Commentary

DOI: 10.5582/irdr.2016.01025

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

Released online in J-STAGE as advance publication October 5, 2016.

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Table 1. Several major acquisitions and partnership deals in the orphan drug industry

Buyer	Seller	Type of deal, year of transaction	Estimated value of the deal	Major rare disease assets acquired
Sanofi	Genzyme	acquisition, 2011	$20.1 billion	Gaucher's disease treatment Cerezyme and the Fabry disease drug Fabrazyme
Shire	Baxalta	acquisition, 2016	$32 billion	several approved orphan drugs for hemophilia and Gaucher's disease, along with a rich pipeline in rare diseases
Shire	Dyax	acquisition, 2015	$5.9 billion	several late-stage assets in HAE + early-stage pipeline
Shire	NPS Pharma	acquisition, 2015	$5.2 billion	Gattex for shore bowel syndrome, Natpara for hypoparathyroidism
Alexion	Synageva BioPharma	acquisition, 2015	$8.4 billion	Kanuma for LAL deficiency + a pipeline of rare disease programs
Alexion	Enobia	acquisition, 2011	$1.1 billion	Strensiq for hypophosphatasia
BioMarin	Prosensa	acquisition, 2014	$840 million	Disapersen for DMD
BioMarin	Zacharin	acquisition, 2013	upfront $10 million + milestone up to $134 million	small molecules for lysosomal storage disorders (preclinical stage) including MPS III, Tay Sachs and Sandhoff; proprietary SensiPro® platform
BioMarin	ZyStor	acquisition, 2010	upfront $22 million + milestone up to $93 million	ERT for the treatment of lysosomal storage disorders such as Pompe's disease
Pfizer	FoldRx Pharmaceutical	acquisition, 2010	undisclosed amount	Tafamidis for familial amyloid polyneuropathy
Roche	Trophos	acquisition, 2015	$0.5 billion	SMA
Biogen	Ionis (formerly ISIS)	partnering, 2013	$100 million upfront + $220 million in milestone payments.	ALS, SMA
Biogen	AGTC	partnering, 2015	$124 million upfront + up to $1.1 billion in milestone payments	XLRS and XLRP

ALS, amyotrophic lateral sclerosis; DMD, Duchenne's muscular dystrophy; ERT, enzyme replacement therapies; HAE, hereditary angioedema; LAL, lysosomal acid lipase; MPS, Mucopolysaccharidoses; SMA, spinal muscular atrophy; XLRP, X-linked retinitis pigmentosa; XLRS, X-linked retinoschisis.

Table 2. Comparison of orphan drug policies in several major countries/regions

Country/region	USA	EU	Japan	Canada	Singapore	Australia	China	India	Taiwan
Orphan drug legislation	yes	yes	yes	no	yes	yes	no	no	yes
Orphan drug designation	yes	yes	yes	no	yes	yes	no	no	yes
Market exclusivity	7 years	10 years	10 years	no	10 years	no	no	no	10 years + 2 years
Financial incentives	yes	not at EU level	yes	yes	no	yes	no	no	yes
Reimbursement	yes	yes	yes	yes	yes	yes	limited, regional differences	no	yes

EU, European Union; USA, United States of America.

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)

Table 3. Orphan drug programs run by Chinese drug companies

Company	Drug name	Indication	Stage of development
Chipscreen	Chidamide	PTCL	launched in China
Shanghai Genomics	Aisi Rui, Etuary	IPF	launched in China
Hua Medicine	HME01	PD-LID, FXS	preclinical
Prosit Sole Biotechnology	multiple products	chronic norovirus infection, articular cartilage injury, refractory gout, lupus renal failure & uremia	preclinical

FXS, fragile X syndrome; IPF, idiopathic pulmonary fibrosis; PD-LID, Parkinson's disease – L-dopa-induced dyskinesia; PTCL, peripheral T-cell lymphoma.

(*11*). Several newly established innovative biotech companies have been actively working in the area of rare diseases (Table 3), *e.g*., Hua Medicine has been working on several rare diseases such as fragile X syndrome (FXS) and Parkinson's disease – L-dopa-induced dyskinesia (PD-LID) (*12*). Another new biotech company, Beijing Prosit Sole Biotechnology, has also devoted considerable resources to rare diseases including several rare immunological disorders (*13*). In addition, Shanghai Genomics has recently launched a drug for the treatment of idiopathic pulmonary fibrosis (IPF) (*14*).

