blue matter
RARE DISEASES

Addressing the Special Commercial Challenges in Rare Diseases

White Paper

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Biopharmaceutical companies marketing products to treat rare diseases face a range of unique commercial challenges. This paper outlines those challenges, explains their implications for commercial decision makers, and provides frameworks for overcoming challenges and achieving success.

Addressing the Special Commercial Challenges in Rare Diseases

Why We Wrote This Paper

At Blue Matter, we're passionate about improving human health. In particular, we decided to focus special attention on helping biopharmaceutical companies that are battling cancer, as well as a host of rare diseases. Companies working to develop new treatments for oncology and rare disease patients deserve all the help they can get. That's why we've built specialized capabilities in both areas.

This paper outlines the special commercial challenges facing rare disease therapies. It also offers some approaches for overcoming them. The challenges highlighted here are those that were listed time and again in conversations that our team has had with decision makers in rare disease companies. They are:

1. Finding Patients

2. Leveraging Centers of Excellence and Referral Networks

3. Demonstrating Product Value

4. Organizing to Support the "High-Touch" Rare Disease Business Model

Introduction to Rare Diseases

In the European Union, a disease is defined as rare when it affects fewer than five in 10,000 people. In the United States, the definition is similar: fewer than seven in 10,000 people.[1] For those affected by rare diseases—and the physicians who treat them—the official definition of "rare" is merely academic. Of course, they're far more concerned with diagnosis and treatment, often in situations where support and resources are limited.

While rare diseases (RDs) are individually rare, there is a huge number of them. More than 7,000 diseases are classified as rare. The vast majority of them—about 80%—are genetic, can be life-threatening, and chronically affect people's lives from early to late life.

Rare diseases typically do not result from any lifestyle choices made by the patient or from any controllable environmental factors.[2] This contrasts with some of the most common human diseases such as many cardiovascular, metabolic, or oncologic disorders.

Even though there are 7,000 rare diseases, about 80% of all RD patients are affected by a much shorter list of only 350.[3] Due to the mostly genetic nature of RDs, 75% of all RDs affect children and can be life-threatening.[4] About a third of affected children will not live to their fifth birthday.[5] In fact, RDs cause 35% of deaths in the first year of life.[6]

Incentivized by government and regulatory actions, biopharmaceutical companies are increasingly attracted by RDs, and realize the very large unmet needs associated with them. Currently, more than 500 RD drugs are in development.[7]

In 2017, the worldwide market for RD (or orphan) drug sales was $124 billion (US). By 2022, that figure is expected to climb to $209 billion.[8] Clearly, the needs and opportunities are great, but RDs are different, and those differences bring challenges for pharmaceutical and biotech companies.

Why Rare Diseases Are Different

Each rare disease brings its own individual challenges. However, they all share some attributes in common that companies must consider when developing and marketing products in the space.

Low Patient Numbers

As one might imagine, rare diseases mean rare patients, and those patients are typically geographically dispersed. That makes them hard for pharmaceutical companies to recognize and to find. If a company operating in the RD space does not employ effective approaches to patient finding, the implications can be quite serious.

For products in development, it can dramatically slow patient recruitment, extend development timelines, and delay product launch. From a commercial standpoint, the unknown epidemiology in combination with ineffective patient finding can make it difficult for decision-makers to accurately estimate the size of the market. It will also slow market uptake and prevent a product from reaching its full market potential.

In conversations with RD industry leaders, we asked what their top challenges were. Unsurprisingly, finding patients was number one on their list.

Long Journey to Diagnosis

Among physicians—both general practitioners (GPs) and even specialists—knowledge and awareness of rare diseases is usually quite limited. This has significant implications for patients and for pharmaceutical companies.

Often, patients must endure long periods of uncertainty before their conditions are diagnosed. Due to limited awareness among physicians, patients are typically misdiagnosed two to three times before they're diagnosed correctly. On average, proper diagnosis from the time of first symptoms takes about 5 years.[9]

Both misdiagnosis and the lack of a diagnosis contribute to patient suffering and a decreased quality of life.[10] Such delays result in increased disease morbidity and mortality rates. Hence, RDs are typically associated with significantly larger burdens on the patients.

Speeding the time to diagnosis is critical to improving patients' quality of life and outcomes, as well as maximizing an RD product's value. Any company with a rare disease product must deeply understand the typical "patient journey" and the patient's interactions with GPs and specialists along the way. Such an understanding will, among other things, help companies identify strategies for overcoming the awareness problem.

Few Disease Experts

True experts in any given RD are few and far between. As a result, the research focus is usually limited, diagnostic criteria are often unclear or non-existent, and treatment options are very limited.

The few experts that do exist in any given disease are highly important, and pharmaceutical companies must proactively identify and engage with them. They can help serve as a springboard for capturing and sharing information more broadly. This will help overcome the awareness problem mentioned above, resulting in speedier diagnoses, and improving the commercial prospects for the product in question.

High-Value Patients

Due to their rarity, RD patients are quite valuable to a pharmaceutical company. And while the development timeline for RD products can be accelerated, the company must usually recoup its costs—and generate a good return on investment—across a relatively small number of patients.

Consequently, the typical RD treatment costs range between $300,000 and $750,000 (US) per year.[11] Add in that the typical patient needs lifelong treatment, and the "net present value" of a single patient's treatments can easily exceed $10 million over a 25-year period.

Even though treatment options in most RDs are very limited, it's incumbent upon pharmaceutical or biotech companies to make—and support—compelling clinical and economic argu-

ments supporting coverage of any RD product. While the process for doing this is similar for all types of pharmacological therapies (rare or otherwise), it's often more difficult with RDs because of the typically small evidence base and the high costs involved. In our discussions, RD industry leaders placed market access and value demonstration as their second toughest challenge, just behind finding patients.

Complex Rare Disease Business Model

The successful RD business model is relatively complex and comprises three key elements. Below, we briefly explore each.

