KNOW YOUR RARE DISEASE MARKET

Increasing Competition is Driving Changes in Required Commercialization Approach

By Naveen Murthy, Rafal Kokolus, Rohit Sood

Introduction

In recent years, rare disease products have become an attractive area for pharmaceutical and biotech development. They tend to have shorter or accelerated clinical development timelines, lower development and commercialization costs, fewer life-cycle challenges, and increased deal activity. While the average revenue from a product with a rare disease indication may be lower compared with the more traditional therapeutic areas, rare diseases still present a lucrative opportunity and the space has become a focus for many companies in today's competitive drug market. As a company begins to evaluate the requirements for successful development and commercialization of a rare disease drug, the company will need to be cognizant of the unique aspects of the rare disease and how these will drive the commercialization process. Areas of strategic and tactical focus, structural requirements (both internal and customer-facing), level of market noise related to the disease and ease of generating product awareness ultimately impact the required commercial investment and the focus of commercial spend.

A Framework for Initial Commercial Assessment

Patient identification and acquisition has traditionally been one of the most important considerations for commercializing orphan drugs, as by definition, patients are rare and typically require therapy for a lifetime. The rare disease space has proven and continues to be lucrative for biotech and pharma companies for a number of reasons, including easily defined patient populations, lack of alternative treatments for the patients, offering a high return on investment while addressing significant unmet need for patients and premium pricing of orphan drugs.

Rare Disease Fast Facts

- Products with rare/orphan indications accounted for 15.5% of global prescription sales in 2015 ($102Bn of $661Bn WW)
- Phase III development costs are almost half that of non-orphan products ($103M vs $193M respectively, N=1,418)
  - Additionally, a 50% tax credit is provided on R&D costs in the US
- FDA approval times are on average shorter for orphan drugs compared with non-orphan products (10.1 vs 12.9 months, N= 630)
- The US market for rare disease products is rapidly becoming more competitive
  - There were 467 applications for orphan disease designations in 2014 versus 174 in 2004 (10.4% CAGR)
  - There were 3280 cumulative orphan drug designations in 2014 versus 1427 in 2004 (8.7% CAGR)
In the long-term, strategies for improving patient identification and acquisition can still be effective in driving brand value and penetration. However, in markets with multiple inline and pipeline products, there may be limited opportunity to expand the existing market or define market dynamics at all without a clearly differentiated new best in class therapy. Furthermore, with more and more orphan drugs being indicated for the same disease, the ability to command high prices may become difficult to justify in the face of increasing alternatives for what was once a condition with no treatment options. In these more competitive markets, commercial strategy and tactics are more like a traditional competitive pharma market requiring brands to take share from the others and focusing on product characteristics that benefit specific patient segments. Both the ease of patient acquisition and the level of existing commercial development for a rare disease inform the optimal level of investment and the commercialization approach required for success.

In this article, we will discuss a framework that segments rare diseases to help inform commercialization needs. By characterizing each market based on ease of patient acquisition and the level of existing commercial development rare diseases can be compared for investment attractiveness. While there are many other variables that impact commercialization (chronic vs. acute vs. prophylactic, age of onset [infant/pediatric/adult], degree of unmet need, etc.), this framework highlights two critical considerations impacting level of investment and commercialization approach.

Figure 1 outlines potential attributes of products in each segment of the framework. No two rare disease markets are the same, and while some characteristics are quantifiable (prevalence, diagnosis rate, penetration), others require judgment and analysis (likelihood of inducing a patient to switch products, competitive entrenchment).

**Ease of Patient Acquisition**

Patient identification is critical to driving business in rare disease. Size of the patient population is the most quantitative and convenient attribute to assess, although published numbers for a given rare disease can vary widely. As a result, companies may not have a complete understanding of the actual size of the patient population until sometime after market entry. Additionally, diagnosis is inherently difficult due to a lack of disease awareness, complex referral pathways to diagnosing physicians and a lack of conclusive diagnostics for physicians.

