Orphan Diseases: Expansive Opportunity and Unique Challenges

An Analysis of Key Trade-offs for Drug Developers

Orphan drug development is attractive to drug developers for many compelling reasons: tax advantages, extended market exclusivity, accelerated approval timelines, historically favorable access at premium prices, potential for lower cost clinical trials, and recent commercial success stories such as Soliris and Kalydeco. However, orphan diseases do not necessarily offer an easy win. Manufacturers must be prepared for the unique challenges associated with orphan disease drug discovery, clinical trials, and market development, as well as the eventual likelihood that U.S. payers will actively manage pricing and market access for orphan products. Ultimately, considerable opportunity remains for drug developers in orphan diseases, but success will require companies to develop an orphan disease mindset for strategic decision-making and invest in capabilities commensurate with the anticipated nuances and challenges.

Marked Enthusiasm for Orphan Products

Orphan diseases have been a key area of interest in specialty pharmaceuticals for decades and, unsurprisingly, have more recently garnered significant attention from Big Pharma as well.[1] (This paper focuses primarily on non-oncology, non-MS orphan diseases.) Those familiar with the space will recall Sanofi's acquisition of Genzyme for >$20 B in 2011.[1] More recently, in January 2016, Shire inked a $32 B merger with Baxalta to become the largest player in the orphan space[2] – this move ensures additional M&A activity as other manufacturers attempt to maintain their competitive positioning. The Orphan Drug Act (ODA) is the genesis of such interest and was established with the purpose of incentivizing drug developers to invest in orphan diseases.[3] The ODA defines several direct incentives for manufacturers developing orphan disease products: waived regulatory fees, protocol assistance, development tax credits, an accelerated approval timeline, and seven years of exclusivity following launch.

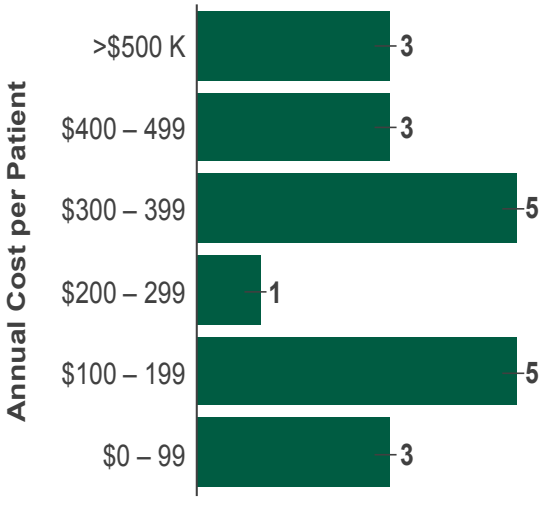
Specifically, the legislation stipulates a 50% tax credit on spending related to the research and development of orphan products, as well as priority review within six months of submission to the FDA.[4]

Beyond incentives in the ODA, there are many additional benefits for developing orphan versus traditional drugs. For one, many orphan diseases are genetically defined, providing relative homogenization of the clinical trial population, helping direct discovery efforts and increasing the probability of success. Additionally, the rarity and severity of many orphan diseases contributes to regulatory flexibility that allows for streamlined clinical development programs as compared to those for more prevalent conditions.

Further, free pricing in the U.S. and historically lenient management by U.S. payers have enabled favorable access even at ultra-premium prices – this phenomenon has not gone unnoticed by the media. In fact, the average U.S. annual cost of the top 20 global earning orphan drugs (excluding non-oncology, non-MS, those launched before ODA enactment, and those with majority non-orphan sales) in 2015 was $250 – 300 K per patient (Figure 1).[5] These high prices have traditionally been accepted by U.S. payers due to relative lack of competition, high degree of medical necessity, and relatively minimal budgetary impact. Thus, many orphan drugs are covered by insurers with minimal restrictions, typically only requiring confirmation that the patient fits within the indicated population.