True Patient-Centricity

As stated earlier, the RD patient typically bears a high burden, as does the patient's family in many cases. Both patient and family become very involved in treatment decisions and exercise a significant amount of decision-making power. The most successful RD companies recognize this and understand that they must place the patient at the center of their business focus. They routinely also evaluate key decisions through the patient's perspective.

Patient-centricity in RDs also means providing a range of support services that go "beyond the pill" and that are designed to holistically ease the patient burden. Such services can include insurance access and coverage assistance, specialty pharmacy access and support, expanded access to experts, patient education, services designed to ease caregiver burden, and more. This approach can improve outcomes, build long-term relationships with patients, and generate a competitive advantage.

High-Touch Customer Model

We've established that rare disease patients are high-value from an economic standpoint. So are the prescribers who treat them, the payers who provide coverage, and other key players in the prescribing and delivery of RD medications.

Those key customers justify a "high-touch" model that delivers premium support and services to them via executive key account management. This model shows a long-term commitment to key customers. It also helps build loyalty and strengthens customer relationships.

RD Organizational Structure

To properly implement a patient-centric approach and the high-touch customer model, a biopharmaceutical company must have the proper organizational structure. The organization must be fully focused on providing patient & customer services. It must be highly competent, sized correctly, and seamlessly integrated through effective communication.

The problem is, most pharmaceutical companies are not organized to support this complex business model. In interviews, decision makers told us that developing the optimum organizational model for RDs is a "top three" challenge.

Challenge 1 – Finding Patients

As one would expect, rare diseases mean rare—and typically geographically dispersed—patients. That makes them hard to identify, and this presents significant problems for three key stakeholder groups: The patients themselves, the physicians who treat them, and the pharmaceutical companies that are working to develop new treatments.

Impacts of Patient Rarity on Key Stakeholders

Patients

The "typical" rare disease patient faces a range of obstacles before ever getting a proper diagnosis. Often, primary care physicians have limited (or no) familiarity with the patient's condition and refer the patient to a specialist after being unable to determine the cause of the patient's symptoms.

Unfortunately, the patient's journey usually does not end with the specialist. Depending on the disease, awareness among specialists can be similarly limited, and patients will often see multiple doctors on their journey to a diagnosis. It can take numerous doctors and multiple misdiagnoses and hence, a long period of time before the correct rare disease is identified.[12]

In a survey from EURORDIS documenting the delay in rare disease diagnosis, 40% of patients received an initial diagnosis and treatment that was wrong; about a fourth of patients had to wait between 5 and 30 years until the correct diagnosis had been established.[13]

Obviously, this process can be frustrating for the patient and his or her family. Frustration, however, is the least of the burden. Delays in diagnosis and proper treatment reduce the patient's quality of life and can increase morbidity and mortality. It's common sense: The more quickly a patient can be diagnosed and treated, the better off they will be.

Physicians

Patient rarity also impacts physicians. As stated earlier, general practitioners (GPs)—and even specialists—often have very low awareness of a given rare disease. This is particularly true when there are no treatments for the disease and little interest in it.

GPs are very unlikely to diagnose and treat a rare disease and will usually refer patients out to a specialist. In most cases, specialists also have limited knowledge of rare diseases. For a particularly rare disease, a specialist may only see one patient in his or her career. The specialist is often uncertain how to diagnose and may not even know to whom the patient should be referred for treatment.

Even experts in a given rare disease face challenges. Diagnostic criteria may be unclear or not fully established. Diagnostic tools and capabilities are often limited, as are treatment options. In some cases, the rare disease expert must be a bit of a trailblazer, trying to determine what is best for the patient with limited external support.

Pharmaceutical Companies

Companies that develop rare disease treatments must answer a fundamental question so they can make effective R&D investments: What is the size of the disease population? Given the rarity and relative isolation of rare disease patients, that question can be incredibly hard to answer. Very typically, the true epidemiology of a rare disease is unknown unless efforts will be made to study it more thoroughly.

When a company is unable to determine the number of patients to estimate the size of the market—and find the patients—it can cause a cascading range of challenges. These can include:

- Slow study recruitment
- Longer development timeline
- Delayed product launch
- Challenges in predicting resource requirements
- Slow commercial uptake
- Difficulty in realizing full commercial potential

Clearly, it's in everyone's best interest if pharmaceutical companies have tools and techniques at their disposal that can help them more effectively find rare disease patients.

Understanding the Patient Journey: A Key to Finding Patients

The first step in identifying patients is to understand the patient journey for a given disease. The patient journey can be defined as the typical pathway (or pathways) that patients go through from the first time they experience symptoms until they receive the correct diagnosis. By exploring the patient journey and "mapping it out," pharmaceutical decision makers can identify the key obstacles that prevent patients from being diagnosed.

During the process of mapping the patient journey, several key questions can be answered (or the pathway to an answer can become more visible). For example:

