

ORPHAN DRUG DEVELOPMENT

Realizing opportunities and addressing challenges

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A FOCUS ON ORPHAN DRUG STRATEGY

Leveraging market intelligence to support orphan drug development and commercialization strategies

Rare diseases offer remarkable opportunities to the pharmaceutical industry, but the prospects are intertwined with clinical and regulatory challenges in addition to unique market dynamics. These challenges have a huge impact on both the development and commercialization processes. There are multiple Market Intelligence (MI) tools and initiatives that could prove valuable in supporting the drug development process. However, the approaches used may need to be tweaked to cater to the rare disease environment.

A growing market opportunity

Although the rare disease market remains relatively small, orphan drug development is growing at an incredible pace. In 2014, there were a record 291 orphan drug designations in the US (which treat fewer than 200,000 patients) and worldwide orphan drug sales are forecast to total \$178 billion between 2015-2020.¹

This surge in orphan drug activity was triggered with the introduction of the U.S Orphan Drug Act

of 1983, and similar legislation in Japan in 1993 and the EU in 2000.¹ The combination of fast-track reviews, reduced research and development costs, tax-breaks, and market exclusivity have led many companies to view this previously overlooked, small market as big business.^{1,2} With significant financial incentives and competitive advantages, the orphan drug market has become a profitable opportunity for companies who are willing to invest in the rare disease space.

Parameters	USA	Japan	EU
Original legal framework	Orphan Drug Act (1983)	Orphan Drug Regulation (1993)	Regulation (CE) N°141/2000 (2000)
Administrative authorities involved	FDA/OOPD	MHLW/OPSR (Orphan Drug Division)	EMA/COMP
Prevalence (per 10,000 individuals)	7.5	4	5
Marketing exclusivity	7 years	10 years	10 years
Tax credit	Yes: 50% for clinical studies	Yes: 6% for any type of study + limited to 10% of company's corporate tax	Managed by the member states
Grants for research	Programs of NIH and others	Governmental funds	"FP6" + national measures
Technical assistance for regulatory filing	Yes	Yes	Yes
Accelerated marketing procedure	Yes	Yes	Yes (via the centralized procedure)

Figure 1: Regulatory Pharmaceutical Incentives³

Adapted from Sharma A et al. Orphan drug: Development trends and strategies J Pharm Bioallied Sci. 2010; 2(4): 290-299. Table 4

A changing competitor landscape

The increased development and licensing of orphan drugs in recent years has led to greater competition and a changing market dynamic. The orphan drug market is now starting to more closely resemble the trends and challenges seen within traditional pharma markets.²

Historically many rare diseases offered limited or no effective treatment options.³ However, as some rare diseases now introduce second and third entrant orphan drugs, the reimbursement challenges are increasing. Products which launch into indications where an approved orphan therapy already exists now require a greater burden of evidence to show value due to a decreased level of unmet medical need.²

A recent article on the maturing rare-disease market has highlighted that in addition to a changing reimbursement environment, companies may now also face significant challenges including study execution obstacles and regulatory hurdles.²

Payer demands are also beginning to change in rare disease indications with multiple treatment options. For example, there is already precedence of payer push back and elastic reaction to pricing in Gaucher disease and cystic fibrosis.²

However this does not appear to be deterring the big pharma players who are starting to dominate the orphan drug space (**see Figure 2**). Despite the changing landscape, those companies with clear strategic planning who require an orphan drug presence can skilfully navigate the clinical, regulatory, and financial challenges.