Other factors that need to be considered include the activity of advocacy groups, the entrenchment of currently marketed products and the ongoing unmet need for treatable patients. A key question that will need to be considered up front is:

“How easy will it be to identify the patients and potentially recruit for a clinical trial? Are clear diagnostic methods available, accessible and implementable?"
Current Commercial Development

Key considerations for the commercial development of a rare disease are similar to those of non-rare diseases: the number of products currently on the market, the extent of penetration of these products and the number of products in the near term pipeline. Beyond these quantitative components, the following question will clarify the impact of the current commercial development on rare disease product launch:

“What infrastructure, systems and resources are in place to support the key stakeholders involved in the care of patients? (e.g., patient registries, centers of excellence, academic research and experts, disease-specific care pathways, patient support groups, disease education and awareness programs, etc.)”

Dynamics of a Rare Disease Market

The dynamics of rare disease markets are impacted by the same key market events and changes as any “traditional” therapeutic market. One key difference is the magnitude of change. Actions and events which may cause a limited impact to a “traditional” market will cause a significant impact in a rare disease market simply because of the underlying market and therapeutic area characteristics:

- Limited population
- Few available products
- Lifelong (common) diseases
- High unmet needs

The primary market movers are outlined in Figure 3.
Increased diagnosis, as a result of awareness campaigns or better diagnosis techniques, is one of the few opportunities for a market to move from the bottom towards the top of parameter space. However, the extent to which a market may “move up” is limited by the fact that a company which has invested to increase diagnosis generally tries to ensure they capture these new patients. This, however, highlights a potential opportunity in some therapeutic areas by increasing the size of the known pie. A great example of this market change is Multiple Sclerosis (MS), which in the 1980s was known as a rare disease but no longer is because diagnosis has greatly improved—there are as many as 500,000 diagnosed patients with MS in the US according to the Multiple Sclerosis foundation (vs ~200,000 patients in the US in the 80s).

In contrast to increased diagnosis, product introductions shift a rare disease market down and to the right. The type of product introduced dictates the magnitude of the move in each direction. While this is similar to a traditional market, the introduction of only one or two products could move these markets completely across the 2x2.

- **Incremental products** (“me-too” or those without significant efficacy or safety improvements) move the market dramatically from left to right. Vertical movement for incremental products is driven by improvements in patient programs and patient “maintenance.”
- **Differentiated products** have the potential to move a market substantially to the right and down depending on the points of differentiation relative to existing products.
- **Curative products** essentially drive a market to the bottom as the curative product eliminates the opportunity to acquire the patient.

When considering all of this, remember that where a market is positioned is not necessarily the same thing as how your product might experience the market.

Over time, rare disease markets move down and to the right, but with varying trajectories and numbers of steps. Figure 4 shows the progression of the Hemophilia A market from the early 1900s to present day. The first wave of products to treat Hemophilia A was first introduced in the 90s, with Baxter gaining a hold in the market. This has impacted subsequent product introductions, and increased the ease with which Baxter has captured share with follow on products and forcing competitors to fight hard for market share. Even the most recent wave of long-acting products have been introduced.

![Figure 4. An Example of Market Progression, Hemophilia A](image-url)
products (requiring less frequent prophylactic dosing) has experienced slow adoption primarily due to heavy competition, thus making it difficult for the new market entrants to acquire patients. Any incremental or even moderately differentiated product entering this now saturated Hemophilia A market should expect to invest heavily to gain market share, with a relatively slow uptake. In order for a new product to "make this market" and not fight for share, it will have to demonstrate significant efficacy and potentially be curative. A curative product would enter the market like it is in the top left, while forcing the market to crash into the bottom.

**Strategic Implications**

There are key strategic differences between a market with high or low current commercial development, and/or high or low ease of patient acquisition. Products entering a market with limited current commercial development have the ability to "create" the market as opposed to fighting for share in a market with established commercial presence. If the commercial market is in its infancy, patient acquisition may be straightforward and focus primarily on patient identification. In a more advanced market, patient acquisition will be driven by marketing and communicating product value to physicians and patients. Across the patient acquisition spectrum, both HCP and patient awareness are critical to adoption.

Marketing a rare disease product is about ensuring the maximum number of patients has access to the treatment and that the commercial potential is maximized to enable future product research and shareholder return on investment.

**Figure 5.** Required commercial investment ($) and expected early adoption rate (syringe) by segment. High level strategic imperatives have also been included by column and row for consideration.

