ASSESSING VALUE IN ULTRA-ORPHAN MARKETS

TRINITY

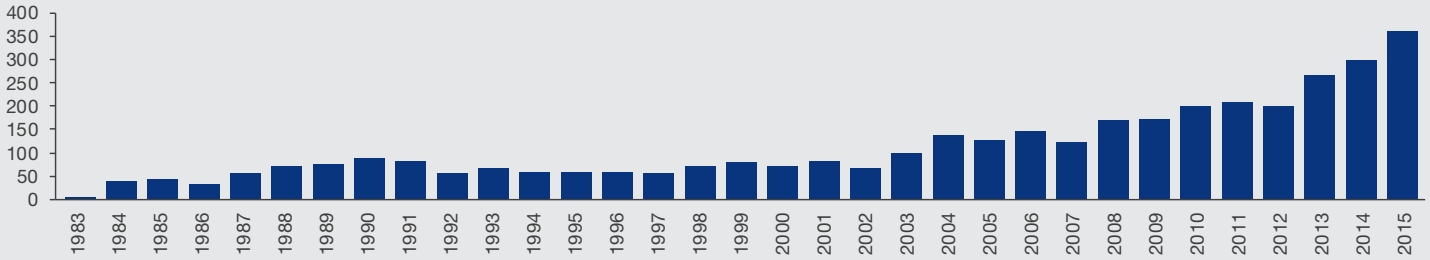
Herman Sanchez, Neal Dunn, Eric Sholk, Krista Perry,
Maria Gumina, Mahaney Sippel, Rachel Halperin

The pharma and biotech industry has changed dramatically in the last few decades, with one key shift being the focus and attention on orphan drugs. In the early 1960s, in response to some incidents (namely, thalidomide), legislation in the United States focused on ensuring drugs were safe and effective, which often necessitated extensive clinical trials and additional costs for development. Therefore, the pharma industry focused on common diseases to maximize potential profits and the possibility of recouping the significant costs of development. This led to concern and pressure from patient groups and families affected by rare diseases. Most notably, the National Organization for Rare Disorders (NORD) was established from a coalition of patient organizations and was instrumental in helping focus attention on rare diseases. In 1983, the United States Congress passed the Orphan Drug Act to facilitate development of orphan drugs by providing incentives for industry investment in treatments for rare conditions. Drugs could qualify for orphan status if they were intended to treat a disease affecting fewer than 200,000 people in the U.S. The incentives included a 7-year marketing exclusivity, tax credits and grants for drug development costs, and fast-track approval.

Of the 3,500 orphan drug designations, the Office of Orphan Products Development (OOPD) has issued since 1983, over 500 have resulted in marketing approval. In FY 2015, OOPD designated a record 355 orphan drugs (Figure 1) and the FDA approved 40 orphan designated drugs for marketing, representing 47% of all new drug approvals.

FIGURE 1

Number of Orphan Designations Granted



Source: Office of Orphan Products Development database. September, 2016. www.fda.gov

Although the 1983 Orphan Drug Act is heralded as the beginning of orphan drug development, there has been a significant increase in focus and funds since 2000, aligning with the boom in the number of requests for orphan designation. Most importantly, the industry began to realize the inverse correlation between population size and pricing power, which was counterintuitive to traditional understanding of commercial success. This was especially born out in ultra-orphan markets (See more discussion on pricing and value here). Typically, the industry has defined an ultra-orphan disease as having less than 10,000 patients in the US. In addition to companies recognizing the attractiveness of ultra-orphan diseases that typically have less competition and better pricing opportunity, many new companies emerged with advancing technology in pharmacogenomics and precision medicine.

In addition to companies recognizing the attractiveness of ultra-orphan diseases that typically have less competition and better pricing opportunity, many new companies emerged with advancing technology in pharmacogenomics and precision medicine.

Today, worldwide orphan drug sales are projected to grow at roughly double the rate of overall prescription sales (EvaluatePharma Orphan Drug Report 2017) and the pharma/biotech industry is seizing the opportunity. In the last 5-10 years, the attention to orphan development has exploded. From acquisitions (Sanofi-Aventis paid $20 billion to buy orphan drug maker Genzyme in 2011) to creation of separate rare disease units (e.g., Pfizer), pharma companies large and small are all trying to get a slice of the orphan market. Additionally, in December 2016, the 21st Century Cares Act was signed into law with strong bipartisan support, due to the focus on

fighting and funding critical national health concerns such as the opioid epidemic, Alzheimer's disease, and cancer. It also had (controversial) support from big pharma, due to the regulatory rollbacks focused on the quicker, easier paths to approvals. However, the Act was pivotal in continuing key incentives for rare diseases (including, the Rare Pediatric Disease Priority Review Voucher Program) and expanding the Patient-Focused Drug Development Initiative, increasing the role of patient advocacy groups that continue to grow.