FIGURE 1

Among orphan drugs launched post-ODA, the top 20 earning products have an average annual price per patient of $250 – 300 K



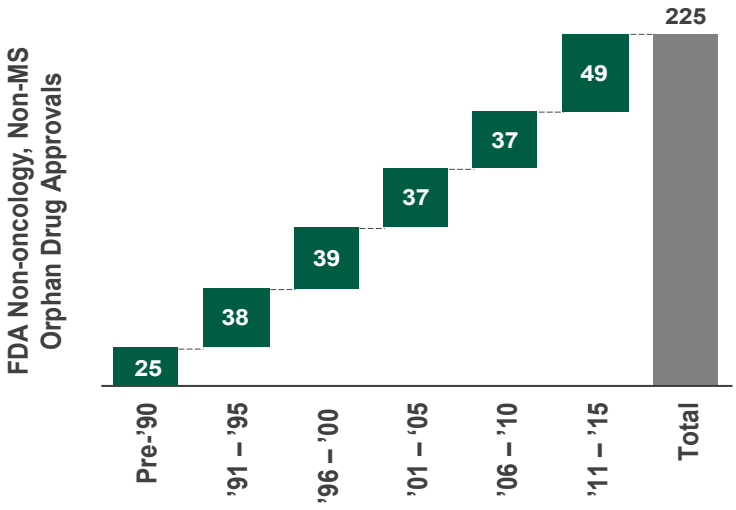
Overall, these attractive characteristics have resulted in increased benefits for patients and have inspired substantial interest in orphan drug development. Since the enactment of the ODA in 1983, 225 non-oncology, non-MS orphan drugs have been approved by the FDA (Figure 2), and orphan disease approvals more broadly accounted for ~45% of FDA approvals in 2015, as compared to only ~25% in 2005.[6] However, even considering this progress, an FDA-indicated treatment is available for only <5% of the ~7,000 known orphan diseases.[7] Such opportunity underlies the continued interest from drug developers.

Unforeseen Challenges and Unique Considerations

While there is undoubtedly substantial unmet need for orphan disease therapies, the statis-

FIGURE 2

The number of orphan drug approvals has increased since the 1983 Orphan Drug Act (and particularly in recent years)



tic that <5% of orphan diseases possess an FDA-approved therapy overstates opportunity for orphan drug developers. Manufacturers must take into account challenges and considerations unique to orphan drug discovery, clinical trials, and commercialization.

Many orphan diseases are not amenable to pharmacological intervention. For one, the etiology and mechanistic underpinnings for most orphan diseases are poorly understood. Basic understanding of pathogenic genes has only been achieved for ~50% of genetically-defined orphan diseases[8] – such lack of knowledge is, in many cases, an insurmountable barrier. Further, many of the well-characterized diseases may be poorly suited for a drug intervention. For example, select diseases are best addressed surgically: simple syndactyly (fusion of adjacent digits without bone involvement), select forms of primary hyperaldosteronism, etc. Other orphan diseases cause too significant of an *in utero* defect for a drug therapy to have a meaningful benefit. For example, particularly severe cases of autosomal recessive polycystic kidney disease, where infants experience substantial renal damage prior to birth. Conversely, many orphan diseases have relatively low severity, reducing unmet need and the necessity of a therapy (e.g., congenital adermatoglyphia, the inherited absence of fingerprints).

Even after a drug candidate has been discovered, clinical trials in orphan indications pose unique challenges. First, disease natural history is often poorly understood, and therefore the range of symptoms and complications are not well known. Incomplete understanding of disease characteristics complicates identification of an appropriate clinical trial endpoint. The rarity of these diseases makes clinical trial recruitment difficult and may hinder enrichment efforts. Such uncertainty both complicates discussions with the FDA regarding endpoints and significantly increases clinical trial uncertainty and risk.

The difficulties associated with orphan drug development persist beyond FDA approval. Orphan diseases require considerable market development that may exceed the capabilities or willingness of many manufacturers. For one, patient identification is notoriously challenging. A study by the European Organization for Orphan Diseases (EURORDIS) found that ~40% of orphan disease patients were

initially misdiagnosed. Further, for ~25% of patients a correct diagnosis was only achieved after >30 years of symptoms.[9] Patient advocacy and/or support networks can be helpful, but only exist for ~15% of orphan diseases.[10] These challenges are compounded by a general lack of awareness and interest in these diseases among many referring and treating physicians. As a result, manufacturers often need to invest substantial resources to establish disease experts and to increase disease awareness.

