

# Established Orphan Disease Markets: Innovators Wanted

Meaningful product differentiation is required for new drugs to enjoy the rapid clinical development and commercial success that have made orphan disease markets increasingly attractive to developers of all stripes.

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- As pharmaceutical players begin their fourth decade under the Orphan Drug Act, easily addressable unexploited orphan disease markets are becoming more rare, forcing drug developers to consider established orphan markets in addition to those diseases without treatments.
- Here we evaluate the nature of competition in orphan disease markets and whether first-movers are protected from subsequent entrants by development or commercial barriers.
- New entrants in established orphan markets must bring novelty to the table to enjoy the rapid clinical development time lines, quick ramp, and pricing power associated with unexploited orphan diseases.
- As in other specialty markets, benefits flow to products able to meet substantial unmet need in orphan diseases. Drug developers able to exploit deficiencies in dosing or efficacy in the initial product, or carve out new market segments, are rewarded.

There may be thousands of orphan diseases, but some of the lowest-hanging fruit has already been picked. Drug developers are increasingly exploring orphan markets with established therapeutics and a standard of care.

This state of affairs is not surprising. The pursuit of therapeutics for orphan indications has been one of the dominant trends in drug development in recent years. In the past 20 years, medicines for rare diseases have grown to over 35% of new drugs approved by the FDA, up more than twofold from the 1990s. As traditional specialty drug markets have become increasingly crowded, large pharmaceutical companies and biotech companies alike have successfully turned previously ignored rare diseases into a robust business model. Are these first-mover products protected from competition by virtue of being in orphan markets? Here, we argue that new therapeutics in established orphan markets must differentiate themselves to succeed, similar to strategies employed in other specialty markets.

Orphan drug markets are considered to have several advantages over traditional drug markets. Benefits associated with orphan drug markets are both those derived from the Orphan Drug Act (ODA) and those that are not. The ODA created several distinct incentives for orphan drug developers, including seven years of market exclusivity, tax credits for development costs, and application fee waivers. Beyond the ODA, the coupling of well-understood etiologies and often significant unmet need drives a higher probability of clinical success, an often shorter duration of clinical development, and substantial pricing power.

Beyond these factors, orphan indications have been thought of as attractive for several strategic reasons. First, orphan indications have a track record of serving as beachheads for adjacent indications. **Novartis AG's Gleevec** (imatinib) and **Roche/Genentech Inc.'s Rituxan** (rituximab), originally launched in oncology orphan indications, have expanded to multiple indications with related pathophysiology.

Second, drugs for orphan indications may enjoy a durable first-mover advantage over subsequent entrants due to ODA-mandated exclusivity, low patient numbers, perceived barriers to drug switching, and high loyalty. This perspective has largely been driven by the sustained monopolies of pioneer orphan drugs. Until recently, **Sanofi's Genzyme Corp.** had a monopoly in Gaucher disease, a market that the company helped establish with *Cerezyme* (imiglucerase). In peripheral arterial hypertension (PAH), first-entrant *Flofan* (epoprostenol), from **GlaxoSmithKline PLC**, dominated the market for many years until **United Therapeutics Corp.'s Remodulin** (treprostinil), another PG2 analogue with much improved dosing, slowly chipped away at *Flofan's* market dominance. **Bayer AG's Prolastin** (alpha-1 antitrypsin), the first-mover in alpha-1 antitrypsin deficiency, has also continued to dominate the market despite years of sustained pressure from competitive products from **Baxter International Inc.** and **CSL Ltd.**

A vast majority of orphan indication hype has been derived from "unexploited" orphan indications. These pinnacles of orphan drug development are characterized by diseases with small patient populations for which there is no clinically meaningful standard of care, high unmet need, a quick ramp, and substantial pricing power. Many of the prominent stories of orphan drug development fall into this vein, ranging from successful single product companies such as **Alexion Pharmaceuticals Inc.**, to companies built around orphan product portfolios such as **Genzyme** and **BioMarin Pharmaceutical Inc.** However, a focus on these select companies and their markets ignores the broader picture of orphan drug development and marketing.