Rare diseases have the attention of the industry and the incentives continue to be strong. However, finding success in the orphan market is not easy–the challenges afforded by targeting a very small population are numerous. Disease rarity, although correlated with pricing power, isn't all a company needs for success. With increasing scrutiny on the value and price of orphan drugs, a company must prove its worth. The goal of this whitepaper is to elucidate what drives success in this space, specifically for ultra-orphan products.

While companies such as Genzyme, Shire, and BioMarin have built very strong orphan franchises, not all are as successful. The idea that you can leverage a great clinical solution to an ultra-orphan condition, price it high given the small population, and be successful is a myth. For example, Glybera (UniQure), widely heralded as the "first gene therapy" when it launched in Europe in 2012 as the only treatment for familial lipoprotein lipase (LPL) deficiency, was only used commercially in one patient and subsequently removed from the market in April, 2017. The clinical development (finding patients, structuring trials without a placebo, etc.) and regulatory process was challenging and lengthy, but UniQure persevered and Glybera was approved with a one-time price of ~$1 million (USD) per patient, depending on the patient's weight. Regardless of it being such a novel therapy with a high price, its commercial demise was mainly due to the lack of understanding around how to drive market demand in an ultra-orphan space. Companies looking to launch an ultra-orphan product can learn from this example by considering key clinical and commercial attributes for success and recognizing the effort needed to navigate the complexities of commercializing a product in an ultra-orphan market.

Although there are multiple pathways to success, potential products (to acquire or for portfolio planning) must first be assessed on several different commercial and clinical criteria specific to ultra-orphan markets. The clinical rationale behind pursuing a product's development in an orphan market is a necessary foundation for recognizing commercial opportunity (Table 1). Products in conditions for which there is a high degree of pathophysiological understanding have a greater chance of clinical success as there is an identified target for the drug. This may manifest itself by mimicking a deficiency specific to a certain disease (e.g., KUVAN in PKU) or by addressing an underlying pathway that plays a role in numerous diseases (e.g., Soliris). The timing of disease onset, diagnosis of the condition, and a patient's life expectancy

TABLE 1

Clinical Rationale

Rating	Degree of Pathophysiological Understanding	Window of Treatment Opportunity	Transformative Value (Is it Disease Modifying?)
Low	Unknown etiology or many genes affected	Small/No Treatment Window—Significant in utero damage or irreversible damage before diagnosis and/or short lifespan	No or indirect link of target to disease pathophysiology or no evidence of efficacy
Moderate	Some understanding of pathophysiology or few genes affected	Moderate Treatment Window—Infancy onset of symptoms and/or moderate lifespan duration SOLIRIS	Target plays a role in disease pathophysiology directly demonstrated in appropriate animal model KUVAN Glybera
High	Clearly understood etiology SOLIRIS KUVAN Glybera	Long Treatment Window—Childhood or adult onset of symptoms and significant lifespan KUVAN Glybera	Target has established a role in disease pathophysiology in human or evidence of transformational benefit demonstrated in human SOLIRIS

are a few key considerations in determining the window of treatment opportunity. This metric is important to be able to realize the commercial opportunity; if the window is too short, it will be more difficult to find and treat patients. Finally, the clinical data of a product and its impact on patients' life expectancy, function, and quality of life must be evaluated, as products with limited effect or little differentiation from competitors will face significant hurdles in their uptake.

The clinical data of a product and its impact on patients' life expectancy, function, and quality of life must be evaluated, as products with limited effect or little differentiation from competitors will face significant hurdles in their uptake.

Equally important, on the commercial side, a company must evaluate the disease severity and unmet need of the target condition, the level of competition (both current standard of care, whether indicated or not, and future) in the market, the effort required to develop and/or prime the market, and the addressable market size (Table 2). Disease severity and unmet need can be assessed by looking at the impact of the disease on life expectancy, function, and quality of life—due to a higher demand for the product, a life-threatening disease will have a greater commercial potential than a condition with little effect on function or quality of life. Beyond just focusing on markets with less competition, market assessments need to explore inexpensive or easily accessible products (even if used off-label or not tremendously effective) as those will be harder to penetrate.