Importantly, while U.S. payers have historically provided favorable market access for orphan drugs at premium prices, they have recently begun to capitalize on increased competitiveness in select markets and implement more stringent restrictions. Most orphan products continue to enjoy relatively unhindered market access. However, recent examples illustrate not only a developing trend towards greater restrictiveness, but also the *ad hoc* character with which such restrictions are often implemented (Figure 3). Payers' management of nephropathic cystinosis, idiopathic pulmonary fibrosis, and growth hormone deficiency highlights their willingness to implement tactics similar to those traditionally used for specialty products in more prevalent indications. Competitiveness in the orphan drug market is likely to increase in the future, and manufacturers should assume that payers will gradually take a more proactive role in managing orphan drugs, requiring manufacturers to adjust drug/disease investments accordingly.

Further, despite payer coverage of these treatments and manufacturer reimbursement support, the financial burden to patients and their families is often considerable. A substantial portion of orphan disease patients are covered by public insurance (i.e., Medicare, Medicaid, or dual-insured) for which direct reimbursement assistance is prohib-

Increasing Degree of Restrictiveness

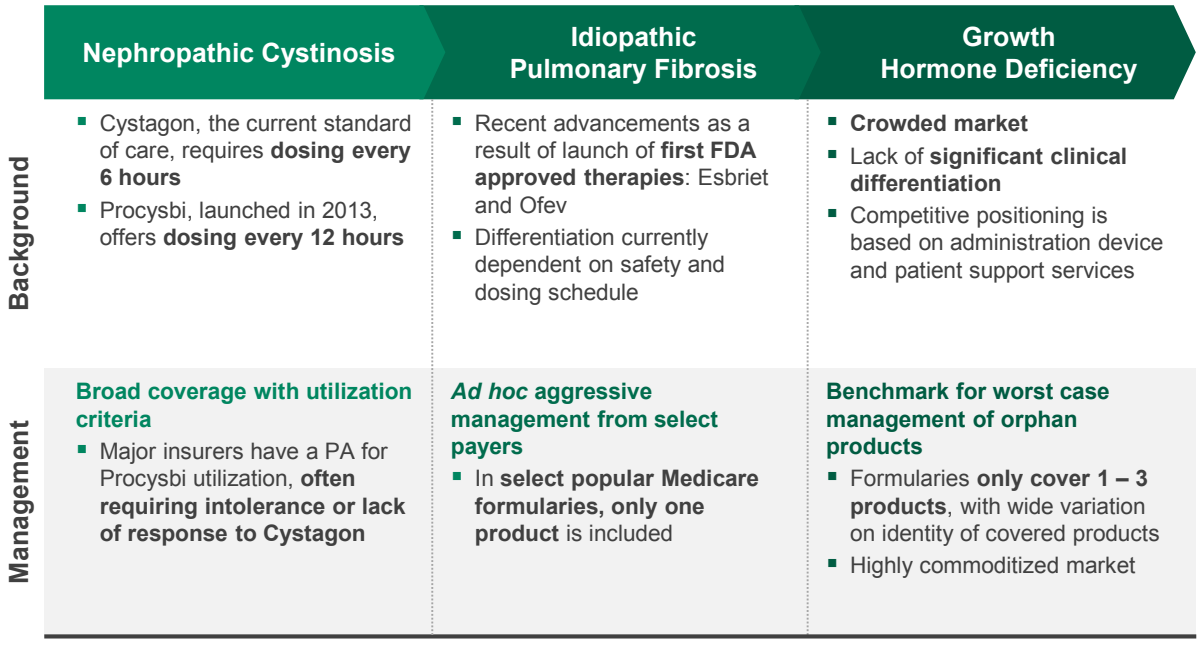


FIGURE 3

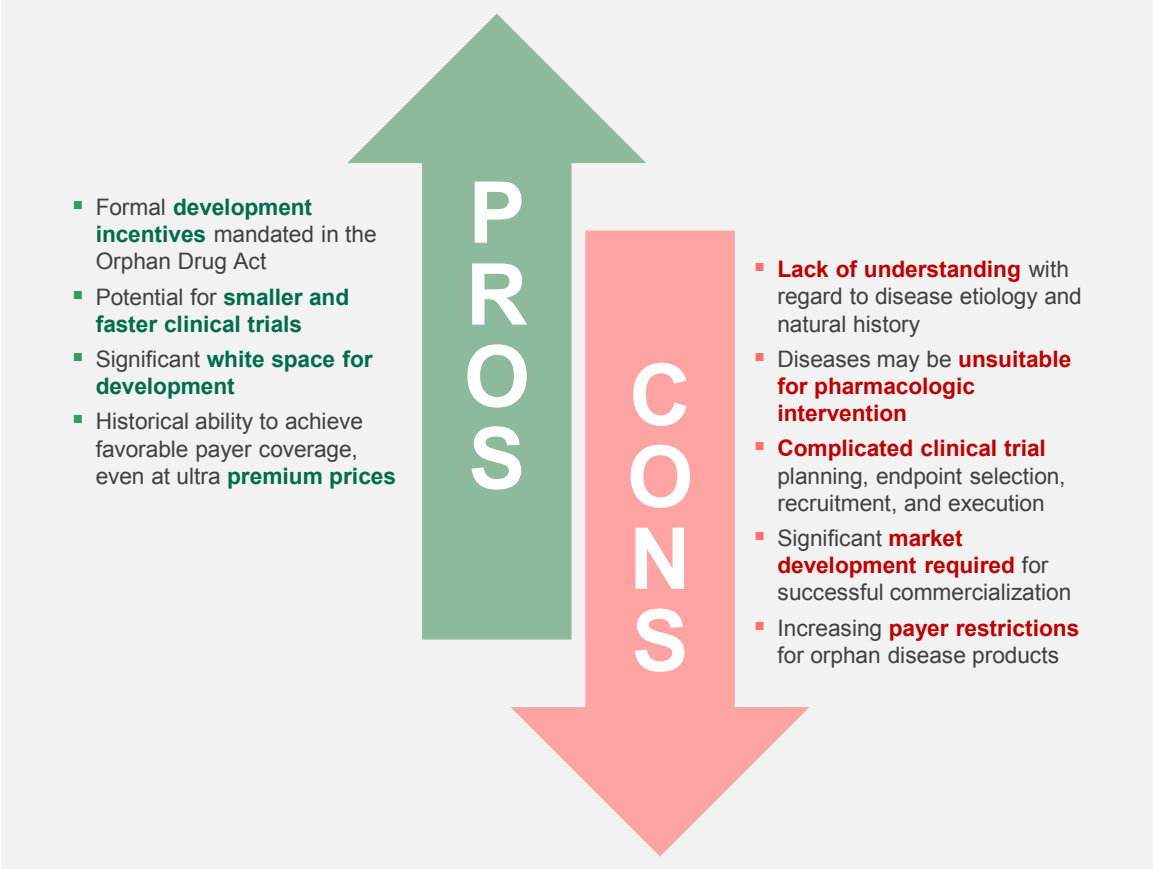
ited. Patients may receive support from copay assistance foundations (e.g., HealthWell Foundation) or patient advocacy groups (to whom manufacturers may provide unrestricted grants) but these funds are often limited or insufficient. Taken as a whole, these substantial headwinds illustrate a shifting, and potentially challenging, orphan drug environment for manufacturers.

Key Implications for Drug Developers

While significant opportunity exists in the orphan disease space, drug developers should not expect guaranteed success. Despite the halo effect from select, sensationalized products, only 5 non-oncology orphan drugs achieved blockbuster status on sales from orphan indications in 2014. In fact, excluding blockbusters, the top 50 orphan products earned an average of ~$410 M in global sales from orphan indications in 2014 (Figure 5).[11] Furthermore, <10% of orphan drugs have gained multiple indications, often simply by the nature of being a targeted therapy.[12] As a result, orphan disease products often have limited opportunity for life cycle management. Ultimately, the vast majority of orphan products are better considered "niche-busters" than blockbusters.

