Drugs for Rare and Orphan Diseases: From Endpoints to Endgame

April 20, 2016
Overview

The Need for a Commercial Team Early

Rare and Orphan Diseases Landscape

Early Commercial Support

Case Examples

Conclusions
Deep Insights; Experienced Perspective, Robust Assessment

- Opportunity Assessment
- New Product Forecast/Valuation
- Pre-Launch Commercial Support
- Brand Rejuvenation
The pathway to success is driven by continued product usage.

**Evolving Company Concerns**

- Will the product get used?
- Will it be reimbursed?
- Will it get approved?

- Which patients?
- Which MDs?
- How often?
- How long?
- At what price?

**Future Success**
The earlier you address commercialization issues, the better

Most companies worry about commercialization too late
A product’s uptake trajectory plateaus very quickly post-launch.

**Launch trajectories in the US**

- New-to-Brand is defined by therapy naïve, switch-to or add-on prescription.
- ~150 US launches (2004 – 2012), patient acquisition uptake inflects on average 14 weeks post launch:
  - New indication and data could change the level of patient acquisition.
  - Some marketing events (DTC) can provide a change in patient acquisition.
  - Managed care reimbursement shifts can expand the pool of potential patients.

**SOURCE:** IMS Health. “Launch Excellence study”
**RED TEAM APPROACH**

**Early commercial input during development minimizes unnecessary costs and accelerates product uptake**

![Go/No-go Decision Point](image)

<table>
<thead>
<tr>
<th>Exploratory Phase</th>
<th>Confirmatory Phase</th>
<th>Clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery/Opportunity assessment</td>
<td>Proof of concept clinical trials</td>
<td></td>
</tr>
</tbody>
</table>

**Decision Point**

- Target selection
- High unmet need
- PK
- PoC
- Effective and safe
- NDA/ANDA submission

**Early Commercial Input**

- Assess the business case for the potential product asset
- Develop an initial target product profile
- Demonstrate proof of concept
- Establish dose selection

- Identify target patient population, confirm optimal dose & dosing regimen, and establish benefit/risk ratio
- Adaptively incorporate new clinical and commercial findings into trial designs
- Develop Go-to-Market Model
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Rare and Orphan Diseases: Narrow markets, little competition

Why Do I Need to Bring on a Commercial Team Early?
What Do a Drug for a Rare or Orphan Disease and the New Tesla Have in Common?
What Do a Drug for a Rare or Orphan Disease and the New Tesla Have in Common?

In Both Cases, **Noise Precedes Signal** vs Signal Preceding Noise
Managing Information and Controlling Expectations Pre-launch are Critical Priorities

The Zero Moment of Truth

SOURCE: Google; Red Team Associates
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Conclusions
Why are the Rare and Orphan Disease Markets Booming?
Many Orphan Products Have Entered the Market in Recent Years

Number of Orphan Drugs Approved for Cancer vs Other Areas, 2006-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Oncology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>2007</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>2008</td>
<td>5</td>
<td>2</td>
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<tr>
<td>2009</td>
<td>9</td>
<td>6</td>
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<tr>
<td>2010</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2011</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>2012</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>2013</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>2014</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>2015</td>
<td>21</td>
<td>10</td>
</tr>
</tbody>
</table>

SOURCE: FDA; Red Team analysis
Favorable Drivers for Pharma to Pursue Orphan Products

• Significant unmet need: Only 7% of NIH defined rare diseases have therapeutic treatments
• High commercial potential and significant ROI
• Regulatory incentives

Current Environment

<table>
<thead>
<tr>
<th>Year</th>
<th>Orphan Status</th>
<th>Expedited review</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>299</td>
<td>50</td>
</tr>
<tr>
<td>2014</td>
<td>326</td>
<td>157</td>
</tr>
<tr>
<td>2015</td>
<td>394</td>
<td>182</td>
</tr>
</tbody>
</table>

