage in social media,[27] and many are limited to a one-way conversation or limit topics to non-product, disease information and corporate matters.

In January 2014, the FDA finally released a heavily anticipated draft guidance regarding some issues related to approved pharmaceutical and device products in social media, including responsibility for user-generated content.[28]

The guidance, which has yet to be finalized, states that the agency will not "ordinarily view [user-generated content] on firm-owned or firm-controlled venues such as blogs, message boards, and chat rooms as promotional content. . . as long as the user has no affiliation with the firm and the firm had no influence on the user-generated content."[28]

After years of waiting, it appears that the FDA has given industry the green light to meaningful two-way patient engagement vehicles. The conversation can start pre-approval when disease education is permitted to drive awareness, then continue post-approval as long as the company remains in compliance regarding funding and influence over the site. In fact, several legal experts conclude that supporting nonbranded, online sites for patient communities is no different than providing unrestricted educational grants to organizations that drive disease awareness efforts.

Adverse Event Reporting. A separate but related concern is that if patients discuss adverse events pharmaceutical companies must report them to the FDA. While tracking comments on adverse events on Facebook and Twitter might be challenging, a closed social network using natural language software monitoring can flag such comments, significantly improving pharmacovigilance efforts.

Regardless, comments that would require ADR reporting are rare. An analysis of 500 healthcare-related messages posted online across multiple diseases found just one message that met FDA requirements for reporting adverse effects, and just 11 percent contained patient identifying information at all.[29]

collaborative and dedicated online communities are here to stay

Research into treatments for rare diseases is an extremely robust area in the biopharmaceutical industry. Incentives for research and development of these drugs coupled with a supportable business model ensures continued expansion over the next decade.

The rare disease community tends to be more active in its efforts to learn about their disease and identify potential therapies. Quite often, that activity occurs online, with heavy reliance on groups and websites. This activist combination makes the community an ideal partner for pharma in its search for new therapies.

As the evidence shows, an engaged rare disease community can provide access to patients for clinical trial enrollment; valuable information about the disease state, including clinical and nonclinical areas; and opportunities to cultivate relationships with the patients who will ultimately use new products.

Illustration 2: Working in concert - stakeholder collaboration in rare disease communities

Achieving greater and more effective patient engagement, however, requires that pharmaceutical and device companies partner with, and listen to, patients. An important opportunity lies in multi-stakeholder online communities that address the unmet needs patients with rare diseases encounter, including emotional support, knowledge, and clinical trial tools. This, in turn, will contribute to a company's commercial success – both financially and socially.

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