Orphan drug development in China – Turning challenges into opportunities

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Summary

Of over 7,000 known rare diseases, only 5% currently have an available treatment option worldwide. Moreover, the vast majority of rare disease patients in China have no access to treatment due to limited availability and the lack of appropriate infrastructure in China’s healthcare system. Despite increased interest in orphan drug development, drug companies in China with active programs on drugs to treat rare diseases are still limited. Hence, there is a huge unmet need in China, with over 10 million patients suffering from rare diseases. Nonetheless, this has created unprecedented opportunities for the Chinese drug development market. Life science innovation in China has recently received a healthy boost from the 13th National Five-Year Plan and from on-going reform of the China Food and Drug Administration (CFDA). Rare diseases are now recognized as a national priority with increasing governmental support, creating tremendous opportunities for both domestic and multinational drug companies. China is anticipated to play an increasingly important role in the global fight against rare diseases. To ensure future success, Chinese drug companies should leverage the valuable knowledge assembled over the past three decades by Western countries in the area of orphan drug development.

Keywords: Orphan drug development, rare disease in China, challenges and opportunities

Recent successes in development of orphan drugs to treat rare diseases are in stark contrast to the challenge of decreased productivity faced by the global pharmaceutical industry with traditional research and development (R&D) models for more common diseases. Following this trend, several large multinational pharmaceutical companies such as Pfizer and GlaxoSmithKline have established in-house business units specializing in rare diseases (1,2). Many others have been actively working to acquire or partner with orphan drug companies, e.g., Sanofi acquired the leading orphan drug company Genzyme in 2011 (2); Biogen has partnered with Ionis to target spinal muscular atrophy (SMA) and with Applied Genetics to develop gene therapies for X-linked retinoschisis (XLRS) (3). Furthermore, several large companies specializing in rare diseases such as Shire and Alexion have seen tremendous growth over the past few years (2). Rare diseases are now such an attractive sector that orphan drugs have become the global drug industry’s leading area of specialization (Table 1).

Despite recent success in the orphan drug sector, effective therapies are only available for less than 5% of over 7,000 rare diseases, many of which are life-threatening and debilitating. The situation is even grimmer in China and many developing nations, where the vast majority of patients with a rare disease currently have no access to appropriate care due to low awareness of the diseases and limited access to specialists, diagnostic testing, and treatment. As a result, less than one-third of the > 500 orphan drugs that have been approved in the United States of America (USA) and other Western countries are available in China and developing nations. In China, the main type of indication for currently available orphan therapies is rare cancer, accounting for almost half of all orphan drugs (4). Since the majority of orphan drugs in China are not covered by health insurance, this further limits accessibility because of the high cost of most orphan...
drugs, low reimbursement rates, and low incomes; this translates into less affordability for the majority of the Chinese rare disease patients (Table 2) (5). In addition, only a few drug companies in China are specializing in rare diseases mainly due to the lack of legislative incentives that have been deemed essential for the success of the orphan drug industry in the USA.

Since the Chinese Government launched its first pilot project in 2013 to improve healthcare for rare disease patients (6), significant progress has been made at every front in the fight against rare diseases in China (Supplemental Table S1) (6-10). The recent announcement of the first National Committee of Experts on Rare Disease Treatment and Patient Protection (7) is another encouraging sign that policy-makers and legislators have begun to recognize the impact of rare diseases and are starting to consider those diseases as a national healthcare priority.

There are currently only a handful of drug companies in China with in-house R&D programs devoted to rare diseases, although this number is expected to grow tremendously thanks partly to increased public awareness. Chipscreen is a successful example, since the China Food and Drug Administration (CFDA) recently approved Chipscreen’s innovative cancer drug Chidamide for the treatment of peripheral T-cell lymphoma (PTCL).
played a critical role in the early stage of rare disease research and drug development. Rare disease organizations that rare disease research and drug development are commercially viable in China and the rest of the world. Several key criteria include:

1. Drug companies need to work closely with all stakeholders, including policy makers and regulatory agencies as well as rare disease communities, to create a healthy ecosystem as is essential for life science innovation.

2. Chinese drug companies interested in rare diseases should adopt a global outlook by eyeing the global market while operating in China and they should foster innovation through global collaboration by tapping into the intelligence and expertise of Western companies and joining forces with global partners.

3. Drug companies should decide areas to focus on by adopting a systematic approach with pre-defined criteria based on in-depth analyses prior to embarking on a program targeting a specific rare disease. The final decision should represent the best opportunities based on the information and resources available and focus on urgent, unmet needs that are medically addressable and commercially viable in China and the rest of the world. Several key criteria include:

   i) Vast unmet needs with no or limited options available, and especially those with the greatest impact on China.

   ii) Examples of major rare diseases in China include thalassemia, osteogenesis imperfecta, SMA, and Duchenne's muscular dystrophy (DMD).