At 30 years post-ODA approval, we are afforded the opportunity to evaluate not only companies that have successfully built franchises in unexploited orphan diseases, but also those that have taken advantage of the experience of the first-mover to enter and exploit established orphan markets. Such markets have several potential advantages over unexploited ones. Not only are market dynamics potentially better understood due to the experience of the initial entrant, but patient groups and specialists are already engaged and mobilized, the disease biology is in some cases better understood, and genuine advances in treatment can use the

standard of care as a price floor. The appeal of established orphan markets depends on the extent by which first-movers are protected from additional entrants.

A durable first-mover advantage associated with orphan drugs can be segmented into several components. First, market exclusivity guarantees some protection from competition from similar products. Second, clinical development may be more difficult for subsequent entrants due to potential requirements for comparative trials versus the marketed agent, and problematic trial recruitment. First-mover advantage also extends after marketing approval. Patients on existing standard of care may be unlikely to switch to novel agents, resulting in a smaller population addressable by subsequent entrants. Finally, physicians and patients may be loyal to the initial drug, potentially slowing the adoption of later entrants. Here we evaluate whether first-movers in orphan markets are protected from subsequent entrants.

Starting with all drugs that have received FDA orphan designation, we have identified a basket of orphan indications with multiple therapeutic entrants. This list, tailored to minimize confounding factors such as off-label usage, allows an analysis of barriers to entry confronted by subsequent entrants. Included orphan indications range from ultra-orphan indications with under 1,000 patients globally, such as cryopyrin-associated autoinflammatory syndrome (CAPS), to diseases with greater than 5,000 patients worldwide such as Gaucher disease, to larger, more mature orphan markets such as pulmonary arterial hypertension (PAH).

### NOVELTY IS NECESSARY FOR RAPID CLINICAL DEVELOPMENT

A primary component of a durable first-mover advantage is the presence of significant clinical development barriers for later entrants. These barriers may include both difficulty in patient recruitment and higher standards for clinical trial design for later entrants. Both of these potential barriers should be reflected by comparing the clinical development time for initial and subsequent entrants. For example, a late entrant having difficulty recruiting patients and held to more stringent trials should have a longer development time than the initial mover in an orphan indication. As long as an orphan drug has the same mechanism of action

(MOA) as the initial entrant, we find that this is true. In general, subsequent entrants with the same mechanism as launched agents experience a longer clinical development time with later entrants having, on average, a 1.7 times longer clinical development time (here defined as initiation of Phase III to marketing approval) compared with the earlier entrant. (See Exhibit 1.)