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<th>Level of Commercial Investment</th>
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In the top half of the framework, where ease of patient acquisition is high, patients are readily diagnosed and/or visible to the manufacturer, leading to rapid product adoption driven by awareness and differentiation marketing. In contrast, the bottom half of the framework represents patients that are not readily available to new market entrants due to lower disease awareness, poor diagnosis and/or due to entrenched (and potentially similar) products for the same rare disease with whom patients are comfortable, loyal and not easily convinced to switch from. This increases the activation energy required to capture new patients, thus increasing relative investment and slowing relative uptake.

Broadly speaking, the left half of the framework necessitates increased disease awareness. A market entrant has the ability to create the market for these diseases, shaping the expectations of
The Take-Away

The rare disease market is a lucrative one, making it an increasingly common component of biotech and pharma portfolios. However, it is also a rapidly evolving one that is coming under increasing scrutiny by lawmakers and payers because of escalating costs. When considering which rare disease market to enter and how to enter it, the framework described above is a useful starting point for deep strategic and financial analysis. Alignment on expectations is critical for commercial and corporate leadership. This framework should not define how attractive a market is or how much investment is required to support the new product; rather, it should be used to help formulate the initial questions that will need to be answered during the commercialization process and frame a high-level approach for bringing the product to market.

patients, becoming the standard of care, increasing diagnosis and treatment rates, identifying and developing centers of excellence and even shaping the KOL landscape. This market maker ability may result in solid returns with less commercial investment. Alternatively, the right side of the framework is much more competitive and requires traditional brand and product promotion efforts in order to achieve product maximization which often require significant additional commercial investment. While the rare disease space is not typically thought of as requiring significant competitive marketing and brand differentiation, it is increasingly the case as more manufacturers expand focus into the rare disease space and pipeline products from previously “early” markets are approved.

By using this framework to categorize rare diseases, manufacturers can begin thinking strategically about where to play and at what level to spend. Additionally, they can set investment and return expectations early, both internally and externally. While this approach serves as a foundational starting point, all successful product launches require ongoing market analysis and strategic refinement.

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On the Runway to Commercialization, Define Value

By Meg Alexander, Head of Reputation and Risk Management, inVentiv Health

The explosion in orphan-designated therapies has led to miraculous results—a hopeful signal for rare disease patients and their families who previously had few options. But today, when companies decide to pursue the development of a rare medicine, they need to do it with eyes wide open to the environment they are entering—and the reception they might receive—where there have been dramatic shifts in recent years. Gone are the days when orphan drug prices flew under the radar. Research by inVentiv Health shows that negative media coverage on the price of rare medicines has increased nearly five-fold since 2012. Critical news coverage and Congressional inquiries have recently prompted manufacturers to “hit the pause button” on the launch of a new drug, or reconsider their pricing strategy entirely. And intensified scrutiny is coming from virtually all rare disease stakeholders. For example, while often desperate for new therapies, key opinion leading physicians, patient advocates and providers are progressively raising concerns about the affordability of medicines in orphan diseases.

All this signals a bumpier road ahead for investigational orphan medicines racing toward the market. Companies need to prepare for turbulence well in advance of launch by building a compelling case for product value, making that case to an expanding list of stakeholders and setting expectations appropriately—and early. All too often, the discussion about an orphan drug’s price is oversimplified and comes too late in the commercialization process. The result can be public sticker shock when the medicine hits the market and the focus is immediately on the list price. To prevent this, developers must be prepared to engage with their key stakeholders in larger discussion about what the community needs, and the value the company can deliver to address those needs. A deeper understanding of company efforts can help patients and physicians better understand the factors accounting for a rare therapy’s price. In addition to developing the medicine, biopharmaceuticals commonly invest in a number of efforts that carry value for the communities they serve, such as:

- Medical study to uncover the underlying cause of a poorly-understood disease
- Educating physicians who may know little about a condition impacting so few people
- Identifying and recruiting patients to participate in research (which, in rare diseases, can be like finding the tiniest of all needles in a haystack)
- Conducting registries so the treater community can learn more about the disease and methods of care over time
- Preventing patients from coming under increasing scrutiny by lawmakers and payers because of escalating costs.

Developers must also communicate at launch the actual range of out-of-pocket costs patients will pay for the medicine following insurance coverage discounts. All too often, the list price is the only context and alarms patients who fear they will not be able to afford the medicine they desire.

The bottom line? If you don’t define the value of your medicine—early and often—then others will do it for you.

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