Table 4. Several of the major organizations dealing with rare diseases in the USA, EU, and China

<table>
<thead>
<tr>
<th>Organization name</th>
<th>Type</th>
<th>Focus</th>
<th>Country/region</th>
<th>Link</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Organization for Rare Disorders (NORD)</td>
<td>umbrella</td>
<td>all rare diseases</td>
<td>USA</td>
<td><a href="http://rarediseases.org">http://rarediseases.org</a></td>
</tr>
<tr>
<td>Global Genes</td>
<td>umbrella</td>
<td>all rare diseases</td>
<td>USA</td>
<td><a href="https://globalgenes.org">https://globalgenes.org</a></td>
</tr>
<tr>
<td>EURORDIS</td>
<td>umbrella</td>
<td>all rare diseases</td>
<td>EU</td>
<td><a href="http://www.eurordis.org">http://www.eurordis.org</a></td>
</tr>
<tr>
<td>Chinese Organization for Rare Disorders (CORD)</td>
<td>umbrella</td>
<td>all rare diseases</td>
<td>China</td>
<td><a href="http://www.hanjianbing.org">http://www.hanjianbing.org</a></td>
</tr>
<tr>
<td>Rare Diseases International (RDI)</td>
<td>umbrella</td>
<td>all rare diseases</td>
<td>global</td>
<td><a href="http://www.rarediseasesinternational.org">http://www.rarediseasesinternational.org</a></td>
</tr>
<tr>
<td>Cystic Fibrosis Foundation (CFF)</td>
<td>focused solely on CF</td>
<td>CF</td>
<td>USA</td>
<td><a href="https://www.cff.org">https://www.cff.org</a></td>
</tr>
<tr>
<td>Spinal Muscular Atrophy Foundation (SMAF)</td>
<td>focused solely on SMA</td>
<td>SMA</td>
<td>USA</td>
<td><a href="http://www.smafoundation.org">http://www.smafoundation.org</a></td>
</tr>
<tr>
<td>Huntington Disease Society of America (HDSA)</td>
<td>focused solely on HD</td>
<td>HD</td>
<td>USA</td>
<td><a href="http://hdsa.org">http://hdsa.org</a></td>
</tr>
<tr>
<td>ALS Association (ALSA)</td>
<td>focused solely on ALS</td>
<td>ALS</td>
<td>USA</td>
<td><a href="http://www.alsa.org/">http://www.alsa.org/</a></td>
</tr>
<tr>
<td>SMA Europe</td>
<td>umbrella, with SMA patients and research organizations from countries across Europe</td>
<td>SMA</td>
<td>Europe</td>
<td><a href="http://www.sma-europe.eu">http://www.sma-europe.eu</a></td>
</tr>
<tr>
<td>European Huntington's Disease Network (EHDN)</td>
<td>umbrella, with HD patients and research organizations from countries across Europe</td>
<td>HD</td>
<td>Europe</td>
<td><a href="http://www.euro-hd.net">http://www.euro-hd.net</a></td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; CF, cystic fibrosis; EU, European Union; HD, Huntington's disease; SMA, spinal muscular atrophy; USA, United States of America.

Table 5. Companies developing gene therapies and the diseases they treat

<table>
<thead>
<tr>
<th>Company</th>
<th>Platform</th>
<th>Diseases treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spark Therapeutics</td>
<td>AAV-based gene therapy</td>
<td>rare forms of blindness, IRDs, such as RPE65-mediated IRDs (positive Phase III results), and choroideremia (Phase I/II on-going)</td>
</tr>
<tr>
<td>AveXis</td>
<td>AAV-based gene therapy</td>
<td>SMA (positive Phase I/II results)</td>
</tr>
<tr>
<td>AGTC</td>
<td>AAV-based gene therapy</td>
<td>rare ophthalmological disorders such as XLS and XLRP (early clinical stages or IND-ready programs)</td>
</tr>
<tr>
<td>uniQure</td>
<td>AAV-based gene therapy</td>
<td>familial LPLD (Glybera® approved), hemophilia B (Phase I/II), Sanfilippo B (Phase I), and PD (Phase I) and other rare genetic diseases of the liver/metabolism, CNS, and cardiovascular system</td>
</tr>
<tr>
<td>Bluebird Bio</td>
<td>Lentivirus-based gene therapy</td>
<td>severe genetic disorders such as CALD (Phase II/II), transfusion-dependent β-thalassemia (also known as β-thalassemia major) (Phase II/II), and severe sickle cell disease (Phase I/II)</td>
</tr>
<tr>
<td>Regenxbio</td>
<td>AAV-based gene therapy</td>
<td>HoFH (Phase I/II trial); MPS type I &amp; wet AMD (IND-ready)</td>
</tr>
<tr>
<td>Bamboo Therapeutics</td>
<td>AAV-based gene therapy</td>
<td>rare genetic disorders such as GAN (Phase I/II on-going), DMD, and FA</td>
</tr>
<tr>
<td>Voyager Therapeutics</td>
<td>AAV-based gene therapy</td>
<td>rare CNS diseases, such as PD (Phase I/II on-going), ALS, and HD</td>
</tr>
<tr>
<td>Dimension Therapeutics</td>
<td>AAV-based gene therapy</td>
<td>rare genetic liver disorders, including hemophilia B (Phase I/II)</td>
</tr>
<tr>
<td>Ionis Pharmaceuticals</td>
<td>antisense -based therapy</td>
<td>HoFH (KYNAMRO® approved) &amp; pouchitis (Alicaforsen approved) and a wide range of rare genetic diseases, including SMA (positive Phase III results) and HD (Phase II on-going)</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals</td>
<td>RNAi-based therapy</td>
<td>a wide range of rare genetic diseases, including hereditary amyloidosis ATTR (Phase III), hemophilia, and rare bleeding disorders (Phase II)</td>
</tr>
</tbody>
</table>