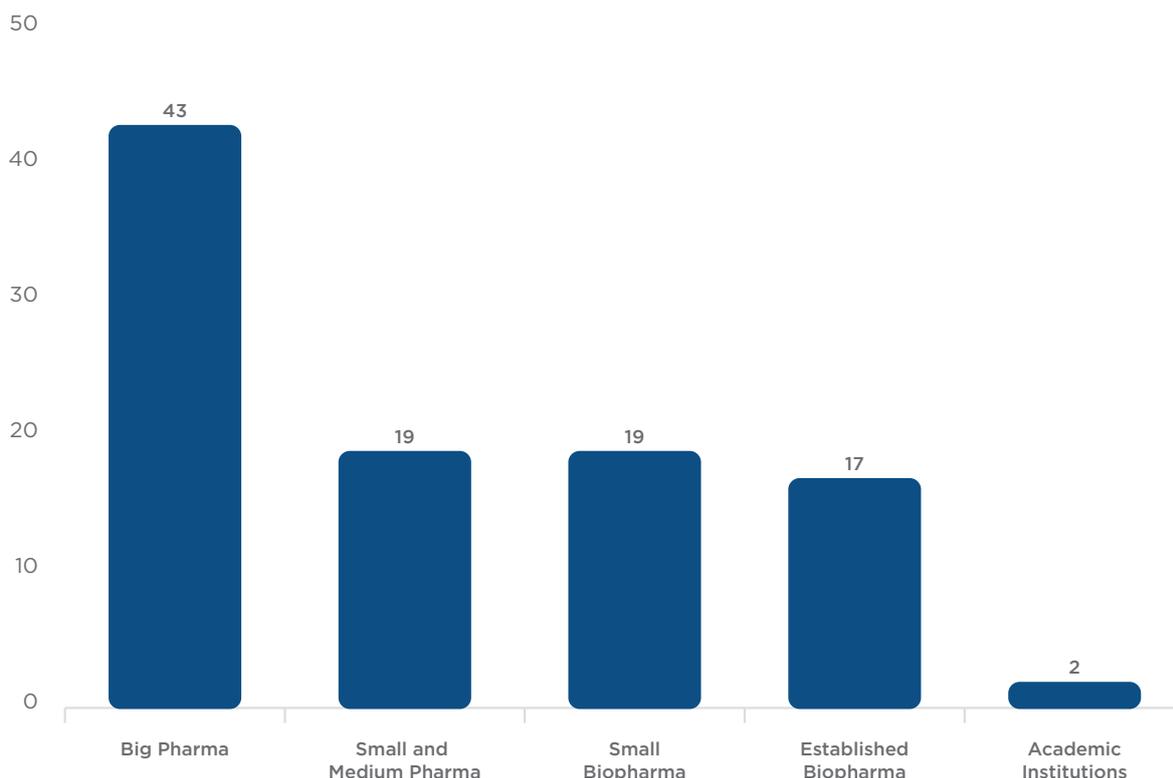


Figure 2: FDA Orphan Drug Approvals⁴

Adapted from Ariyanchira S. Big Pharma Steps Into Orphan Drug Market. Genetic Engineering and Biotechnology News 2010; 30(12).

Challenges through the development pathway

Each step in orphan drug development presents specific challenges. In the rare disease space, there are a number of key considerations to contemplate at every development stage. Although similar issues are encountered in typical non-orphan drug development programs, they are frequently more difficult to address in the context of a rare disease, as there is often limited medical experience. These issues often become more acute with the increasing rarity of a disorder.

Early Drug Discovery

At the early drug discovery phase, one of the key challenges centers around disease pathogenesis, as there is often limited knowledge and medical expertise available.³ Another consideration with challenges is the biological target identification, which may involve limited basic research conducted amongst the scientific community and inadequate identification of signals specific to the rare disease.⁵ Companies should be aware that there may be potentially increased resources required to find a lead compound.

Pre-Clinical Research

Pharma-toxicology testing is often limited and no animal models of the rare disease may exist, which can present a challenge. Disease pathophysiology also presents a barrier due to limited knowledge or documentation of the natural disease history, such as disease manifestation and subtype identification.⁵ Additionally with Investigational New Drug (IND) applications for orphan drugs, there is limited precedent and often evolving pre-clinical requirements.

Clinical Development

Patient recruitment during clinical development can be at times problematic since there is a limited and small eligible patient pool with a wide geographical spread. A traditional trial design may be difficult to implement given that rare diseases often involve unclear or unknown endpoints.⁶ Novel statistical data analysis methods may be necessary to take into consideration as well.² Proper trial site identification is also quite crucial, as under- or mis-diagnosed rare diseases lead to limited availability of 'Centers of Excellence'.

Regulatory Review and Launch Preparation

Several factors need to be considered during the regulatory review process. There will often be a limited dataset and sample size with unfamiliar endpoints, which requires closer interaction with the FDA to optimize approval probability. For example, adaptive trials designs can create questions around the data, which may lead to review delays. Furthermore, pharma companies may face setbacks in preparation for launch due to lack of disease awareness, which can make it difficult to recruit a suitable field force for pre-launch activities. Establishing an early position amongst the medical and patient community within the rare disease may be a critical step toward success.

Access and Post-Market

Pricing and reimbursement is a key challenge as orphan drugs typically attract higher price points with difficult reimbursement. Post-market commitments can be unclear and may be associated with long-term risk/benefit need. Competitor trials may also block patient recruitment. Patient Access & Support Programs are key differentiators and critical for success due to marginalized patients with financial hardships and access burden, who depend on patient centric solutions offered by the pharma company.

Putting Market Intelligence into Practice

Rare Disease Drug Development Case Study

Background and Business Challenge

There is currently a heated race among several competitors to develop the first FDA-approved treatment in a rare disease that affects around 30,000 patients worldwide. The current treatment approach only focuses on symptom management and mis- or under-diagnoses are common.

Competitive Landscape

Two established rare disease competitors are vying for first-to-market advantage with Phase 3 trials currently ongoing in the U.S. and EU markets, respectively. There are several competitors in early-stage development as well.