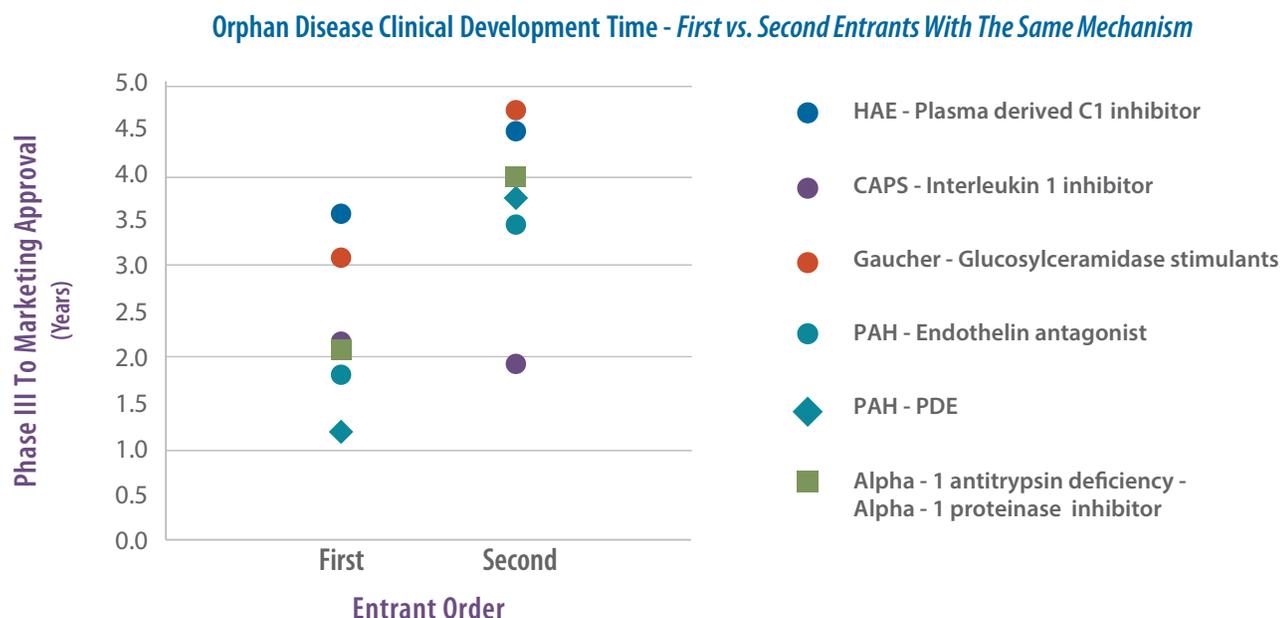
The longer development times experienced by these later entrants are driven by a small incident population available for trials and physician loyalty to the initial drug. By their very nature orphan diseases have few patients initiating treatment each year. As a result, particularly for drugs with difficulty articulating a value proposition, trial recruitment may be problematic as relatively undifferentiated agents compete with the established standard of care for available patients. If a later entrant has the same mechanism as the standard of care, the agent may be viewed as undifferentiated by physicians and patients, necessitating more stringent trials and slowing the recruitment process. **Gilead Sciences Inc.'s Cayston** (aztreonam), for example, a drug competing against the initial entrant in the antibiotic class, **Novartis' Tobi** (tobramycin), experienced a more difficult path to market. *Cayston's* clinical development was more than twice as long as *Tobi's* a decade before, with the manufacturer ultimately deciding to run a head-to-head trial against *Tobi* to encourage adoption.

Longer clinical development time is also driven by physician loyalty to the initial entrant. The *Fabry* disease market provides a case study of this dynamic. Prior to the launch of enzyme-replacement therapies such as **Genzyme's Fabrazyme** (agalsidase beta), *Fabry* disease eventually led to patient death, with average life expectancy of 40 to 50 years. With the advent of enzyme replacement therapy, the condition has become more manageable, but is still considered to be lethal. Thus, physicians have been relatively hesitant to participate in placebo-controlled trials. **Amicus Therapeutics Inc.**, the developer of *migalastat*, faced this problem in its initial Phase III studies, having substantial difficulty recruiting a relatively small number of patients for its placebo-controlled study due partially to existing enzyme replacement therapies.

However, if a subsequent entrant has a new mechanism that meets an unmet mar-

Exhibit 1

## Later Entrants With The Same Mechanism As Launched Entrants Are Disadvantaged



SOURCE: Health Advances analysis; ADIS; ClinicalTrials.gov; Pharmaprojects; Drug labels

ket need, clinical development is much less of a barrier. Due to the extant high unmet need associated with many orphan diseases, validated end points, and established patient networks, subsequent entrants coming to market with an innovative mechanism or targeting specific patient populations enjoy relatively rapid clinical development. For example, in PAH, the launches of **Actelion Pharmaceuticals Ltd.'s Tracleer** (bosentan), the first endothelin receptor antagonist, and **Pfizer Inc.'s Revatio** (sildenafil), the initial PDE-5 inhibitor entrant, were rewarded with Phase III to marketing authorization time lines of less than two years. (See Exhibit 2.) In CF, spurred by significant unmet need, initial entrants with different mechanisms than the initial marketed product, Genentech's mucolytic **Pulmozyme** (dornase alfa), have enjoyed relatively rapid clinical development times. Tobi sped through Phase III trials in under two years, and **Vertex Pharmaceuticals Inc.'s Kalydeco** (ivacaftor), a drug that acts by yet another mechanism that targets a small, genetically defined subset of the CF population, enjoyed marketing authorization less than three years after the initiation of the Phase III trial. In all these examples, the new entrants not only brought a new mechanism of action

to the table, but also positioned the new mechanism to address patient populations not optimally served by existing therapies, thus fulfilling unmet needs.