SOURCE: FDA; Red Team analysis
High Prices of Orphan Drugs x Duration of Therapy = Unique Commercial Opportunities

Drug Costs per Patient by Orphan Status
Average Cost per Patient per Year 2010-2014

- Every patient is “a walking asset”
- Cost effective to invest heavily in the population
- Challenge is identifying value added capabilities and executing them effectively

SOURCE: EvaluatePharma
Being First Matters

First Mover Advantage

• Receive the maximum benefits of accelerated approval

• Get the opportunity to set the pricing for the treatment category

• Raises the bar for later entrants either in terms of product differentiation or need to demonstrate added value

• Later entrants often spend almost as much as first mover companies but rarely enjoy the market penetration of first movers
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How Does a Commercial Team Support the Development and Commercialization of a Rare Disease Product?
1. Understanding the Patient Journey is the foundation for future value

The patient journey is the foundation for creating future value
Recognize that it takes a village to Dx, treat, and manage patients suffering from a rare or orphan disease.
Marketing Drugs in Rare Diseases Poses Unique Challenges

- High Unmet Need
- Getting a proper Dx and treatment often takes years
- Physicians know little about the condition
- Often difficult to find KOL’s knowledgeable in Dx and management of the patient
- Parents are often better informed than physicians
- Support is general vs specific
**Minor, Unique or Unfamiliar Symptoms**

**Extremely Low Prevalence**

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**Lack of Awareness of Rare Disease Symptoms Leads to Delays or Mis-Diagnoses and Treatment**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Est. Diagnosis Rate</th>
<th>Est. Treatment Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pompe</td>
<td>6%</td>
<td>83%</td>
</tr>
<tr>
<td>Fabry</td>
<td>10%</td>
<td>60%</td>
</tr>
<tr>
<td>Gaucher</td>
<td>20%</td>
<td>70%</td>
</tr>
<tr>
<td>Hemophilia(^1)</td>
<td>30%</td>
<td>44%</td>
</tr>
</tbody>
</table>

\(^1\)Percent diagnosed patients on prophylaxis is shown for Hemophilia

SOURCE: Sanofi/Genzyme; WHF 2015 Global Survey; Red Team engagements

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Broad Strategies that Can Be Done Pre-Launch to Accelerate Proper Dx

- Provide Disease Awareness and Education
- Connect Patients and Caregivers
- Make Patients Aware of Treatment Specialists
- Make Patients Aware of Resources to Support Treatment
Specific Opportunities for Companies to Consider in Commercializing Rare Disease Treatments

- Financial Assistance & Reimbursement
- Clinical Development vs Standard of care
- Patient and family support
- Care coordination
- Physician/patient education
- Target Patient Segment(s)

SOURCE: Red Team Associates
### Some Best Practices in Commercializing Drugs in Rare Diseases are Emerging

<table>
<thead>
<tr>
<th>Customer Segment</th>
<th>Examples</th>
<th>Time to Initiate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engage KOLs</td>
<td>• Understand the natural history of the disease&lt;br&gt;• Obtain feedback on clinical trial designs, etc.</td>
<td>• Phase 1/Start of Phase 2</td>
</tr>
<tr>
<td>Engage FDA and Payers</td>
<td>• Work with regulators and payers to evolve clinical trial strategy recognizing that many orphan diseases are uncharted territory</td>
<td>• Phase 2</td>
</tr>
<tr>
<td>Support Physicians and other HCPs</td>
<td>• Develop and disseminate educational materials to recognize symptoms and facilitate more rapid diagnosis&lt;br&gt;• Multiple treaters + EMR = More asynchronous communication which is not necessarily better for patient care</td>
<td>• End of Phase 2/Start of Phase 3</td>
</tr>
<tr>
<td>Connect with Patients and Caregivers</td>
<td>• Patients/caregivers are often highly organized and motivated&lt;br&gt;• Engage with advocacy groups who may have registries of patients&lt;br&gt;• Develop websites, educational materials, etc.</td>
<td>• Phase 2/3</td>
</tr>
<tr>
<td>Engage with Specialty Pharmacies</td>
<td>• Understand prior authorization criteria&lt;br&gt;• Reimbursement support&lt;br&gt;• Dissemination of patient educational materials&lt;br&gt;• Outcomes data collection</td>
<td>• Phase 3</td>
</tr>
<tr>
<td>Address financial obstacles</td>
<td>• Develop Financial Assistance Programs for patients&lt;br&gt;• Think about ways to help patients/caregivers deal with non-drug related financial challenges as a result of their disease</td>
<td>• Phase 3</td>
</tr>
</tbody>
</table>