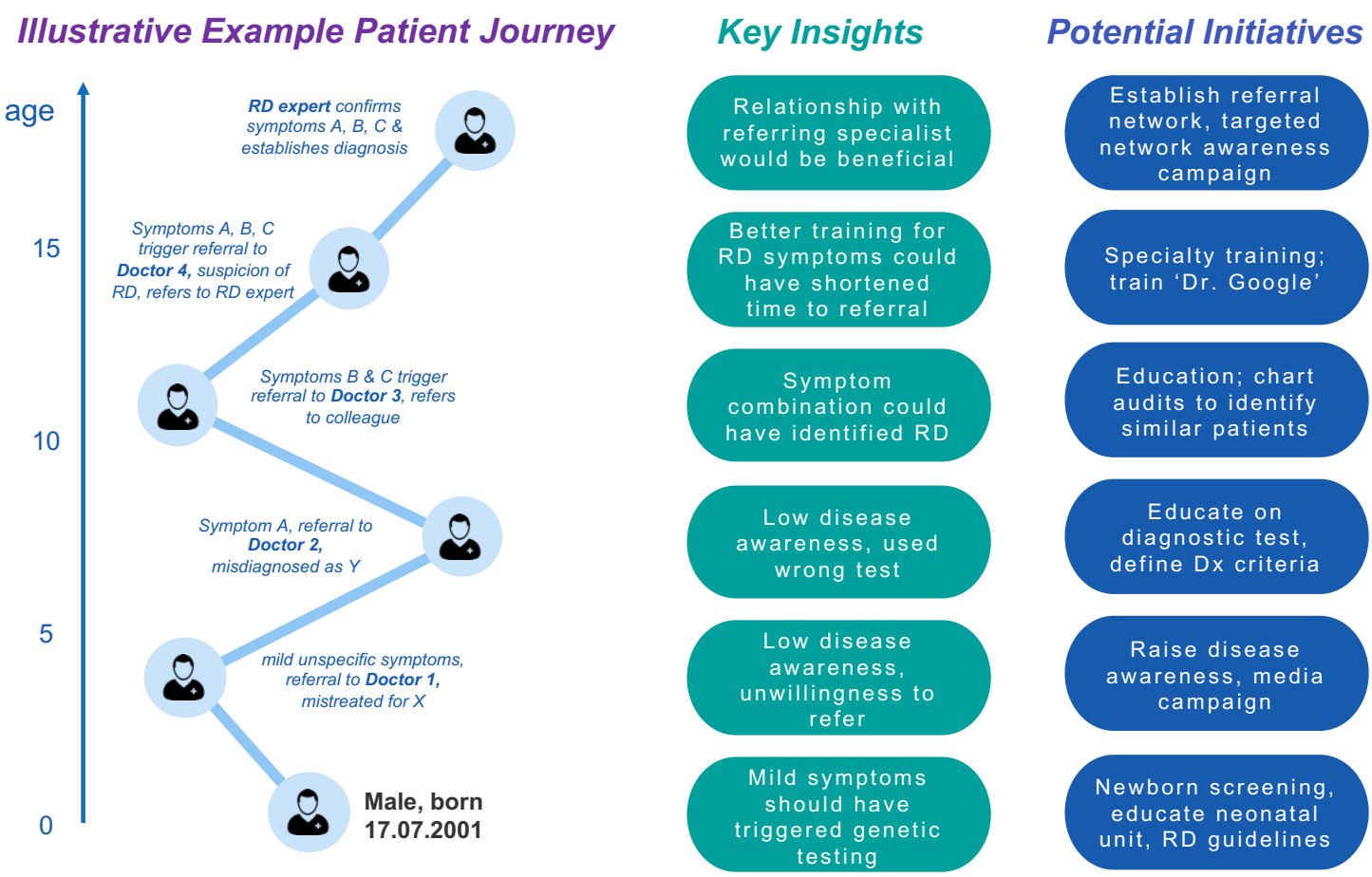
- What were the typical disease symptoms?
- What specialties were usually involved in assessing the patients?
- At what point was the RD typically first suspected?
- Who most often established the correct diagnosis?
- How long does the journey usually take and what are the typical milestones?
- Where might we find undiagnosed patients?
- What were the key obstacles to diagnosis?

Mapping the patient journey can be a complex process that involves leveraging a range of resources and techniques. These can include:

- Secondary research (likely of limited value due to disease rarity)
- Primary research with patients / caregivers and patient advocacy groups (interviews or focus groups)
- Patient chart audits
- Review of patient databases or registries (often working with RD patient organizations)

Once the patient journey is mapped out, it becomes easier for decision makers to identify key points along the journey where interventions might make a positive difference in identifying patients more quickly and accelerating the time to proper diagnosis. Figure 1 shows a simplified example to illustrate this concept.

Figure 1



Examples of Patient Finding Strategies

While no two situations are identical, there are a range of interventions that pharmaceutical companies can use to find rare disease patients, more accurately size their markets, and help get treatments to patients. Some of these are briefly described below.

Centers of Excellence

Centers of Excellence (COEs) bring together multidisciplinary expertise in one place, serving as a locus for patient care, knowledge, and research in a disease state. They address the challenge of experts in a specific rare disease—or group of related rare diseases—being "too few and far between." COEs can enhance their effectiveness by collaborating with referring networks of healthcare providers and by educating physicians about how to suspect, identify, and properly refer patients.

COEs and effective referral networks can represent a key strategy for patient identification. A pharmaceutical company operating in a rare disease market must identify the relevant COEs and develop a plan for engaging with them effectively. In cases where no COE exists, it may be possible to help establish one.

Awareness and Educational Campaigns

As mentioned, many rare diseases can go undiagnosed for years because patients and physicians fail to make the connection between the symptoms—or combinations of symptoms—and the disease itself. Awareness campaigns can raise disease awareness and educate patients, their families, and physicians about the symptoms and how to recognize them.

Patient-directed campaigns, typically using social media, disease awareness days, and advertising efforts can certainly help identify individual patients. This usually happens when parents, relatives, or other individuals are exposed to the campaign and make the connection between the symptoms described and a particular patient.

Over time, awareness campaigns—and physician-directed educational efforts—work to inform both physicians and patients. They raise general disease awareness and can make the entire referral and diagnosis process

far more efficient.

Some examples of these types of outreach efforts include International Gaucher Day, as well as various awareness campaigns and an educational website for Hunter syndrome supported by Shire Pharmaceuticals.

Innovative Information Technology Solutions

With some rare diseases, the creative use of IT solutions can be used to aid physicians in identifying and diagnosing patients. As an example, computer-based algorithms such as IBM's Watson are being used to augment and dramatically shorten the time-consuming process of rare disease diagnosis.

As another example, sufferers of DiGeorge syndrome and some other rare diseases will often exhibit specific phenotypic features, such as facial dysmorphologies, that can be identified by facial recognition software.