In sum, subsequent entrants face a durable barrier to entry during clinical development if they enter an orphan market with the same mechanism as already marketed products. However, drugs able to bring novelty to the table, particularly in diseases with high unmet need, such as what has been observed in PAH and CF, may enjoy the same rapid clinical trial experience as the initial player in an orphan indication. In the absence of new mechanisms, the clinical trial process serves as a durable first-mover advantage.

This advantage is also reflected in the approval criteria that the FDA applies to orphan drugs. The FDA can approve drugs based on either "conventional" definitions of effectiveness ("adequate and well-controlled studies"), under a rule of "administrative flexibility" (a formal, expressed FDA system for approval flexibility), or by a "case-by-case flexibility" (flexibility is not based on any formal FDA expression of flexibility). Due to high unmet need, a vast majority of orphan drugs examined here were approved under the more lenient "case-by-case" or "administrative

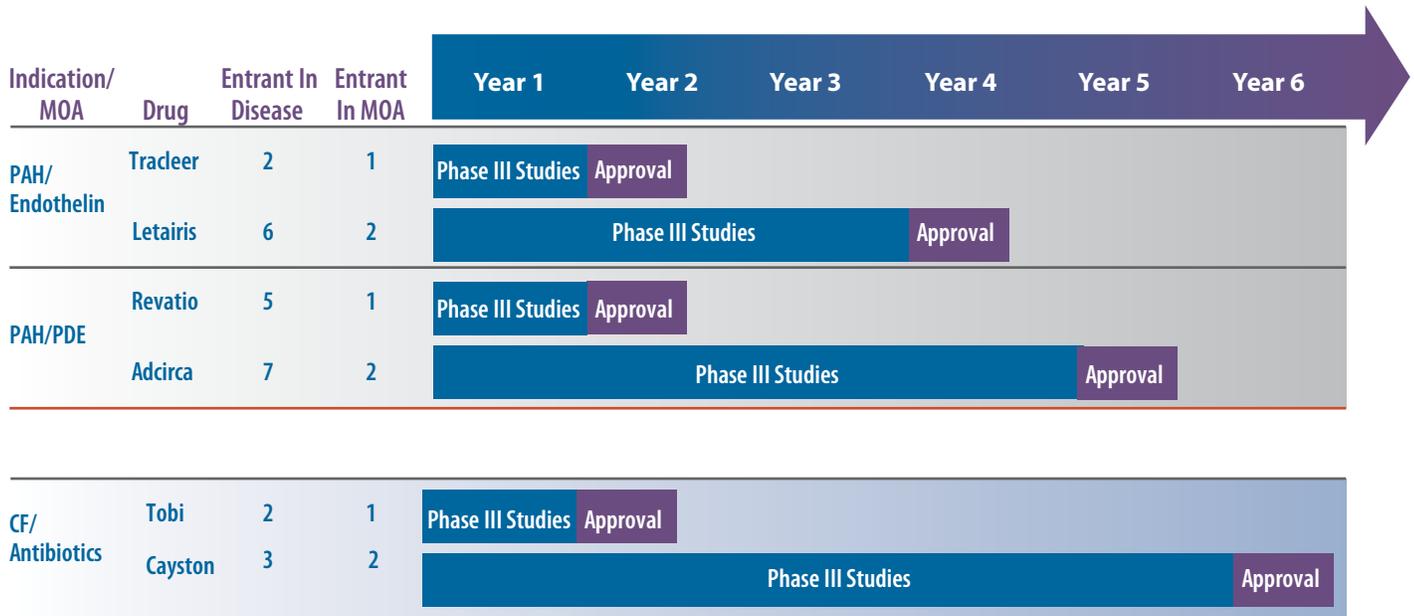
flexibility" basis. However, second-entrant products with the same MOA as marketed orphan drugs tend to drive greater FDA scrutiny. Both **Vpriv** (velaglucerase alfa), a drug from **Shire PLC** for Gaucher disease with the same MOA as initial entrant **Cerezyme** and **Novartis' Ilaris** (canakinumab), and a drug for CAPS with the same mechanism (IL-1 inhibition) as **Regeneron Pharmaceuticals Inc.'s** initial entrant **Arcalyst** (rilonacept) were considered by the FDA under "conventional" processes as opposed to approaches that emphasize greater flexibility.