Company Profile

A mid-size pharma company has several rare disease products in clinical development; however no products are currently marketed. The company has a new drug which has recently completed Phase 2 trials in the U.S.

Business Challenge

The company is interested in increasing their rare disease presence and is looking to understand how to best move forward into a global Phase 3 development program and optimize their path to regulatory approval.

Project Outcomes

By compiling various sources of information and validating the strength of local enrollment, the company was able to prioritize a list of trial sites to approach for participation in their Phase 3 trial. Furthermore, the project identified other untapped ex-U.S. and ex-EU centers that could boost overall enrollment and speed development timing.

How MI supported the development and regulatory strategy

Project Objective

The company conducted a Market Intelligence project that assessed the ease of patient enrollment, specifically aimed at compiling a list of potential global trial sites that could enhance clinical trial timing.

Methodology

The U.S. and EU trials sites participating in competitor Phase 3 trials were mapped and primary research was conducted with Principal Investigators (PIs) to understand ease of local enrollment, as well as information on other key ex-U.S./ex-EU global centers.

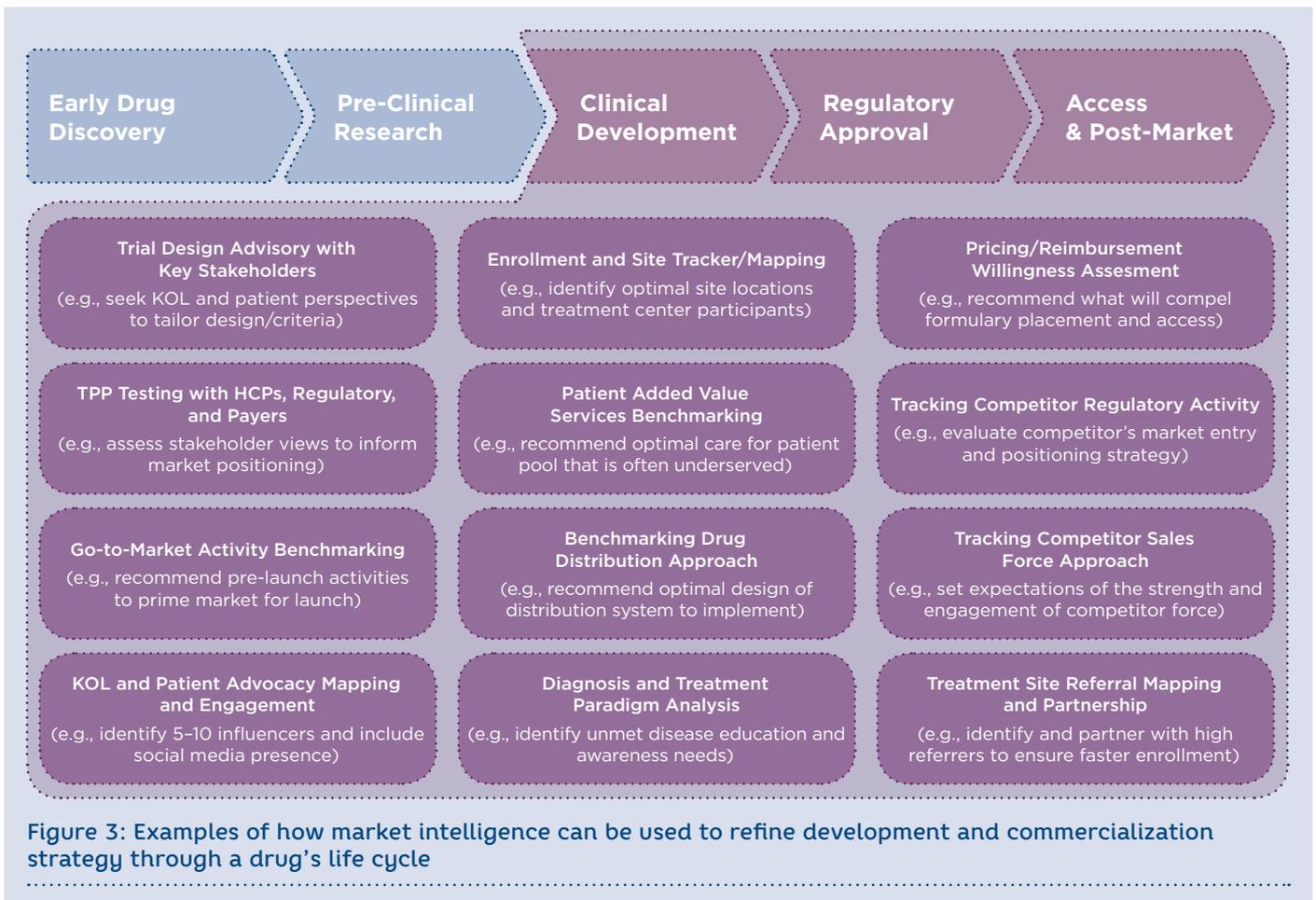
Challenges

- Many PIs were difficult to reach
- Some PIs were unfamiliar with other key global centers
- Recruitment insights were generalized