While the specific application of IT solutions will vary by disease state, it's clear that smart-phone apps, artificial intelligence, and similar tools can represent valuable additions to the diagnostic armamentarium.

Bringing It All Together

To succeed in a rare disease market, a pharmaceutical company must become adept at finding patients. Often, that means developing educational materials, diagnostic tools, and other solutions to help patients and physicians more quickly recognize symptoms and associate them with the disease.

Doing this effectively requires a process that typically includes the following steps:

1. **Analyze**: In this first step, it's critical to understand the drivers for—and barriers to—diagnosis and patient origination. Mapping the patient journey is core to developing that understanding.
2. **Identify Options**: Once the patient journey is mapped, decision makers can identify key leverage points along the way that might be ripe for intervention. After identifying those leverage points, the team must get creative about brainstorming and prioritizing potential strategies.
3. **Test**: Before committing to any strategy at scale, it's wise to pilot it in selected areas and evaluate the results. This will help identify those strategies that are most likely to work on a larger scale, as well as uncover needed refinements.
4. **Refine**: The pilot process will expose gaps and opportunities for improvement. Before a full-scale implementation, it's important to address those gaps and issues.
5. **Implement**: Once the prioritized strategies and tactics have been pressure-tested and refined, they can be implemented at full scale. To ensure they deliver the desired results, the company must monitor and evaluate them on an ongoing basis.

Finding patients is critical for any company operating in a rare disease market. In fact, when we asked commercial decision makers about their challenges in rare diseases, finding patients was top on their list. To properly address this challenge, pharmaceutical companies must use a combination of process discipline and creative thinking.

Challenge 2 – Leveraging Centers of Excellence & Referral Networks

In rare diseases, Centers of Excellence (COEs) and reference networks can be highly valuable for physicians, as well as life-saving for patients. Without them, physicians have extremely limited options for accessing specialized knowledge and expertise, and more patients are likely to be "lost" in the system, not receiving the high-quality care they badly need.

Likewise, without COEs and reference networks, pharmaceutical companies are at a distinct disadvantage trying to get therapies to patients. Therefore, they should factor heavily in the commercial strategy for any RD product.

Centers of Excellence and Reference Networks: Definition and Benefits

As noted previously, RD patients often face significant obstacles on their journeys to diagnosis and treatment. Primary care physicians have limited (or no) familiarity with a patient's condition, and often refer the patient to a specialist after being unable to make a diagnosis.

Too often, even specialists are unable to help as they are unfamiliar with a particular rare disease. Also, with many rare diseases, neither reliable diagnostic tools nor clear treatment paradigms have been developed. The COE and reference network concepts have been established to address this situation.

Centers of Excellence

In broad terms, COEs are physical expert structures that combine and coordinate a wide range of services to provide multidisciplinary expertise and specialized care for patients suffering from a given rare disease (or a related group of diseases). A COE acts as a locus of knowledge, research, treatment, and services in the disease state. COEs often serve a given "catchment area" on a regional, national, or international level.

One key attribute of COEs is that they provide a multidisciplinary perspective and care. Providing proper treatment in rare and complex diseases typically requires a diverse range of expertise. COEs bring these resources together, including:

- Disease experts, clinicians, and nurses
- Diagnostic experts
- Researchers
- Genetic counselors
- Social services
- Patient advocates

While there are no universal standards for what makes a rare disease COE, various groups and agencies have developed standards or guidelines. For example, the UK Plan for Rare Diseases outlines a range of characteristics that COEs should have. These include:

- Coordinated care
- Adequate caseload for expertise
- Not dependent on a single clinician
- Able to transition from children's to adult's services
- Actively engaged in research[14]

The European Union Committee of Experts on Rare Diseases (EUCERD) issued a more robust and detailed set of recommendations that follow the same line of thinking.[15] In addition, patient advocacy groups will sometimes develop guidelines for COEs in the diseases on which they focus.

Incidentally, EUCERD (now the EU Commission Expert Group on Rare Diseases), in collaboration EURODIS, has mandated that EU member states generate national action plans for creating rare disease "Centres of Expertise" throughout the continent. As a result, a growing number of COEs are being established. Currently, there is no parallel effort in the United States.

European Reference Networks (ERNs)

More recently, the European Commission has launched the formation of ERNs for rare and complex diseases. ERNs are "virtual networks involving healthcare providers across Europe. They aim to tackle complex or rare diseases and conditions that require highly specialized treatment and concentration of knowledge and resources."[16] The concept is similar to COEs but is more focused on networking together experts across a wide area, rather than physically co-locating them. An ERN is basically a linked supranational network of COEs.

The first ERNs were launched in March of 2017. At their inception, the networks comprised more than 900 specialized healthcare units located in 313 hospitals across 25 member states (plus Norway).[17] The 24 ERNs work across a range of disease areas or themes, including bone disorders, neuromuscular diseases, rare adult cancers, pediatric cancers, and others.[18]

These networks share information, convene virtual advisory boards of medical specialists across different disciplines, and work to provide patients with the best care possible. A dedicated information technology (IT) platform and telemedicine tools are key to helping the ERNs operate.[19]

Importance to Biopharmaceutical Companies

It's clear that COEs and reference networks are beneficial to patients and the physicians who treat them. But what about the biopharmaceutical companies who produce RD therapies?

COEs and reference networks can play a critical role in successful RD product commercialization. For one, they are vital in identifying patients and in securing proper diagnoses. They act as referral centers for patients at the end of the patient funnel.

COEs house key opinion leaders and become key points of contact for the company, housing a range of brand advocates and champions (assuming the company interacts with the COEs in a helpful and value-added manner). As long as the relationships are managed properly, COEs can become a company's hubs for R&D and commercial activities.

Currently, there is no formal way for a company to interact with the ERNs. However, legal entities are being set up to provide companies with a potential entry point to interact with the ERNs in the future.[20] This will provide an important future opportunity for biopharmaceutical companies to engage with the network of COEs as part of the ERNs.