### PRODUCT DIFFERENTIATION IS REQUIRED TO COMPETE IN ORPHAN MARKETS

A second major aspect of the first-mover advantage occurs after drugs are launched. As discussed above, in established orphan diseases, it may prove difficult to switch patients from existing standard of care to a newly launched drug. Patients and physicians, enamored with existing products, may be loyal to marketed products, leading to significant stickiness. Assuming similar pricing strategies between initial and subsequent entrants, both of these aspects should be reflected in the ramp and market share

Exhibit 2

**Novelty Buys Expedited Clinical Development**



SOURCE: Health Advances analysis; ADIS; ClinicalTrials.gov; Drug labels

in subsequent drug launches.

To ensure comparisons across our basket of orphan indications, we screened for indications for which multiple entrants utilized similar pricing strategies. For the markets examined, it was relatively uncommon for second entrant products to dominate the market two years following launch. In both Gaucher disease and acromegaly the first to market drug still had the majority of market share following the launch of subsequent products. In the genetic immune disorder hereditary angioedema, another market with multiple entrants, Viropharma’s *Cinryze* (human C-1 esterase inhibitor), the initial entrant, also continued to dominate the market two years following the launch of competitor products. *Cinryze*’s edge over subsequent entrants is solidified by a broad label allowing for prophylactic use compared with competitors limited to acute disease episodes, and eventually led to Viropharma’s \$4.2 billion acquisition by Shire in 2013.

Much like larger specialty markets, the key for subsequent entrants in orphan indications is product differentiation. Differentiated second entrants with the same mechanism as the initial entrant are able to rapidly capture the orphan indication despite their late entry.

(See Exhibit 3.) Irrespective of orphan disease prevalence, subsequent entrants are able to dominate orphan disease markets if they make clinically meaningful contributions to efficacy, dosing, or side-effect profile. Similar to other drug markets, a favorable convenience profile, leading to greater patient quality of life and, ultimately, improved efficacy, can serve as an important differentiator. The second entrant in an already established MOA, *Ilaris*, was able to dominate the CAPS market in three years as a result of improved dosing. In the prostanoid MOA in PAH, *Remodulin*, a drug with a superior convenience profile, has slowly replaced *Flolan* as the preferred prostanoid.

Subsequent entrants with a different mechanism than marketed products find success by applying strategies successful in larger specialty markets. Much like in other specialty markets, subsequent entrants able to be used in combination with the standard of care enjoy a quick ramp due to an already identified patient and prescriber population. Hence, *Tobi* hitched onto a centralized prescriber base, high CF diagnosis rates, and *Pulmozyme* use to sustain 20% annual growth rates several years post launch.

