

## Raising Orphans: How Pharma Can Capture Value While Treating Rare Diseases

Orphan drugs have become the pharmaceutical industry's favorite children, and are on the leading edge of the specialty trend. At a time when pharmaceutical firms are grappling with an increasingly challenging industry environment, the orphan sector offers the enticing prospect of strong growth and attractive profit margins—all while making a real impact on often devastating rare diseases. Thompson Reuters estimates that this market is already worth more than \$50 billion, and it's expected to continue growing at a pace that other sectors of the pharma industry will struggle to match.

Still, it's increasingly difficult to become a serious player in the orphan space. It's not just that the competition is heating up; commercial success is not a guarantee and the regulatory and access bars are rising. In this *Executive Insights*, we look at the changing dynamics of the orphan market and identify strategies designed to capture value within it.

### An Attractive Sector

It is estimated that there are in excess of 7,000 orphan diseases – rare conditions that affect fewer than 200,000 people per year in the U.S.<sup>1</sup> While there is significant diversity among the diseases that fulfill this criterion, there are several attributes that are common among the orphan diseases that pharmaceutical companies have traditionally chosen to target. In general, these characteristics are more likely to be found in diseases that impact fewer than

10,000 patients in the U.S., which are known as “ultra-orphan” diseases, and it is these diseases that the pharmaceutical industry usually refers to when it discusses orphan drugs.

First, orphan conditions of interest to pharma are characterized by conditions that are chronic or degenerative and thus lead to poor quality of life and/or shortened lifespans — that is to say, conditions that generate an extremely high need among patients for an effective treatment. Duchenne's muscular dystrophy, for example, leads to progressive muscle deterioration and paralysis in about 1 in 3,500 boys, resulting in an average life span of less than 30 years, and no treatments are available.

Another attribute that makes certain orphan diseases attractive to pharmaceutical companies is that effective treatments have historically been rewarded with exceptionally high prices. This precedent was established in 1992 when Genzyme's Cederase for Gaucher disease hit the market with an annual price tag per patient of around \$200,000. Since then, a high pricing strategy has become common (see Figure 1), with Alexion's Soliris for paroxysmal nocturnal hemoglobinuria (PNH) priced at approximately \$400,000 per year and uniQure's gene therapy treatment Glybera for lipoprotein lipase deficiency priced at more than \$1 million for a single treatment.

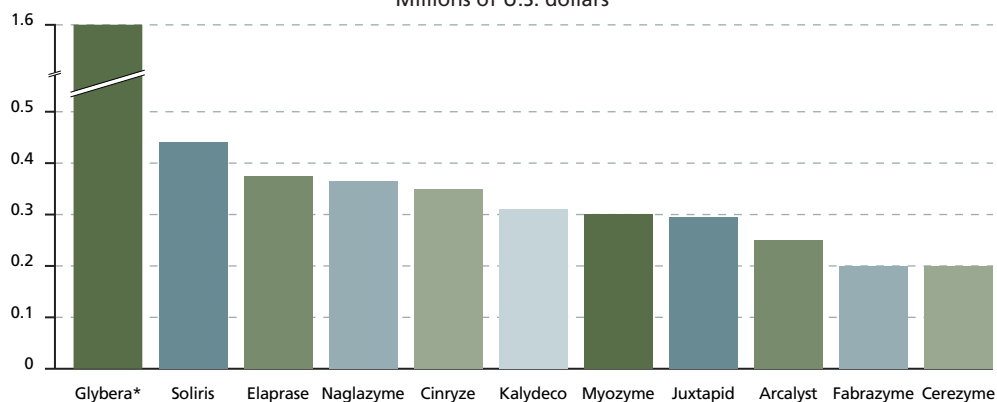
<sup>1</sup>Orphan diseases impact 1 in ~1,500 people in the U.S. In the EU and Japan orphan diseases are defined as those impacting 1 in ~2,000 and 1 in ~2,500 people, respectively.