Building a COE Strategy

Any RD product team should factor COEs into its commercial strategy. Doing that effectively requires a disci-

plined process, combined with some creativity.

Understand Existing COEs and Networks

When developing a COE strategy, planners must first understand the existing COEs and associated networks in the disease area. To develop this understanding, pharma companies must ask and answer a range of key questions, including:

- Who are the key experts in the rare disease?
- Where is the existing expertise located?
- What COEs, treatment centers, or ERNs currently exist for the disease?
- What existing COEs could integrate the rare disease?
- What are the existing standards defining COEs?
- What are the gaps (geographic, expertise, or otherwise)?
- What are the referring specialties and is a referral network established?
- What is the competitive situation?

The key methods and tools for answering these questions can include:

- Key Opinion Leader (KOL) mapping will identify the relevant experts in the field.
- Geographic expertise mapping will show the geographic distribution of the relevant research, clinical, and disease experts.
- COE maps and capability analyses will show where existing COEs are located, as well as their relative strengths and weaknesses. This effort can also identify prospective or developing COEs.
- A gap analysis will outline the difference between the status quo and an optimal / efficient network of COEs for the disease.
- A competitive analysis will expose how other companies are engaging with or leveraging the relevant networks.

Develop the COE Blueprint for the Disease

For a given disease state, the COE blueprint can include a wide range of strategies and tactics, depending on the situation. In most cases, it involves determining the best way to engage with existing KOLs and leverage existing COEs (or networks such as ERNs).

When engaging with existing COEs, it's vital that the pharmaceutical company develop strong relationships based on providing value and building trust. A very effective way to engage is by providing early and favorable clinical experience, and by involving the COE in pivotal clinical trials, EAPs (early access programs), advisory boards, and other key strategic initiatives.

There is a range of other things that a pharmaceutical company can do in coordination with KOLs and COEs, as long as they add value and are geared toward helping the centers provide better patient care. Research grants, preceptorships, speaker programs, educational materials and tools, and so on are all possible. It really depends on what a COE needs and how creative the company can be in helping meet those needs.

Sometimes, there may not be any existing COEs, or the existing COE network may not be robust. In those cases, the pharmaceutical company may want to help create a COE or help improve a network to fill significant gaps. This is harder to do.

There have been examples where companies have driven the generation of COEs from scratch by working with specific doctors early in their careers, helping them to focus on a specific RD, supporting their research efforts, and so on. In today's environment, this is obviously more challenging than in the past, but there are things pharmaceutical companies can do by coordinating with the right KOLs, patient advocacy groups, and others. These "from scratch" initiatives typically require pilot-level implementation first, then expansion to a larger scale after various gaps and issues are addressed.

For example, Shire and Genzyme have successfully established a global network of COEs for their enzyme replacement therapies. These COEs specialize in rare genetic enzyme storage diseases such as Hunter Syndrome, Fabry, Gaucher, and Pompé disease.

The European Reference Networks (ERNs) mentioned above are essentially linked COEs. They should also be addressed in any COE blueprint. At the moment, industry involvement is not being encouraged. However, as stated earlier, that may change as time passes. In the end, the pharmaceutical industry and the ERNs are working toward the same goal: Better patient care. Aligning the efforts of the two, in the appropriate ways, would be a positive thing.

Clearly, COEs and ERNs can provide tremendous benefits to rare disease patients. They link clinicians and others to share knowledge and best practices, advance diagnostic and treatment tools and methods, and improve patient care. COEs and ERNS are also critical to biopharmaceutical companies operating in rare diseases. It's imperative that those companies fully understand the COE / ERN environment in their disease areas and have clear plans for engaging effectively.

Challenge 3 – Demonstrating Product Value

To ensure that patients can access the therapies they urgently need, pharmaceutical companies must work with payers to secure the desired levels of market access and reimbursement. To do this, they must successfully demonstrate the value of their therapies.

In rare disease markets, however, demonstrating value is far easier said than done. While achieving the desired levels of access and reimbursement is never easy, there are special challenges associated with rare diseases. Here, we outline 10 of those challenges. We'll also review their implications for pharmaceutical decision makers.

Challenges to Demonstrating Value

High Drug Costs

As stated above, RD treatments are expensive. Smaller target patient populations for RD products often force companies to price their products higher. While the total budget impact for a given RD is still small and has traditionally not been questioned, high drug prices are coming under increasing scrutiny from public and private payers.

Unclear Patient / Disease Burden

The burden of a disease is a quantitative measure of the negative impact that disease has on a patient's life. It can be measured by assessing parameters such as disease morbidity, mortality, direct and indirect financial costs, as well as other indicators. National payers and others often attempt to measure a disease's burden on the patient's quality of life, boiling it down to a monetary figure.

This helps them to determine how much to invest in treating the disease and in improving the patient's quality of life. For many RDs, the disease burden and the extent of the unmet medical need has not been adequately quantified, making it difficult for pharmaceutical companies to incorporate that information in their messaging to payers.

Unclear Natural History

The natural history of a disease is the course an untreated disease takes from its inception to its natural resolution at recovery or death. For national health systems and other payers, understanding a disease's natural history is critical for measuring its burden at various points, and for evaluating the impact of a potential treatment.

For many rare diseases, the natural history is poorly understood. This denies payers a reliable baseline for measuring the impact of a treatment, making it more difficult to determine its value.

Rare Genetic Disease Heterogeneity

Most rare diseases—about 80% are of genetic origin.[21] They are often highly complex with heterogeneous phenotypes. Three patients with mutations in the exact same gene may display very different levels of disease severity and rates of progression.

Spinal muscular atrophy (SMA) is one example. Type 1 SMA is most severe and will usually kill most of the affected infants before their fourth birthday. Type 3 on the other hand is much slower progressing with symptoms usually appearing after the first 18 months of life and many patients will live into adulthood. And yet, the mutations behind both types occur in the same gene. Hence, genetic mutations in the same gene can result in very different phenotypes.

