The Evolving Market Access Landscape for Orphan Drugs

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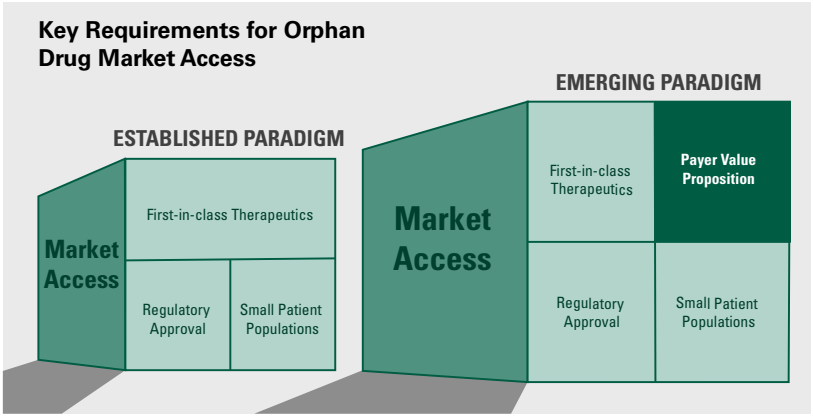
The historical access environment for orphan drugs was based on a few critical factors, namely that these products addressed very small, high unmet need populations that led to low overall budgetary impact despite high per-capita treatment costs. However, recent developments in the U.S. and Europe suggest payers are becoming more aggressive in scrutinizing price and implementing restrictions to patient access that have traditionally been reserved for competitive, high budget impact drug classes.

Consequently, the need to demonstrate value to payers for orphan drugs – even those with no therapeutic alternatives – is becoming increasingly important and requires earlier diligence and strategy development from manufacturers.

Established Orphan Drug Market Access Paradigm

Payers have historically been opportunistic in restricting access in competitive rare disease areas in which payers perceive modest differentiation. In today's environment, these include hemophilia, pulmonary arterial hypertension, and Type 1 Gaucher disease. Within each of these conditions, payers have a choice of fairly similar therapeutics and can steer customers towards the most cost-favorable options. For example, in the UK drug developers tender a best-possible price bid for hemophilia products. This aims to ensure that treatments are provided at the lowest possible price, even if this comes at the expense of significantly restricting or excluding select products from the market. In the U.S., managed care organizations have begun to prefer select products in these therapeutic areas, reducing out-of-pocket expenses and prescribing hurdles (e.g., prior authorization criteria) for those deemed to provide the greatest value at a given price.

FIGURE 1 THE EMERGING PARADIGM



The Emerging Risk for Orphan Therapeutics in Europe

Unlike many prevalent diseases, which have numerous therapeutic options and an established standard of care, many of the ~7,000 rare diseases have few, if any, effective treatment options. Therefore, manufacturers that successfully bring a new therapy to market may be in the enviable position of having no true competitors. Approved orphan drugs with this high level of competitive protection traditionally have been reimbursed by payers, regardless of price and strength of clinical evidence. However, new actions by payers indicate an emerging risk of increased price scrutiny and restrictive access, even for drugs that represent the only approved treatment for a given indication. This risk is greatest for drugs perceived to have a low or incomplete level of compelling clinical evidence.

The degree of pricing and access risk for orphan drugs varies considerably by country. For example, Germany still has favorable policies in place, in which EMA-approved orphan drugs are automatically considered to have an added clinical benefit over standard of care (regardless of data strength or comparator), as long as Germany's spend for the product does not exceed €50 million in a given year. This generous attitude is not universal. France may cap the annual price of an orphan drug at €50 K based on demonstrated improvements in medical benefit, or ASMR (Amélioration du Service Médical Rendu). In England, the pricing and reimbursement environment for orphan drugs is mixed. While most orphan drugs are ultimately reimbursed by NHS England, in several instances, NICE (National Institute for Health and Care Excellence) delays, limits, or recommends to deny reimbursement for select orphan drugs.

ORKAMBI®: Variable P&R Outcomes in Europe

For a subset of cystic fibrosis patients, Orkambi represents the only EMA-approved therapy that directly targets the underlying cause of disease. In France, Vertex is encountering challenges with health authorities. In its HAS (Haute Autorité de Santé) evaluation, Orkambi was compared to Pulmozyme, the symptomatic standard of care, due to an absence of morbidity, mortality, or long-term data. This is despite Orkambi's mechanism of action which addresses the underlying causes of CF for patients with select mutations. HAS claimed Orkambi provides only a minor health benefit (ASMR of IV) compared to symptomatic treatment, and as a result, was benchmarked to Pulmozyme's ~€8 K annual price negotiations, ~80% below Vertex's target price.