TABLE 2

Commercial Rationale

Rating	Addressable US Market Size	Disease Severity/ Unmet Need	Competition	Market Development Need/Opportunity
Low	<2,500 addressable patients Glybera	No impact on lifespan AND limited impact on quality of life/asymptomatic	Disease modifying treatment exists or there is a significant number of products in development	Low disease awareness/ significant effort is required to identify patients Glybera
Moderate	2,500-5,000 addressable patients	Variable severity from mild to severe; Moderate impact on quality of life KUVAN	Treatment options exist, but are only symptomatic; moderate number of pipeline agents	Moderate effort is required to raise awareness around the disease and identify patients SOLIRIS
High	5,000-10,000 addressable patients SOLIRIS KUVAN	Impact on lifespan OR significant impact on quality of life SOLIRIS Glybera	No significant drug therapies exist and limited/no products are in development SOLIRIS KUVAN Glybera	Significant disease awareness already exists and patients are easy to identify KUVAN

Finally, it is important to keep in mind the need for market development. A product will likely face greater challenges if there is low disease awareness and significant effort is required to identify, diagnose, and target patients; define applicable patients; and/or develop understanding of the burden of disease. Therefore, when talking about ultra-orphan diseases, which have a very small market to begin with, the greater the population of patients for all indications the

product can treat (for a lot of products this will be just one indication), the greater the opportunity as well. To note, these metrics can act in contrast to each other (e.g., a market with greater current treatment options usually requires less market development/awareness), complicating the potential opportunity.

In addition to the metrics noted above, manufacturers need to consider additional factors when planning for development and/or commercialization, including clinical trial development needs (finding patients, design–using a surrogate endpoint if needed), early access programs, reference pricing and launch sequencing, clinic/HCP/patient training and support programs, relationships with KOLs and key clinics, and specialty distribution, among others. Most importantly, the role of patient advocacy has been a major influential factor in recognizing commercial success across many orphan markets from Cystic Fibrosis to Duchenne Muscular Dystrophy. It is paramount that companies engage and activate these communities early in development to prime their support and readiness to accept a new therapy.

> **The role of patient advocacy has been a major influential factor in recognizing commercial success across many orphan markets from Cystic Fibrosis to Duchenne Muscular Dystrophy.**

Case Studies

To evaluate the overall potential opportunity of a product, we consider both the commercial and clinical metrics elucidated above to arrive at a combined framework. Despite this framework, success in the ultra-orphan market does not follow one formula. Soliris (Alexion) and KUVAN (BioMarin) are two assets that score high with regard to clinical and commercial opportunity, yet followed a very different path to success.

Soliris (Alexion)

Soliris is known as a “pipeline in a product” given its breadth of potential indications. Alexion developed a very effective monoclonal antibody that selectively targets and inhibits the C5 complement system, which is applicable in a range of autoimmune conditions. Although initially approved in 2007 for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), it had been studied in five other conditions prior to PNH and continues to be studied in many indications. In 2011, Soliris received approval in atypical hemolytic-uremic syndrome (aHUS) and just recently, in August, 2017, for generalized myasthenia gravis (gMG) in the EU. The high unmet need and limited and invasive treatment options in these markets, coupled with remarkable clinical improvement exhibited by patients, justified high pricing (~$500,000) that could counteract the small markets. Soliris has been able to capitalize on its clinical attributes by finding commercial success in multiple indications.