This disease heterogeneity causes problems on several levels. For one, it makes clinical development more challenging because it's tougher to recruit homogeneous patient populations. The challenge of patient rarity is always there, but when the heterogeneity factor is added to the mix, pharmaceutical companies have a much more difficult time recruiting for the patient profiles they need.

Per the focus of this section, it also causes problems for patient access and reimbursement. Continuing with the SMA example, consider Biogen's SPINRAZA (nusinersen). This product is indicated for all patients with SMA, regardless of type. However, some national payers try to restrict treatment access to most severe cases, and some EU health care systems are particularly restrictive with SPINRAZA.

Challenging Clinical Studies

We've already mentioned that patient rarity makes clinical studies—specifically patient recruitment—more difficult. However, we'll dig a little deeper into the problem.

With a more traditional product, such as a cardiovascular medication, a pivotal Phase 3 trial might have a few thousand patients. Such a large study population in a basically homogenous disease will provide a robust base of evidence.

Now consider an ultra-orphan indication like Hunter Syndrome. Pivotal studies related to Hunter Syndrome would likely have fewer than 50 patients. Given the heterogeneity issue described earlier, patient sub-groups could number in the low single-digits!

As a result, the overall evidence base is smaller and less robust for rare disease products. This exacerbates the challenges associated with developing well-supported arguments related to a product's value.

Unclear Regulatory Path and Study Endpoints

In rare diseases with no existing treatments, the regulatory pathway is uncharted territory. Clinical study endpoints that will be relevant for patients, physicians, and payers need to be defined by the drug company that is developing the novel treatment.

Unfortunately, those companies often have few experts (healthcare providers, patient advocacy groups, etc.) to consult with regarding study design and data generation plans. In some countries, there may be no one, leaving the company to forge ahead as best it can.

Poorly Understood Epidemiology

The epidemiology of a disease involves the study of its incidence and prevalence in a given population. When a pharmaceutical company submits a product reimbursement dossier to a national payer, it must include a range of information designed to help that payer determine the disease burden, the treatment's likely impact, and the overall budget expenditure that will be required to cover the treatment. Good epidemiology data is critical to this process.

When a payer understands the patient population size and the cost of treatment, it can effectively allocate a budget for the treatment. After all, budget impact basically equals price multiplied by volume.

Unfortunately, the level of epidemiological understanding is limited for many rare diseases. Pharmaceutical companies are often placed in the position of having to make projections based on incomplete data and educated estimates that are based on smaller studies in a given geography.

If those estimates end up being wrong, then the funds budgeted by the payer might be insufficient. For example, let's assume that a pharmaceutical company uses available epidemiology data to successfully argue that a payer should allocate a certain level of budget for its product. Then assume that the company's disease awareness and patient finding campaigns are more successful than it had anticipated.

As usage of the product increases beyond expectations, the payer may quickly approach its allocated budget. In countries that utilize budget caps, that means that the price will need to be cut or some patients will need to be denied coverage. This sub-optimal result could have been avoided if better data had been available. Unfortunately, better data is often not available.

Competition

Increasingly, multiple competitors are developing treatments in rare diseases that would commercially only have space for a very limited number of players. The added focus on rare disease research will be a great positive for patients, but it's increasing the competition for those companies operating in the space.

Shire, Genzyme / Sanofi, and others are developing or marketing products for Fabry and Gaucher disease. In Duchenne muscular dystrophy, competitors include Sarepta, Roche, Pfizer, and others. Returning to our SMA example, Novartis / AveXis and Roche are developing products, while Biogen's SPINRAZA is the current standard of care.

That's a lot of leading companies competing in some relatively small market spaces. All these future comparators will impose a further hurdle to developing robust payer evidence, and payers may even request comparative data.

Complex Mechanisms of Action (MOAs)

Rare disease assets often have complex and novel MOAs. These may be hard to explain to payers, though this obstacle is certainly not the most difficult one facing pharmaceutical companies.

HTA and CE Methodologies Not Suited for Rare Diseases

Health technology assessment (HTAs) and cost-effectiveness (CE) evaluations are systematic evaluations of a health technology's impact, both direct and indirect. HTA/CE evaluations are used by a number of cost-conscious countries, notably by the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) in the United Kingdom, to inform reimbursement and coverage decisions.

A key metric used in HTA/CE evaluations is the quality-adjusted life year (QALY), a generic measure of disease

burden, including both the quality of life as well as the quantity of life lived. A year of life in perfect health basically equates to one QALY. As one might expect, being dead is good for exactly zero QALYs. A treatment's value can be estimated by assigning a value to a QALY (or some fraction thereof), then determining how the treatment alters the QALY score.

In the past, NICE has applied a standard threshold of £20,000 to £30,000 for each QALY gained. With drug prices that far exceed these thresholds, it's clear that for many rare diseases, the QALY and existing metrics are not sufficient for evaluating a product's value. Some companies have advocated novel frameworks for determining pharmacoeconomic value. They must lobby national health services to accept those frameworks.

Implications for Pharmaceutical Companies

Novel rare disease treatments must address clear unmet needs. Companies must develop robust clinical data across the largest spectrum of patients possible (different age groups, disease type and severity populations, etc.). They must also formulate powerful value stories—backed by sound pharmacoeconomic data—to ensure the appropriate levels of coverage. As they work to do all that, they should keep the following thoughts in mind.

Establish the Natural History of the Disease (NHoD)

As stated earlier, the natural history of many rare diseases is poorly understood. Companies should make a significant effort to understand the natural history of the disease(s) they are addressing. Disease registries and NHoD studies may be required to help define optimal study populations, clinical study endpoints, as well as the patient disease burden.

Establish Patient Burden

Related to establishing the natural history of disease, companies must also work to more fully understand and fully quantify all aspects of the patient disease burden. Partnering with patients, patient advocacy groups (PAGs), and others will help with this effort, enabling the company to build an important part of the payer value story.