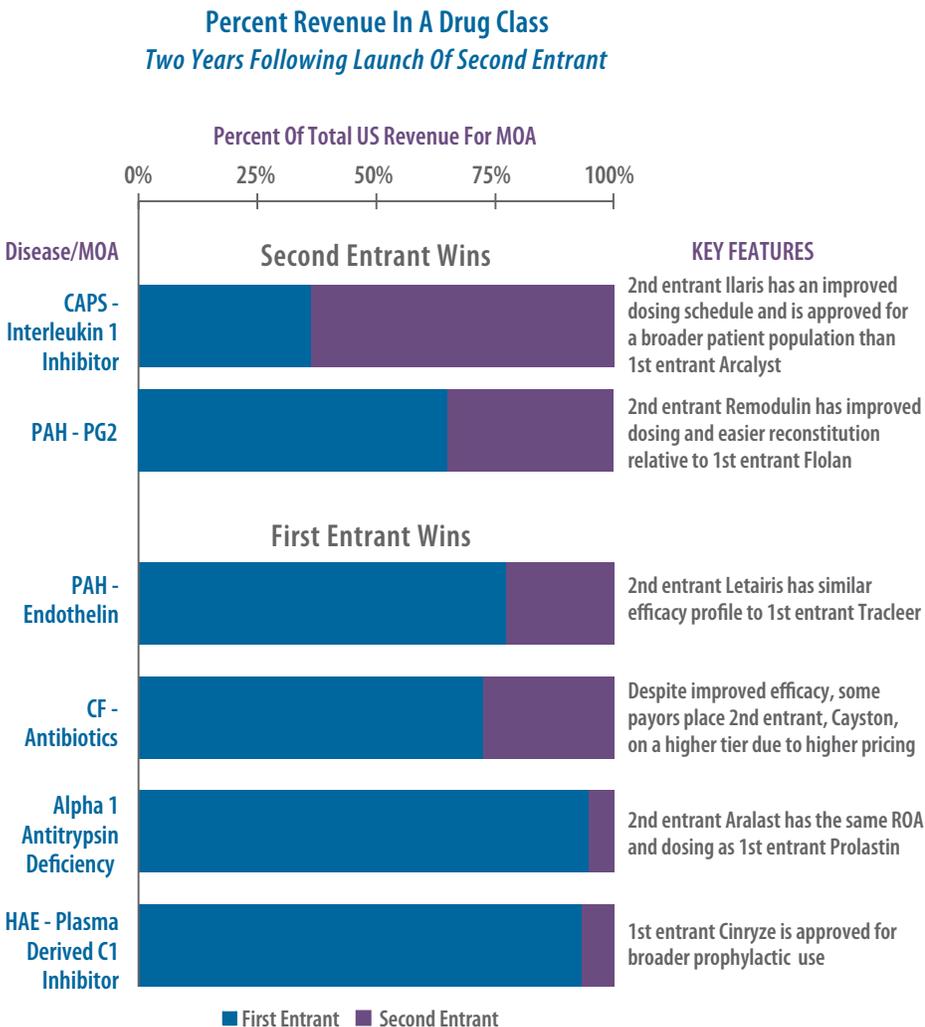
Subsequent entrants are also able to take

advantage of increasing diagnosis rates that characterize many orphan indications. In many orphan diseases, particularly those that may have been poorly diagnosed prior to the introduction of effective therapeutics, the diagnosed patient population grows in response to the presence of launched efficacious agents. Subsequent entrants, whether with the same mechanism as marketed products or not, are able to take advantage of growing disease awareness to address a larger market than the initial entrant. In PAH, for example, the prevalent diagnosed PAH population increased from 4,500 patients in the US at the time of launch for *Flolan*, the initial entrant, to 8,000 when the next entrant entered the market seven years later. Now, with multiple drug classes on the market, a defined diagnostic paradigm, and recognition of more mild cases of the disease, more than 32,000 patients have been diagnosed with the disease in the US.

Subsequent entrants are also able to succeed by fragmenting an orphan disease market into addressable and differentiated market segments. The maturation of the PAH market serves as an excellent example of this strategy. The market has developed to accommodate multiple lines of therapy

Exhibit 3

## Differentiated Subsequent Entrants Can Capture The Indication



SOURCE: Health Advances analysis; Company 10-K; Analyst reports

for different levels of disease severity. From the launch of the market in the 1980s with Flolan, a prostacyclin, the market has grown to accommodate PDE-5 inhibitors and endothelin receptor agonists for earlier lines, particularly among patients diagnosed with mild to moderate stages of disease. These agents have met needs in these less severe disease lines that were not initially well addressed by IV prostoglandin therapies previously. The launch of Kalydeco in a genetically distinct CF population is another recent example of the fragmentation of an orphan disease market. By addressing the cause of CF in a small patient subset with a highly efficacious agent,

Vertex has effectively created an ultra-orphan disease within the CF indication, setting the tone for pricing and creating a robust barrier to entry for subsequent entrants.