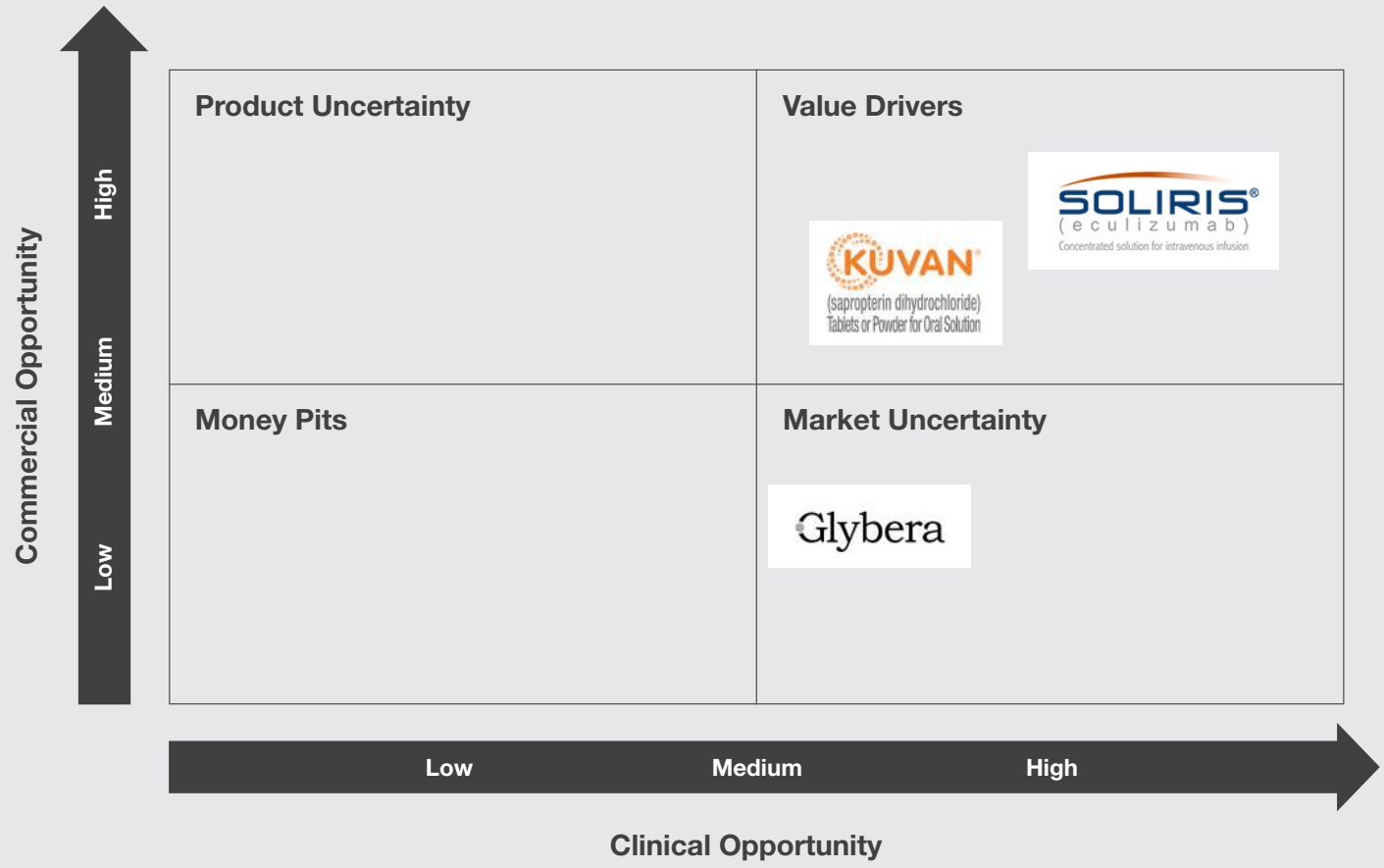
KUVAN (BioMarin)

KUVAN, approved for Phenylketonuria (PKU) in 2007, was developed specifically for PKU and has been successful despite less severe unmet need and much lower pricing ($50,000-$100,000). The combination of newborn screening, a long treatment window, and a strong patient organization allowed BioMarin to foster strong ties with the PKU community and build a market for their product. BioMarin’s patient-centric platform includes dedicated support teams who provide guidance in supporting clinics getting patients on KUVAN and in obtaining KUVAN at little to no out of pocket cost, as well as assistance coordinating all aspects of patients’ treatment plan. KUVAN and Soliris both benefit from very strong efficacy and safety data and target markets with little pharmacological competition, however, their success was achieved in very different ways. Alexion built markets around their product while BioMarin focused their efforts and attention to developing one market with continued growth.

> **Alexion built markets around their product while BioMarin focused their efforts and attention to developing one market with continued growth.**

Plotting Soliris, KUVAN, and Glybera on our framework (Figure 2), it’s clear that Soliris and KUVAN have strong clinical and commercial rationale and ultimately indicate successful commercialization. Products landing in the top right quadrant are clear drivers of commercial and clinical value, which demands high pricing power. In contrast, Glybera was limited in its commercial success in large part due to lack of driving market development and limited addressable patient population. It is critical for companies to recognize early products landing in the left-hand quadrants that have limited value in clinical rationale, to limit effort and costs in developing a likely poor product.

FIGURE 2



The complexities surrounding success in the ultra-orphan market will continue to grow as competition rises alongside increased payer and pricing sensitivity. Clinical rationale is the foundation, recently fueled by the advancement of more targeted therapies. Companies that focus on diseases with high unmet needs and the need for transformative therapies and that are further able to pull through the commercial infrastructure to drive the product can find blockbusters. Importantly, a highly targeted therapy like Glybera can fail, exhibiting that need and scientific rationale are not enough. Orphan markets require significant investment to prime patients, physicians, and payers to capitalize on the full commercial opportunity. Leveraging this framework can help navigate the potential opportunity in ultra-orphan markets. Given that there are over 7,000 rare diseases with only 500 approved treatments (NORD), there is still a large unmet need and opportunity for success. The industry is driving to more targeted therapies, including many exciting gene therapies, and many of them could become success stories. Companies looking to capitalize on this wave should follow this roadmap to recognize the critical metrics that determine success and the efforts needed to achieve them.