Engage Early with Patients and PAGs

While establishing disease burden is important, there are other reasons to engage early with patients and PAGs. Early engagement can also inform clinical study design and endpoint development, as well as facilitate patient recruitment into clinical studies. In addition, the relationships will become even more valuable as patients and PAGs can act as advocates for patient access and funding. Early engagement and establishing trust is critical for RD companies.

Engage Early with Payers

It's almost always a good idea to engage with payers early in a drug's development cycle. With rare disease drugs, it's even more highly recommended. Early and transparent engagement with payers can help the company understand payer requirements and objectives, get input on endpoints, test and refine the value story, and educate payers about the product and its value.

Generate Epidemiology Data

Early generation of robust and credible epidemiology data is critical. In many geographies it is critical to generate country-specific data as epidemiological data from other countries may not apply and might not be accepted by payers.

Provide Early and Favorable Clinical Experience

If a novel product demonstrates good results during clinical development, companies should provide that data as quickly as possible. PAGs will be extremely interested in seeing it, and they will likely share it with relevant healthcare providers and affected patients.

Potentially, the medication could be made available even before a company starts commercializing an RD drug via an early access program (EAP). EAPs offer a unique opportunity to provide the best possible early experience with an RD drug for both patients and health care providers. Obviously, an early and favorable experience will have very positive effects for successfully launching a novel RD drug.

Generate Real World Evidence

Continuing with the point about providing early and favorable clinical experience: It's very important that the company complement clinical studies with real world evidence (RWE), either in the context of an EAP or any kind of post marketing data. To do this requires a clear plan, of which disease and treatment registries can be important parts.

Develop Effective HTA/CE Frameworks for RDs

Pharmaceutical companies should work with national payers to pioneer novel approaches for expressing the value of rare disease assets by adapting existing HTA/CE frameworks to the specific situation of RDs. As an example, NICE has recently started to fund a few drugs for ultra-rare diseases under NICE's Highly Specialised Technologies Programme and also intends to raise the threshold of the cost per QALY to £100,000 and higher. Companies will need to lobby national payers to accept novel RD-specific

frameworks to make the difficult task of demonstrating value easier in the long-run.

Create "Humanistic" Arguments for Rare Disease Funding

Value stories for RD products must be robust and well-supported from a pharmacoeconomic standpoint. However, they can be supplemented by arguments from the human perspective.

For example, most RDs are genetic conditions that have nothing to do with personal choices made by the patients. By contrast, many large disease categories, such as diabetes, cardiovascular disease, obesity, and cancer are life-style related (though not always).

RD patients are innocent victims in the truest sense of the concept and deserve to get the treatments they need. These arguments won't be enough to achieve reimbursement goals by themselves, but they can bolster well-constructed value stories.

Challenge 4 – Organizing to Support the "High-Touch" Rare Disease Business Model

We've discussed the fact that rare disease (RD) patients are quite special. The same is true for the specialists who treat them. In RD markets, these dynamics create the need for patient-centric treatment approaches and a "high-touch" business model with key customer groups. Biopharmaceutical companies operating in RD markets must ensure that they are properly organized to succeed in this patient-centric, high-touch reality.

Unfortunately, the typical organizational approach employed by many specialty pharmaceutical companies is not ideally suited to rare diseases. This can limit effectiveness and hamper a company's ability to realize maximum value from its RD assets.

Here, we define "patient centricity" and explore why RD markets require patient-centric treatment approaches. We'll also define what a "high-touch" business model is and why it's so critical for RD companies to deploy. Finally, we'll outline a process that RD companies can use to develop the optimal organizational strategy.

Patient Centricity and Why It's Important

As one might expect, a "patient centric" approach puts the patient at the center of important business and treatment decisions. It evaluates all key decisions from the patient's viewpoint and it typically involves a range of holistic "beyond the pill" services to help facilitate treatment and ease burdens on the patient and his or her family. In rare diseases, patient centricity is especially important because of a handful of factors.

One of those factors is the high disease burden. While the symptoms themselves are bad enough, it often takes years of suffering from symptoms and visiting multiple doctors before the rare disease patient is even correctly diagnosed. In fact, getting a proper diagnosis takes an average of 5 years from the time symptoms first appear.[22]

Another factor is the high cost of treatment. The typical RD treatment costs between $300,000 and $750,000 (US) per year.[23] Given the long-term nature of most RD treatments, the "net present value" of a single patient's treatment is typically quite significant.

Given the limited awareness and small number of clinical experts in any RD, the patients themselves are often the "true experts" on their diseases. As a result, they wield a significant amount of power when it comes to making treatment decisions.

All these factors combine to necessitate a patient-centric approach. Biopharmaceutical companies must take that into account—and operate accordingly—in RD markets.

Adopting a Patient-Centric Approach

What does it mean for a pharmaceutical or biotech company to adopt

a patient-centric approach? In short, it means that the company must:

- Build long-term relationships with patients and patient advocacy organizations
- Ensure that the patient's voice is heard and understood
- Integrate the patient perspective into key clinical and business decisions
- Build a holistic set of patient services designed to help facilitate treatment while easing burdens on patients and their families

This holistic, "beyond the pill" approach often involves things like:

- Comprehensive patient support services
- Counseling and support by specialized health care individuals, e.g. nurse support
- Insurance access and coverage assistance
- Financial assistance
- Specialty pharmacy access and support
- Education and training for patients and their caregivers

One example of how a pharmaceutical company has put the patient-centric approach in action is Shire Pharmaceuticals' OnePath® program. OnePath® provides personalized support services to rare disease patients and their caregivers. Various products in the Shire RD product portfolio can be paired with OnePath® support.