A point worth noting is that many academic institutions and major hospitals in China have been playing an important role in translational medicine for the treatment of rare diseases, and particularly in the area of cutting-edge technologies. As an example, the Shanghai Institute of Materia Medica (SIMM) of the Chinese Academy of Sciences recently announced that one of their orphan drug programs targeting pulmonary arterial hypertension (PAH) was approved by the CFDA to begin human clinical trials (*15*). With respect to cutting-edge technologies, Sichuan University's West China Hospital in Chengdu recently announced that they are preparing to conduct the world's first human trial using *CRISPR* gene editing technology (*16*). In addition, a team of scientists from Tongji Medical College have, in collaboration with FivePlus Molecular Medicine Institute in Beijing, successfully conducted a long-term trial of gene therapy in human patients with a rare genetic disorder known as Leber's hereditary optic neuropathy (LHON) (*17,18*), more than 10 years after the world's first gene therapy was approved in China (*19*).

Nonetheless, the orphan drug industry in China is still in its infancy with tremendous challenges to overcome. Compared to the USA and many Western countries with more mature industries as well as legislative and regulatory systems, currently, there are almost no large domestic pharmaceutical companies with significant resources allocated to rare diseases, although government funds allocated to rare disease research and DNA sequencing have increased significantly in China, along with funding from the private sector.

A major difference between the USA and China is that rare disease research and drug development are primarily driven by rare disease organizations and the private sector in the USA. Rare disease organizations played a critical role in the early stage of rare disease drug development and have been a nexus connecting patients, specialists, drug developers, and regulatory agencies. Rare disease organizations in China have only recently been established through grass-root efforts. One such organization, the Chinese Organization for Rare Disorders (CORD), has become highly influential as a patient advocacy group. Table 4 lists several major rare disease organizations in the USA, European Union (EU), and China.

Revolutionary technological advances in next-generation gene sequencing have enhanced our understanding of genetic risk factors and underlying genetic defects that are linked to rare diseases. Gene therapy has quickly emerged as an effective and powerful approach to treat or even potentially cure many rare diseases (Table 5).

In order to maximize and efficiently utilize available resources to successfully develop orphan drugs to treat rare diseases in China, a framework is presented here with several specific recommendations for drug companies interested in capitalizing on opportunities in the market:

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 (*20*). Examples of major rare diseases in China include thalassemia, osteogenesis imperfecta, SMA, and Duchenne's muscular dystrophy (DMD) (*20*).

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

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

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

Company	Platform	Diseases treated
Spark Therapeutics	AAV-based gene therapy	rare forms of blindness, IRDs, such as RPE65-mediated IRDs (positive Phase III results), and choroideremia (Phase I/II on-going)
AveXis	AAV-based gene therapy	SMA (positive Phase I/II results)
AGTC	AAV-based gene therapy	rare ophthalmological disorders such as XLRS and XLRP (early clinical stages or IND-ready programs)
uniQure	AAV-based gene therapy	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
Bluebird Bio	Lentivirus-based gene therapy	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)
Regenxbio	AAV-based gene therapy	HoFH (Phase I/II trial); MPS type I & wet AMD (IND-ready)
Bamboo therapeutics	AAV-based gene therapy	rare genetic disorders such as GAN (Phase I/II on-going), DMD, and FA
Voyager Therapeutics	AAV-based gene therapy	rare CNS diseases, such as PD (Phase I/II on-going), ALS, and HD
Dimension Therapeutics	AAV-based gene therapy	rare genetic liver disorders, including hemophilia B (Phase I/II)
Ionis Pharmaceuticals	antisense -based therapy	HoFH (KYNAMRO® approved) & pouchitis (Alicaforsen approved) and a wide range of rare genetic diseases, including SMA (positive Phase III results) and HD (Phase II on-going)
Alnylam Pharmaceuticals	RNAi-based therapy	a wide range of rare genetic diseases, including hereditary amyloidosis ATTR (Phase III), hemophilia, and rare bleeding disorders (Phase II)

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.

ii).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.

iii). 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.

iv). A rare indication with the same therapeutic target as a common disease is ideal, since it offers the potential for expanded indications in the future. This allows a company to build a portfolio based on multiple shots on goal with reduced risk and operational synergy.