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Third, many orphan drugs can often be supported with a targeted commercial footprint, which helps keep costs down. For example, Aegerion's Juxtapid for homozygous familial hypercholesterolemia is being supported by about 25 sales reps that focus on key specialists.

Finally, while often uncharted, the regulatory path for orphan drugs has traditionally consisted of small clinical trials given the size of the addressable populations. Shire's Elaprase, for example, was approved for Hunter syndrome after a 96-patient Phase II/III trial, a tiny sample size when compared to, say, the 20,000-patient Phase III clinical trials currently being conducted for PCSK9 mAbs, specialty drugs in their own right intended to treat hypercholesterolemia.

**Figure 1**  
Estimated U.S. annual price for select orphan drugs  
Millions of U.S. dollars



Note: \*Price for a single treatment  
Source: Forbes, L.E.K. analysis

Given these attributes, orphan drugs arguably embody the best qualities of a specialty drug from both a profit-making and human-impact perspective. It is small wonder, then, that drug manufacturers have turned to this sector to boost the bottom line, while also improving lives. Nevertheless, there are several trends that make entering an orphan drug market an increasingly challenging proposition for pharmaceutical companies (see Figure 2).

## An Increasingly Challenging Market

Despite industry enthusiasm for orphan drugs, achieving revenues for a rare disease treatment of more than \$1 billion is the exception, not the rule. In fact, only a handful of drugs have cleared this threshold and the average revenue for an orphan drug is approximately \$250 million—hardly a panacea for the ailments of the pharmaceutical industry. Depending on the growth imperatives and size of a company, achieving meaningful success with orphan drugs may require multiple products rather than a single one.

Historically, orphan markets have been mainly served by a few players. In fact, there is only one approved treatment in the U.S.

and EU for conditions such as Hunter syndrome (Elaprase), Pompe disease (Myozyme), and paroxysmal nocturnal hemoglobinuria (Soliris), even though these conditions have been treatable for more than five years, and each treatment generates revenue in excess of \$600 million. This highlights potentially substantial benefits for companies that are first to market, which may result in several years of cultivating and capturing an orphan market

with limited competition. Even in situations where new entrants emerge, they are usually limited to one or two competitors, as evidenced by Gaucher disease and Fabry disease, both of which have been historically served by drugs from Genzyme and Shire.

These levels of relatively low competition are unlikely to last. Even though developed orphan markets have been observed to peak at about \$1 billion, increasing competition looms. Indeed, the “mature” markets of Gaucher disease and Fabry disease are expected to face increasing competition from other treatment options such as oral therapies, chaperone approaches, and biosimilars that may fragment these markets without necessarily growing them.

Intensifying the competition is the fact that while orphan markets were once the domain of smaller, independent operators, big pharma companies are now positioning themselves to compete for orphan treatments in the hope of offsetting declining productivity and patent expiries to key products. Over the past few years, companies such as Pfizer and GlaxoSmithKline have established research units that specialize in rare diseases. Big Pharma has also been racing to partner with — or acquire — dedicated orphan companies. Most notably, Sanofi purchased Genzyme for \$20 billion in 2011, gaining control over its industry-leading portfolio of orphan drugs (in addition to other attractive assets). What's more, companies such as Shire, BioMarin, and Alexion, among the largest remaining free-standing players with a strong orphan presence, have been the subject of numerous acquisition rumors.

In addition to competitive considerations, the regulatory path for orphan drugs can be difficult to navigate. Orphan diseases are so rare that they are often little understood even among medical experts and regulatory agencies. As a result, the drug manufacturers must become regulatory trailblazers, equipped to engage agencies in complex technical discussions in areas where there are often no established regulatory pathways. Conducting clinical trials can also be challenging as recruiting patients may require multiple trial sites that may only enroll a couple of patients each.