How challenges were addressed

- Enrollment Potential
 - Additional sources, such as trial site coordinators, were contacted to provide further perspective on enrollment
 - Sites were contacted every 3 months to track recruitment rate in order to assess the local potential of the area
- Global Site Identification
 - Specific conferences with some level of focus on the rare disease were attended to identify and establish relationships with ex-U.S./ex-EU PIs
 - International patient advocacy groups were contacted for additional information about other potential ex-U.S./ex-EU centers

There are multiple other ways that MI can be used throughout drug development. Some of these examples are given in Figure 3.



MI approach considerations and additional market pressures

When commissioning Market Intelligence engagements in the rare disease space, companies must be aware of some of the challenges from the outset. For example, limited target sources mean there is an increased need to build relationships and conduct creative primary research including attending domestic and international conferences to speak to hard-to-reach healthcare professionals and advocates. Specific to reimbursement stakeholders, a lack of disease education or precedent may require more reliance on case analogs to inform payer engagement.

Increasing the confidence of insights gathered can prove difficult, therefore companies may consider partnering with patient advocacy stakeholders and creatively corroborate insights beyond traditional primary research techniques by tracking social media sites and online patient communities. To increase the source pool, it can be important to obtain additional source referrals from healthcare professionals and patients.

As there is often a higher risk and exposure level dealing with a limited source pool, expanded or more sparsely distributed primary research timing is required. For example, overlapping and limited trials sites may require more focus on secondary tier sources. Also due to lack of market precedence, there is greater reliance on market analogs and consideration of patient perspectives.

There are also additional rare disease market pressures that are impending in the years to come. A few examples include:

- Increased effort to repurpose drugs in the rare disease space
- Broader competition across the industry as rare disease drug development becomes a trend
- Growing interest in rare diseases by generic manufacturers

These will certainly necessitate even further refinement of MI techniques as the market grows savvier and more competitive.

Conclusion

Market Intelligence is an important tool to help pharma companies have confidence in their assumptions about the external environment and improve the decision making process. In the rare disease space, although many challenges are presented throughout drug development, there remains an exciting opportunity for the industry. Understanding what these challenges are from the outset, and how they might impact product development, will allow you to optimally leverage MI tools.

About the Authors



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Hormoz is a Senior Consultant in the Deallus Los Angeles office. He has primarily focussed on rare diseases within CNS, respiratory, nephrology, hepatology, endocrinology, and cardiovascular therapeutic areas. He has successfully led global strategic and tactical rare disease engagements involving product launch, market landscaping, conference coverage, competitive benchmarking, market access, and regulatory advisory.

Hormoz has been a crucial thought partner to a variety of cross-functional stakeholders responsible for an array of pipeline and marketed rare disease products. He has extensive knowledge of key rare disease market dynamics (e.g., significance of biomarkers and companion diagnostics, innovative clinical trial design trends, development of novel endpoints, optimizing reimbursement and regulatory positioning).

Hormoz holds a PhD in Neuroscience and an MS in Biomedical Engineering from USC. He has over eight years of laboratory research experience at USC as a graduate student and Johns Hopkins University as an undergraduate student.



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Inass is a Principal based in the London office. She has worked with a broad spectrum of global leaders in the orphan disease space providing strategic consulting services across various stages of the drug life cycle. Key disease areas of focus have been in cardiovascular, inherited metabolic disorders, growth disorders, oncology and many more. Inass has typically helped clients develop and pressure-test their go-to-market and commercialization strategies in Europe to suit the unique orphan drug market dynamic, largely with a focus on field force strategy, patient advocacy, key customer centric initiative development, and competitive positioning.

Inass also leads Deallus' Strategic Workshop and Gaming Practice, and has extensive experience in designing and facilitating brand strategy workshops.

Inass embarked on her consultancy career after completing a Doctorate of Engineering (EngD) in the field of Biochemical Engineering from University College London.

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About Deallus Consulting

Founded in London in 2004 with offices in New York, Princeton, Los Angeles, Singapore, Tokyo, China and LATAM. Deallus Consulting is a strategy consulting firm focussed on the Life Sciences industry. Deallus Consulting improves strategy by developing, testing and refining the key market assumptions that underpin it through comprehensive research and our rigorous analysis.

Our presence in the USA builds on a strong foundation of regional knowledge from the JPAC HQ based in Singapore and a Japan office based in Tokyo, with on-the-ground support from local consultants.

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