In the UK, Vertex is in extensive negotiations with NHS England to secure reimbursement for Okrmabi and has been for over two years. Carole Longson, the previous director of the NICE Centre for Health Technology Evaluation explained, "For the benefits it offers, the cost of Orkambi is too high." Orkambi is priced at ~£104 K per year per patient in England. Based on NICE analysis, the cost of Orkambi was too expensive when considering cost-effectiveness and budget impact. Vertex and NHS England are seeking to negotiate a "portfolio approach" to provide access to its current CF therapies, and also pave a pathway for future products. The details of the proposed agreement is uncertain to date, but may include price concessions and budget capping.

Conversely, given Germany's favorable policies and approach for assessing orphan drugs, Vertex was able to secure a ~€130 K price point, and achieve full reimbursement for patients.

Real-world Evidence's Growing Role

Real-world evidence is also beginning to a play a role for orphan drugs when uncertainties in demonstrating clinical value exist based on pivotal trial data alone, as seen in England. VIMIZIM® is the only EMA-approved product for the treatment of mucopolysaccharidosis type IV (MPS IV), a severe and rare lysosomal storage disease. Despite its status as the only indicated therapy for the <100 patients in England suffering from this condition, NICE expressed uncertainties in the value of VIMIZIM, particularly at an annual per patient cost of approximately £395 K. Among other items, NICE questioned whether the short-term benefits seen along surrogate endpoints (e.g., 6-minute walk test, urine keratan sulphate) would translate to improvements in long-term clinical outcomes (see VIMIZIM).

VIMIZIM: RWE's Role in Supporting Reimbursement in the UK

To address this uncertainty regarding long-term clinical outcomes, NICE requested BioMarin to enter into a managed entry agreement with NHS England in order to attain reimbursement. The managed entry agreement requires BioMarin to share real-world outcomes data with NICE and NHS England for MPS IV patients tracked through a newly established registry. The managed entry agreement also includes a confidential discount to the list price of VIMIZIM® through a patient access scheme (PAS) and stipulates starting and stopping criteria for therapy use. Following a data collection and evaluation period, NICE will make an updated recommendation regarding the continued reimbursement of VIMIZIM® by NHS England.

As demonstrated by the case study of VIMIZIM® in England, even when only a single therapeutic option is approved for a rare, severe condition, health technology assessment agencies and payers are seeking approaches to offset uncertainties in clinical outcomes and "value" more broadly. Real-world evidence generation can be a tool to address these uncertainties in select markets such as the UK.

Shifting U.S. Assumptions

In the U.S., we see a shift occurring in the management of orphan drugs that have relatively limited clinical evidence and significant competitive protection (Figure 1). Historically, these drugs experienced modest payer scrutiny and open patient access, but recent actions by payers indicate a shifting mindset.

For example, Exondys 51™ received accelerated approval from the FDA to treat patients with Duchenne muscular dystrophy (DMD), however, a number of major insurers have implemented policies that restricted access to a narrow subset of the labeled treatment population. These restrictions include requiring patients to meet certain age thresholds and ambulatory requirements. Of the major plans, Anthem was initially the most aggressive, with a decision to outright refuse to cover the ~$300 K per year product. While Anthem later reversed course in late 2017 and began providing coverage to patients who remain ambulatory, the Anthem experience nevertheless signals a desire and willingness of payers to more restrictively manage rare disease products.

In another example, Spinraza™ became the first drug approved to treat children and adults with spinal muscular atrophy (SMA). Spinraza was granted a broad label by the FDA for treatment of all SMA subtypes in pediatric and adult patients, though its clinical trial only included select subtypes. Despite this, several insurers, including United Healthcare, limited the reimbursement of the ~$375 K per year product (~$750 K in year one) to a more narrow subset of the labeled patient population that more closely mirrors its clinical study.

Given the lack of alternative treatment options available for DMD or SMA, the beyond-label restrictions and initial outright denial of coverage of FDA-approved drugs are virtually unprecedented in the orphan space. These cases illustrate how high the bar is becoming for clinical evidence in rare diseases and reflect the important role payers now play as interpreters of clinical data and gatekeepers to access. To maximize chances not just of regulatory approval but of acceptance by payers, drug developers need to closely consider these emerging payer needs when developing a market access strategy for their orphan drug programs. More specifically, orphan drug developers must assess when (e.g., during clinical development, post-launch RWE) and how to (e.g., through risk-based agreements) mitigate payer concerns.