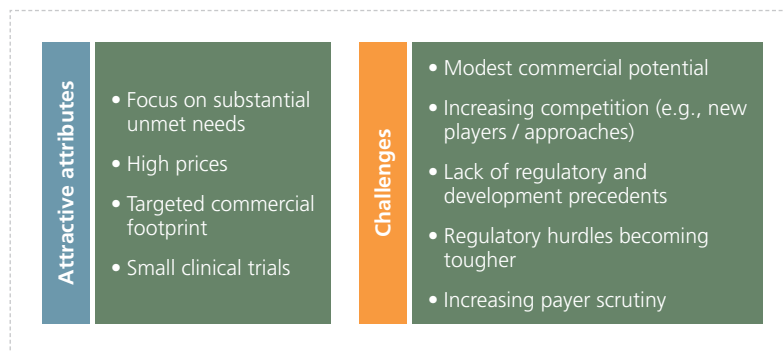
What's more, the regulatory requirements are becoming tougher. In the past, approval for treatments such as Fabrazyme were granted solely based on biomarkers such as Gb3 clearance and without a complete understanding of the broader clinical impact that the treatment would have on disease progression—an intentional gambit given the urgency and severity of the patients' clinical needs. However, such situations are likely to become rarer as the overall orphan market matures. Regu-

lators have already begun to signal that higher standards are starting to apply, as evidenced by the FDA's 2012 request of an additional clinical trial to confirm the efficacy of Pfizer's tafamidis meglumine for transthyretin familial amyloid polyneuropathy. As regulatory standards become more stringent, manufacturers of orphan drugs will likely bear higher development costs.

Finally, many companies have historically operated under the assumption that orphan designation and regulatory approval would all but guarantee market access. However, payers are starting to send signals suggesting that the days of unfettered market access to orphan drugs may be numbered. Given the

**Figure 2**

**Overview of orphans' attractive attributes and challenges**



proliferation of orphan drugs, their impact on payer budgets is no longer negligible. In response to budgetary pressure, payers have started to limit access to orphan drugs by entering into managed-entry agreements or by threatening to deny coverage outright unless prices are lowered. As such, orphan drugs that offer limited differentiation and a modest value proposition are likely to face close scrutiny from payers, as evidenced by rumors surrounding the potential placement in UnitedHealth Group's exclusion list of Procysbi, Raptor Pharmaceutical's treatment for nephropathic cystinosis.

The access environment is becoming especially challenging in the EU. For example, NICE in the UK has been assessing over the last few years whether Alexion's price for Soliris is justified, and recently requested R&D expenses for the drug as an input into its recommendation decision. Market access to orphan drugs may worsen as new competitors enter the market in both developed and emerging countries.

Given this barrage of challenges, the makers of orphan drugs cannot afford to rest on their laurels. For new and existing players alike, it's vital to understand the important shifts in the dynamics of this market. Several key strategies can position companies to navigate these challenges and succeed in an increasingly difficult environment.

## Key Strategies For Orphan Drug Makers

### 1. Focus on substantial unmet needs that are commercially accessible and addressable

As in other areas of the pharma industry, it's crucial to pick the right diseases to tackle. But the orphan sector is especially challenging, since rare diseases are not as well-known or as well-understood as more common maladies. Drug makers must have the capacity to ramp up their expertise rapidly, and also to sort through a multitude of rare diseases to select the best opportunities.

While the rationale for selecting a particular disease can vary, we have identified clinical criteria for investment in orphan disease treatments (see Figure 3).

A common theme is that companies should focus primarily on diseases with significant unmet needs, primarily targeting those that are fatal or highly debilitating. Otherwise, it's difficult to justify the level of pricing required to recoup investments. It is critical for patients to be identifiable and for interventions to take place during a window in which meaningful clinical impact can be delivered.

The goal should be to develop drugs that make a material impact on the patient's quality of life and longevity. This can be achieved by addressing key symptoms or by slowing the progression of the underlying disease pathology. Obviously, a drug that reverses the disease is ideal, but this is not necessary in cases of high unmet needs, as long as key patient outcomes can be improved relative to treatment alternatives.