BioMarin RareConnections™ provides another example. According to the BioMarin website, RareConnections™ "was created to be a partner in care—providing personalized support to help overcome the difficulties of managing a serious and rare genetic disease."[24]

The High-Touch Business Model

If RD patients are special, then so are the physicians who treat them. In any given RD, there are typically few experts. The ones that do exist are incredibly valuable. Consider how valuable a rare disease specialist is who treats multiple RD patients over the course of a career. Due to the high-value nature of these clinicians, pharmaceutical companies must adopt a "high-touch" business model when dealing with them.

The high-touch model:

- Provides premium support and services to high-value customers
- Builds outstanding and long-term customer relationships and loyalties
- Shows long-term commitment to key customers

To implement this model, biopharmaceutical companies must typically consider and implement the following types of tactics and programs:

- Executive Account Management - Key accounts should be handled by highly skilled senior account teams.
- Senior Management Interactions – The company should facilitate regular and planned interactions between key customers and senior management.
- Strategic Account Planning – A fully-integrated multifunctional plan should exist to develop and effectively engage each key account.
- Strategic Key Opinion Leader Development Plans – The company should create multiple opportunities to engage with key customers in high-visibility activities such as clinical trials, research projects, publications, speaking engagements, etc.
- Fully Integrated Approach - Multifunctional teams should seamlessly interact with customers in a highly coordinated fashion.
- 'Non-Sales' Approach - Rather than traditional sales calls, interactions should always focus on providing value to the customer.

Organizing to Support Patient Centricity and the High-Touch Business Model

To succeed in an environment that demands patient centricity and a high-touch approach, a company must adopt an organizational structure that is fully focused on providing patient & customer services, is highly competent, and is properly sized. Often, this means that the organization should be relatively small and nimble.

Most successful RD companies have adopted a highly tailored und unique organizational structure. Some companies, such as BioMarin and Alexion, have focused their entire corporate structures around rare diseases. Others, such as Shire and Sanofi/Genzyme, have adopted a "hybrid" model, in which a rare disease unit is embedded within a larger specialty company.

Regardless of the approach taken, implementing a successful RD strategy requires outstanding alignment of all stakeholders and excellent cross-functional collaboration. This collaboration should be ensured by appropriate incentives, e.g. by driving timely and clear communications.

The successful RD organization often includes the following types of roles, all of which must coordinate effectively:

- Patient Support Providers - Patient case managers (mainly US), providing insurance & coverage support
- Patient 3rd Party Managers - Manage patient support through 3rd parties (mainly EU)
- Policy & Market Access Experts – Act as patient group liaisons, support payer negotiations, provide policy influence
- Patient Ambassadors - Points of contact / liaison for RD patients who navigate their treatment journeys
- Executive Account Leaders - Entrepreneurial field reps with strategic

and commercial acumen who are "patient-finding detectives"
- RD Medical Experts – "Super MSLs" with medical / strategic abilities who engage with and support RD experts

Approach to Developing the Rare Disease Organizational Strategy

Below, we'll outline a multi-step process for developing the optimal organizational strategy for a rare disease company or unit. It's important to note that every situation is different and can't always be reduced to a uniform process. However, this outline should provide a helpful guide.

Step 1: Analyzing Patient & Key Stakeholder Needs

The process should begin by developing an understanding of the key needs of each major stakeholder or stakeholder group, specifically patients, customers, and the company itself. This survey of the landscape will inform all future efforts.

Regarding patients, the company should conduct some research to answer a range of questions. These include:
- What is the typical patient profile and what are the key patient segments?
- What do patients need from the company?
- What do patients expect and need from the product?
- What is the typical patient journey and key "pain points"/unmet needs for patients?
- What kinds of services do patients want?
- What interactions with patients must take place?

For key customer groups, including physicians and others, the company should conduct similar research. Simply put, the company should substitute "patient" with "customer" and answer the same set of questions for each key customer segment.

Step 2: Define the Company and Product Aspirations

At this point, the company should turn a bit inward and ensure that it has properly articulated its mission and vision as a company, and its overall corporate strategy. This exercise should filter down to the product level, as well. It's important for the company to determine specifically what it expects from the product and articulate a strategy for meeting or exceeding those expectations.

Throughout this process, the company should build its knowledge of what competitors exist (if any) and how they are strategically approaching the market. All the while, the company should consider how its aspirations at the corporate and product levels will impact the organization that it must design and build.

Step 3: Define the Patient Centric Model

Here, the company must take what it learned in the patient analysis portion of Step 1 and translate it into an initial action plan. Specifically, it should determine what "beyond the pill" services it needs to offer patients and what providing those services will demand of the organization.

Step 4: Define the High-Touch Customer Model

The company's customer research and analysis from Step 1 heavily informs this step. For each key customer segment, the company must determine and document the customer services it wants to provide and the customer interactions it wants to generate. Clearly outlining this, segment by segment, will inform the decisions to be made in Step 5.

Step 5: Organizational Blueprint

In this step, the company takes everything it wants to do and translates it into an organizational blueprint. Specifically, planners must determine
- Which skills and competencies are needed to deliver the desired services and perform the desired tasks.
- The amount of investment and number of people required in each key area.
- Which governance structures and reporting relationships will be most effective.
- Which tools and technologies are required to support the organization.
- What incentive programs and communications processes are needed to ensure proper coordination across functions.

Once this blueprint is completed, the company can then translate needs into job descriptions and begin building its organization. As stated earlier, many companies operating in the RD space have not developed "purpose-built" RD organizations. As a result, they will have greater difficulty realizing maximum value from their RD assets. However, the process outlined above can be applied to "revamp" an existing organization and is not solely applicable to the development of a new organization.

Conclusion

Clearly, rare diseases present special challenges for patients, physicians, and caregivers. They also present special challenges for the biopharmaceutical companies that are developing new treatments for them.

While it's true that every product, market, and situation is different, we hope that this paper provides some ideas and frameworks that companies can use to make their jobs easier. Tackling rare diseases is very important to Blue Matter, and we stand ready to help.

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