AAV, adeno-associated virus; ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; ATTR, TTR-related amyloidosis; CALD, cerebral adrenoleukodystrophy; DMD, Duchenne's muscular dystrophy; FA, Friedreich's ataxia; GAN, giant axonal neuropathy; HD, Huntington's disease; HoFH, homozygous familial hypercholesterolemia; IRDs, inherited retinal dystrophies; LPLD, lipoprotein lipase deficiency; MPS, mucopolysaccharidosis; PD, Parkinson disease; SMA, spinal muscular atrophy; XLRP, x-linked retinitis pigmentosa; XLRS, x-linked retinoschisis.
iii). Diseases with a more clearly defined history and progressive symptoms that respond to interventions with a clinically meaningful impact within a reasonable period. Additional features include biomarkers that can be used to predict disease progression, stratification of otherwise heterogeneous patient populations, and prediction of the patient response to treatment. Also critical are companion diagnostic kits based on reliable biomarkers that are available or easily developed.

iv). Easy access to local key opinion leaders (KOLs)/hospitals in order to quickly identify and recruit patients for intervention trials and KOLs/hospitals who are willing to fiercely advocate on behalf of rare disease patients and drug companies.

4) Adopting a patient-centric approach, companies should create a corporate culture and business model by incorporating patients’ perspective into program planning and execution. In fact, many rare disease patients and patient organizations have shown a strong desire and willingness to play a larger role in orphan drug development.

5) Drug companies should take advantage of favorable policies while establishing orphan drug R&D capacities in China. Historically, China has placed a high priority on biomedical research with strong governmental support and a favorable regulatory environment for cutting-edge technologies, such as gene and cell therapies (16,19,21-23,24). These technologies hold great promise for treating and even curing genetic diseases. The precision medicine initiative recently undertaken by the Chinese Government will no doubt further accelerate rare disease research in China.

6) Orphan drug development represents one of the best opportunities to create differentiated products to meet vast unmet medical needs. Drug companies should embrace the recent CFDA reform favoring innovative development of drugs for a variety of medical needs, including rare diseases.

In conclusion, patients’ needs should be the focus of coordinated national task forces and investigational networks on rare diseases, and these organizations need to be supported by a long-term strategy and sustained commitment from the Chinese Government. The recently released 13th National Five-Year Plan puts greater emphasis on healthcare and the pharmaceutical industry. The Plan specifically cites genetic research and precision medicine which will support and promote research and drug development for rare diseases. A systematic approach backed by national initiatives will pave the way for robust growth of the healthcare industry, including orphan drug development. With increasing government funding and support for innovative drug development, coupled with on-going regulatory reform, ‘Made in China’ orphan drugs may soon become a reality.

References


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Supplemental Table

Supplemental Table S1: Highlights of major initiatives by Chinese government agencies in relation to rare diseases in China

- In 2009, Fast Approval by the CFDA – a fast approval process for drugs to treat several rare diseases – was implemented. A separate regulation specifies that drugs to treat rare diseases can fulfill fewer clinical trial requirements (8).
- Shanghai model: The Shanghai Rare Disease Society, founded in early 2011, also works to promote legislation, research, and insurance coverage for rare diseases. Over the past several years, the City of Shanghai has covered medical costs for treatment of 12 specified rare diseases (8).
- Qingdao model: In 2012, Qingdao, a coastal city in Shandong Province, approved a proposal to cover a capped amount of the treatment fees for all diseases, including rare diseases (8).
- In 2013, the China Rare Diseases Prevention and Treatment Alliance was established. The Alliance launched China’s first pilot project at the national level to promote better healthcare for rare diseases. The Alliance established a national collaborative network involving more than 100 provincial and municipal medical facilities to implement this project. This network covers 13 provinces, which have a population of 0.7 billion (6,8).
- In January 2016, a National Committee of Experts on Rare Disease Treatment and Prevention was established under the leadership of the National Health and Family Planning Commission of the People’s Republic of China in order to improve the management of rare diseases, to promote the standardization of diagnosis and treatment of rare diseases, and to ensure the basic medical needs of patients with a rare disease are met and their right to health is upheld (7).
- At the end of 2015, the CFDA announced that it would prioritize the review of new technologies and novel therapies for AIDS, tuberculosis, viral hepatitis, rare diseases, and cancer, and particularly for medicines developed for pediatric or elderly patients (9).
- In March 2016, the Ministry of Science and Technology of the People’s Republic of China issued Guidelines for 2016 National R&D Programs Focused on Precision Medicine and other Key Projects (10).

CFDA, China Food and Drug Administration.

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