### ORPHAN MARKETS ARE NOT IMMUNE FROM PRICING PRESSURES

Also much like other specialty markets, subsequent entrants only have the ability to increase price over initial entrants if they deliver a clinically meaningful improvement to patients. Kalydeco in CF was able to command a high price point due to its effective segmentation of the CF market

and improvements in efficacy over the standard of care. We find that subsequent entrants are able to use the price point of the initial entrant as a floor if they increase compliance, and by extension, efficacy. **Hyperion Therapeutics Inc.'s Ravicti** (glycerol phenylbutyrate) in urea cycle disorder was also able to dictate a substantial increase in price due to increased efficacy as a result of improved compliance. Finally, Remodulin in PAH was able to demand a substantial price increase due to a dramatically improved drug half-life, leading to increased compliance. Subsequent entrants not bringing substantial clinical improvement to the market may have challenges claiming a higher price point. Cayston, for example, a subsequent entrant in the same class as the initial player Tobi, priced at a premium to Tobi, ultimately convincing several payors to place Cayston on a higher tier.

However, if a new player does not deliver substantial improvements to the standard of care, more undifferentiated competitors may need to compete in a manner similar to other drug markets, employing aggressive pricing and contracting strategies in order to be placed on a lower tier. Notably, in Gaucher disease Vpriv and Pfizer's *Elelyso* (taliglucerase), later undifferentiated entrants competing against frontrunner Cerezyme, have been priced at a discount in order to claim share. Vpriv, in particular, has garnered substantial share from Cerezyme through its contracting strategy. Novartis' Ilaris, a competitor with the same mechanism as Regeneron's Arcalyst, has also engaged in contracting to help win share in the CAPS orphan market.

### HOW TO WIN IN CROWDED ORPHAN LANDSCAPES

Unexploited orphan diseases, with significant unmet need and without treatment options, will continue to be in demand. However, as a result, and in spite of biotech and pharma's best scientific, development, and BD efforts, these markets will continue to become more rare. Drug developers are increasingly sifting through more populated orphan indications, some with substantial unmet need. How should an ambitious or acquisitive player approach these indications?

The lessons of today's orphan landscape suggest that many of the growth strategies

honed in other specialty markets apply. As in other specialty markets, benefits flow to those products able to meet substantial unmet market needs. Ideally, manufacturers should focus on those developed orphan markets with relatively high unmet need and with marketed therapeutics with significant downsides. In particular, as described above, deficiencies of initial entrants in dosing or efficacy provide ample opportunities for subsequent entrants to differentiate themselves, gaining substantial market share and pricing power. In addition, subsequent entrants can fragment a growing orphan market, splitting an orphan indication into addressable submarkets.

Furthermore, the rapid clinical development benefits often attributed to orphan diseases vary by order of entry. Orphan drugs have the greatest opportunity for expedited clinical development in estab-

lished indications if they launch new classes or mechanisms of action that meet market needs. By bringing novelty to the market, these drugs are able to take advantage of an established disease infrastructure, identified prescribers, mobilized patient groups, and an educated market to quickly move through the development process. In contrast, those drugs not representing a new clinical advance may face greater barriers in clinical development, with potential challenges in recruiting patients away from an entrenched standard of care and a skeptical physician community.

Orphan markets are not immune from the logic of other drug markets. For a manufacturer to obtain the much-heralded rewards of orphan drug development, there is no substitute for innovation and product differentiation. Innovations that improve clinical care have been and will likely con-

tinue to be rewarded, ensuring that these still debilitating diseases will be countered with an increasingly sophisticated array of therapeutics.

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