SOURCE: Pharmaceutical Commerce, August 2015; Red Team analysis
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## CASE STUDY

### Examples of Providing Increased Information Availability to Parents and Physicians

<table>
<thead>
<tr>
<th>Channel</th>
<th>Digital</th>
<th>Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yourtrueid.com – Stories of other people and families navigating life with hemophilia (Baxalta)</td>
<td>Grants supporting regional educational meetings for aHUS patients (Alexion)</td>
</tr>
<tr>
<td></td>
<td>Rare in common – user-generated short-film about the inspiring people in the rare disease</td>
<td><strong>This American Life</strong>, a radio show on NPR, produced a story on one patient’s journey to getting diagnosed</td>
</tr>
<tr>
<td>Digital</td>
<td>CF GeneE™ - Educational application for HCPs (Vertex)</td>
<td>Scientific / Medical Journal Publication</td>
</tr>
<tr>
<td></td>
<td>PNH-specific, online informational resource launched ~2 years prior to the approval of Soliris (Alexion)</td>
<td>Medical conferences</td>
</tr>
<tr>
<td></td>
<td><strong>PNHSource</strong></td>
<td>Fellowships and research grants</td>
</tr>
<tr>
<td></td>
<td>Daily living</td>
<td>Scientific / Clinical</td>
</tr>
</tbody>
</table>
| **Content**      |                                                                        | SOURCE: Company websites; FiercePharma; Red Team analysis
CASE STUDY

Alexion's Diagnostic Initiatives Enabled the Company to Continuously Identify New PNH Patients Since Soliris Launch

Soliris Programs to Support the Patients and Relevant Stakeholders

- **Algorithm**: Worked with clinicians to develop an algorithm to diagnose patients with PNH
- **Biomarker**: Rule PNH in or out using high-sensitivity flow cytometry and comprehensive clinical assessment
- **Partnerships**: Formed partnerships with laboratories

Prior to the launch of Soliris, Alexion launched One Source, a program that pairs PNH patients with a registered nurse case manager
- Dedicated nurse case managers
- Patient education and symptom monitoring support
- Assistance with access to therapy

SOURCE: Soliris investor presentation; Alexion website
CASE STUDY

Achieving Sustained Growth through Increased in Patient Volume

### Soliris’s Sustained Growth, 2007-2015
Product Net Sales in millions

<table>
<thead>
<tr>
<th>Year</th>
<th>Product Net Sales in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>66</td>
</tr>
<tr>
<td>2008</td>
<td>259</td>
</tr>
<tr>
<td>2009</td>
<td>387</td>
</tr>
<tr>
<td>2010</td>
<td>541</td>
</tr>
<tr>
<td>2011</td>
<td>783</td>
</tr>
<tr>
<td>2012</td>
<td>1,134</td>
</tr>
<tr>
<td>2013</td>
<td>1,551</td>
</tr>
<tr>
<td>2014</td>
<td>2,234</td>
</tr>
<tr>
<td>2015</td>
<td>2,603</td>
</tr>
</tbody>
</table>