Spark Therapeutics represents a company heeding this exact advice. In late 2017, Spark received FDA approval for the first gene therapy in the U.S., Luxturna™, to treat a rare genetically defined retinal dystrophy. Instead of waiting for payer reactions to their published price of $425 K per eye, Spark was proactive and creative when contracting with payers to ensure favorable access. For example, Spark will share risk with certain health insurers (e.g., Harvard Pilgrim) by paying rebates if patient outcomes fail to meet a specified threshold. Spark is also engaging in innovative agreements with payers and specialty pharmacies to purchase the gene therapy directly, thereby helping payers avoid costs accrued from traditional "buy and bill" models. Finally, Spark has submitted a proposal to CMS to conduct a pilot that would enable the company to offer commercial and government payers an installment payment option, as well as greater rebates tied to clinical outcomes. As validation of this strategy, Express Scripts' CMO Steve Miller has lauded Spark's approach as "responsible".

New Considerations for Developing Orphan Drug Market Access Strategy

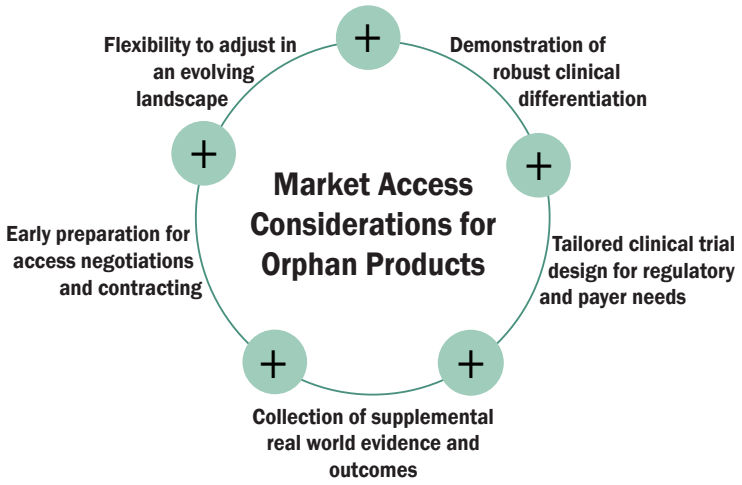
Payers throughout the world are raising the bar for orphan drugs, increasing the scrutiny of their evidence packages as well as their pricing and economic impact. Drugs that fail to meet payers' increasing standards risk being restricted, or in

extreme cases, excluded from reimbursement. Developers of orphan drugs, therefore, must expand their focus when it comes to market access strategy across several, new areas of consideration (Figure 2).

First and foremost, it is advantageous for companies to demonstrate clinical differentiation wherever possible. As payers increasingly manage access to orphan therapies perceived to be generally interchangeable or equivalent, the pharmaceutical industry must adjust by developing products that

FIGURE 2

Considerations for Developing Orphan Market Access Strategies



are sufficiently differentiated in the eyes of not only patients and physicians, but payers and heath authorities. Manufacturers have already responded to this challenge in hemophilia, as exemplified by the recent focus on gene therapies.

Orphan drug manufacturers also need to think critically about clinical trial design, including considerations for payer needs. Designing a pivotal trial for regulatory requirements alone may not translate to commercial success due to an insufficient data package for payers. As discussed above, it is possible that payers may take advantage of new opportunities such as narrowly defined populations or surrogate short-term endpoints to limit access or negotiate more intensely.

Manufacturers, therefore, need to place meaningful focus on pivotal trial design decisions (e.g., endpoints, duration, comparator), recognizing that while significant challenges and limitations exist in developing orphan drugs, payer expectations for evidence are only growing. Additionally, manufacturers need to understand how to leverage real-world evidence studies to drive favorable access where perceived limitations in data exist.

Finally, orphan drug developers need to remain flexible in their market access strategy, including negotiation and contracting approaches, to better position products for favorable pricing and reimbursement. Manufacturers need to be prepared to consider approaches that align risk where there is uncertainty in value given demonstrated evidence. This includes exploring innovative contracting approaches that address payer concerns and consequently positions products for more favorable market access. Having solutions in place ahead of time will be critical to reduce significant delays in providing patient access to critical therapies and realizing the commercial opportunity for the innovation. These solutions need to be proactively developed, even if not leveraged, to meet the potential expectations of payers.

Conclusion

As pharmaceutical companies continue to invest in orphan drugs, it will be increasingly important to account for the evolving market access environment. Payer insistence on getting meaningful value for their expenditures has expanded and now includes therapeutics for rare diseases, even when there are no therapeutic alternatives. In the coming years, the commercial opportunity for orphan drugs will be challenged by access dynamics and the ability to maintain premium prices. Orphan drug developers need to adapt their strategies now to meet this challenge.

About ClearView Healthcare Partners

Founded in 2007, ClearView Healthcare Partners is a global strategy consulting firm serving the life science sector. The firm combines international industry knowledge and deep scientific expertise across a range of therapeutic areas with an extensive network of external stakeholders to deliver practical and actionable recommendations to our clients' most complex challenges. The firm's projects include cross-functional support at the corporate, franchise, and product levels for pharmaceutical, biotech, medtech and digital, and diagnostics companies worldwide.

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