### 2. Commit to a long-term strategy

Success in this sector requires focus, dedication and a long-term financial commitment. This is especially true for large companies, since they are likely seeking strong growth on what is already a large revenue base. Given the small patient populations for orphan diseases, it makes sense to develop drugs for an array of different diseases, instead of approaching the business as a one-off venture.

Smaller companies might be tempted to direct all their resources toward a single product or disease. But to become a long-term presence in the orphan market, they need a strategic vision that carries them beyond their first product. In short, for large and small companies alike, the focus should be on sustained value creation.

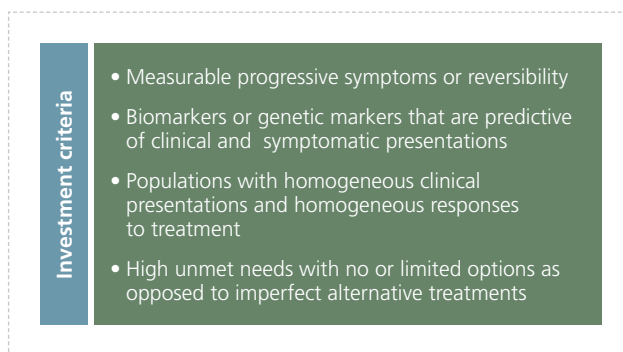
Given the lack of defined regulatory pathways, relatively modest revenue potentials, and other challenges, many orphan diseases would fail to meet the capital-allocation criteria that are typically used by biopharma companies. As such, it is important to recognize that orphan diseases need to be evaluated with

customized criteria that deviate from those used for non-orphan assets. Further, senior management must buy into this exception and become orphan-evangelists within their firm.

Building a portfolio based on multiple shots on goal can help reduce risk and create operational synergies. As an example, companies could

consider strategically pursuing diseases that are related. This is an approach that has proven to be successful in the past, as evidenced by Genzyme initially focusing on diseases that could be addressed with enzyme replacement therapy. Alternatively, synergies could also be achieved by leveraging technology platforms (e.g., chaperones, mRNA, gene therapy) or expanding a product across multiple indications (e.g., Soliris).

**Figure 3**  
Clinical investment criteria for orphan diseases



### 3. Invest holistically in the disease

To create a successful orphan treatment, it's vital to forge deep relationships with all the parties involved in the disease — from patients to physicians to payers. Rare diseases are often poorly understood, and primary care physicians and specialists can easily confuse their symptoms with other diseases. Therefore, orphan drug manufacturers should effectively lead the market by proactively engaging in physician, payer, and patient education. This requires companies to create a robust outreach program, hiring and training teams that have the expertise to deal effectively with these stakeholders. As such, it is critical to invest in a holistic infrastructure through which orphan companies can become a partner to key stakeholders.

Through this investment and other steps, companies should look to build strong alliances with patient-advocacy groups, which play a crucial role in everything from sourcing patients for clinical trials to spreading awareness of the illness and its treatment. Similarly, working with foundations can help smooth a treatment's path from research to approval, since these groups are often well-organized, vocal, and active.

Given the nature of their diseases and often high price of treatment, orphan companies often provide a higher number of services on a per patient basis than their biopharma counterparts. Far from simply touting a drug's benefits to prescribing doctors, orphan companies are often directly involved

with patients on a personal level. They may know patients on a first-name basis, know the details of their symptoms, check in on them on a periodic basis to ensure that treatment is delivering the expected results, and offer direct reimbursement support. This strengthens the ties between the company and the patient, creating a win-win situation in which the drug maker can build its market while also giving the patient much-needed guidance.

To an extent, the orphan market is becoming a victim of its own success, as it has drawn in increased competition, regulatory scrutiny, and access restrictions. As such, companies that aspire to become leaders or drive growth in the orphan space must recognize these environmental challenges as well as key operational and organizational differences from the traditional biopharma model. This can be achieved by focusing on substantial unmet needs that are commercially accessible and addressable, committing to a long-term strategy and investing holistically in the entire orphan-disease ecosystem, including patient support. Following these strategies could help companies develop a differentiated approach to orphan drugs and capture a meaningful opportunity in this market.

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