**CAGR, 2007-2015: 58%**

**YoY Growth**
- 2007: 290%
- 2008: 49%
- 2009: 40%
- 2010: 45%
- 2011: 45%
- 2012: 37%
- 2013: 44%
- 2014: 16%

**Key Growth drivers**
- PNH (FDA)
- PNH (EMA)
- aHUS (FDA)
- aHUS (EMA)
- Price adjustment

**SOURCE:** Alexion’s 10K; Red Team’s Commercial Excellence in Rare Diseases Database; Red Team analysis
## CASE STUDY

**BioMarin Leverages its Experience with Naglazyme When Commercializing Vimizim**

### Building on the success of Naglazyme

- Identified over 1,400+ MPS IVA patients before launch
- Commercial organization was in the field and ready when the product was approved
- Vimizim is expected to achieve the current level of Naglazyme market penetration in half the time
- Commercial organization was ready

### Identifying Patients in Rare Disease...

**Net Sales in millions**

<table>
<thead>
<tr>
<th>Quarter</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Q2</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>Q3</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>Q4</td>
<td>37</td>
<td>58</td>
</tr>
</tbody>
</table>

**Net Sales in millions**

- FDA approval: 2/14/14
- EMA approval: 4/28/14

**SOURCE:** BioMarin’s 2015 JPM presentation; SEC filings; FDA website; EMA website
Developing a Set of Clinical Relevant Endpoints...

### Endpoints from Pivot Trial
- ppFEV1
- CFQ-R
- Sweat Chloride
- Exacerbation
- BMI

### Level of importance
(1=not important; 10=very important)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FDA</th>
<th>Payers</th>
<th>Physicians</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppFEV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFQ-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweat Chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**SOURCE:** Kalydeco’s Ph. 3 Pivotal trials (TRAFFIC and TRANSPORT); Red Team engagements
CASE STUDY

Enabled the Rapid Adoption of Kalydeco by the CF Community

Uptake of Kalydeco
Percent of eligible G551D patients

81% of eligible patients (Dec 2012)

SOURCE: CFF Patient Registry; Sawicki, Dasenbrook, Fink, et al; Red Team analysis
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Conclusions
When Noise Precedes Signal, Managing Clinical Trial Information, and Preparing for Launch are Critical to Driving Uptake and Outcomes

<table>
<thead>
<tr>
<th>Example Value Drivers</th>
<th>Initial Awareness</th>
<th>Good First impression</th>
<th>High Rx Potential</th>
<th>Good Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease awareness</td>
<td></td>
<td></td>
<td>Referral to or managed by “Treaters”</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Patient group support</td>
<td></td>
<td></td>
<td>Out-of-pocket cost</td>
<td>Ease of obtaining drugs</td>
</tr>
<tr>
<td>Internet</td>
<td></td>
<td></td>
<td>PRO’s</td>
<td>Drug adherence</td>
</tr>
<tr>
<td><strong>Physician</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conferences</td>
<td></td>
<td>Clinical trial experience</td>
<td>Awareness—Med Affairs</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Professional orgs.</td>
<td></td>
<td>Peer reviews, Med Affairs</td>
<td>Conferences</td>
<td>Patient satisfaction</td>
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<tr>
<td>Clinical Data</td>
<td></td>
<td>Conferences, Professional Orgs</td>
<td>Clinical data</td>
<td></td>
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<tr>
<td>KOL’s</td>
<td></td>
<td></td>
<td>On patient formulary</td>
<td>Cost-effectiveness of product</td>
</tr>
<tr>
<td><strong>Payer</strong></td>
<td></td>
<td>Clinical trial data</td>
<td>Contracting options</td>
<td></td>
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<tr>
<td>Conferences</td>
<td></td>
<td>HEOR data</td>
<td>Cost-savings</td>
<td></td>
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<tr>
<td>Early active discussion</td>
<td></td>
<td>Justified pricing</td>
<td>HEOR data</td>
<td></td>
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</table>

Source: Red Team Associates
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