Pharmaceutical company interest in orphan diseases is strongly grounded in explicit regulatory advantages, a large number of unaddressed conditions with compelling unmet need, and a history of relatively unhindered market access. Further, the white space available in the orphan disease market allows for development of highly impactful and trans-

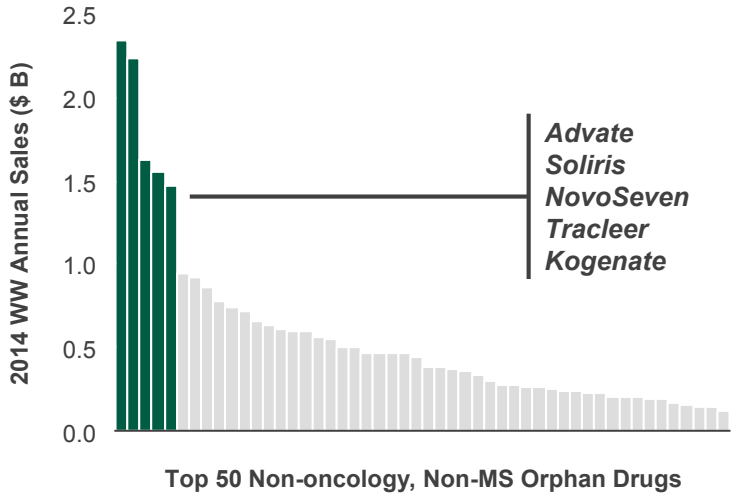
FIGURE 4



formative therapies. However, companies must be prepared for the lack of understanding associated with most orphan diseases, unique clinical trial risks and challenges, substantial market development requirements, and emergence of greater restrictiveness in market access. To be successful, manufacturers must approach discovery, development, and commercialization differently in orphan diseases than for traditional or specialty disease areas. Companies interested in orphan diseases must carefully select target indications based on unique orphan disease considerations, be comfortable with uncertainty inherent to the orphan space, and strategically develop capabilities commensurate with the anticipated challenges.

FIGURE 5

Annual sales in orphan conditions of top 50 non-oncology, non-MS orphan drugs show very few products with revenue >$1 B



REFERENCES:

1. http://www.wsj.com/articles/SB10001424052748703373404576147483489656732

2. Shire Press Release. “Shire to Combine with Baxalta, Creating the Global Leader in Rare Diseases.” January 11, 2016.

3. Orphan status is provided to drugs and biologics intended for the treatments, diagnosis, or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that are not expected to recover the costs of developing and marketing a treatment drug (FDA Regulatory Information: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm2005525.htm).

4. FDA Regulatory Information: http://www.fda.gov/regulatoryinformation/legislation/significantamendmentstothefdcact/orphandrugact/default.htm

5. Red Book Online; ClearView Internal Analysis

6. EvaluatePharma Data; ClearView Internal Analysis

7. EvaluatePharma Data; ClearView Internal Analysis

8. OrphaNet Database; ClearView Internal Analysis (currently, the Orphanet database contains information on genes associated with orphan diseases, with entries for only ~50% of the ~5,500 orphan diseases hypothesized to have a genetic component)

9. EURORDIS. Survey of the Delay in Diagnosis for 8 Rare Diseases in Durope (‘EURORDISCARE 2’). 17 Apr. 2007 (online)

10. Ryan Foundation (http://ryanfoundation.net)

11. EvaluatePharma Data; ClearView Internal Analysis

12. EvaluatePharma Data; ClearView Internal Analysis

Note: Oncology orphan diseases and multiple sclerosis were excluded from our analysis due to unique features of the these landscapes that differ as compared to other orphan conditions, consistent with how the industry approaches these diseases (e.g., pricing and market access trends, regulatory incentives, patient segmentation, disease progression, etc.).

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