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 meeting 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

1. Dolgin E. Big pharma moves from 'blockbusters' to 'niche busters'. Nat Med. 2010; 16:837.
2. Tzeng I, Brau R, Fero D. Raising orphans: How pharma can capture value while treating rare diseases. *http://www.lek.com/sites/default/files/LEK_1609_Orphan_Web_2.pdf* (accessed August 11, 2016).
3. Biogen/AGTC (July 02, 2015). Biogen And AGTC Enter Collaboration to Develop Gene Therapies in Ophthalmology. *http://ir.agtc.com/releasedetail.cfm?releaseid=920411* (accessed August 11, 2016).
4. Comradis. Rare Diseases in China: Rising to meet the challenge (white paper). 2015; pp. xx-xx.
5. Gong S, Wang Y, Pan X, Zhang L, Huang R, Chen X, Hu J, Xu Y, Jin S. The availability and affordability of orphan drugs for rare diseases in China. Orphanet J Rare Dis. 2016; 11:20.
6. Cui Y, Zhou X, Han J. China launched a pilot project to improve its rare disease healthcare levels. Orphanet J Rare Dis. 2014; 9:14.
7. National Health and Family Planning Commission. Notice by the China National Health and Family Planning Commission on the establishment of the Expert Committee on Rare Disease Treatment and Patient Protection. *http://www.nhfpc.gov.cn/yzygj/s7659/201601/c918591a06154c1ea193fc32ba93c085.shtml* (accessed August 11, 2016).
8. Pacific Bridge Medical. Increasing Awareness of Rare Diseases and Orphan Drugs in China. *http://www.pacificbridgemedical.com/news-brief/increasing-awareness-of-rare-diseases-and-orphan-drugs-in-china/* (accessed August 11, 2016).
9. China Food and Drug Administration. Announcement issued by the CFDA on several policies related to the review and approval of drug registration (No. 230, Year 2015). *http://www.sfda.gov.cn/WS01/CL0087/134665.html* (accessed August 11, 2016).
10. Ministry of Science and Technology of the People's Republic of China. Announcement issued by the Ministry of Science and Technology on Guidelines for 2016 National R&D Programs Focused on Precision Medicine and other Key Projects. *http://www.most.gov.cn/tztg/201603/t20160308_124542.htm* (accessed August 11, 2016).
11. Shenzhen Chipscreen Biosciences, Ltd. Chipscreen Biosciences Announces CFDA Approval of Chidamide (Epidaza) for PTCLs in China. *http://www.prnewswire.com/news-releases/chipscreen-biosciences-announces-cfda-approval-of-chidamide-epidaza-for-ptcls-in-china-300017763.html* (accessed August 11, 2016).
12. Jin X, Chen L. Fragile X syndrome as a rare disease in China – Therapeutic challenges and opportunities. Intractable Rare Dis Res. 2015; 4:39-48.
13. Prosit Sole Biotechnology. Prosit Sole Biotechnology company website. *http://prositsole.com/en/index.asp* (accessed August 11, 2016).
14. GNI Group, Ltd. China SFDA Approves F647/ Pirfenidone for the Treatment of Idiopathic Pulmonary Fibrosis. *http://www.gnipharma.com/english/information/docs/20140213170339664s.pdf* (accessed August 11,

2016).
15. Shanghai Institute of Materia Medica. SIMM's anti-PAH Class 1.1 drug TPN171 approved for clinical trials. *http://www.simm.ac.cn/xwzx/kydt/201603/t20160324_4569600.html* (accessed August 11, 2016).
16. Cyranoski D. Chinese scientists to pioneer first human CRISPR trial. *http://www.nature.com/news/chinese-scientists-to-pioneer-first-human-crispr-trial-1.20302* (accessed August 11, 2016).
17. Wan X, Pei H, Zhao MJ, Yang S, Hu WK, He H, Ma SQ, Zhang G, Dong XY, Chen C, Wang DW, Li B. Efficacy and safety of rAAV2-ND4 treatment for Leber's hereditary optic neuropathy. Sci Rep. 2016; 6:21587.
18. Yang S, Ma SQ, Wan X, He H, Pei H, Zhao MJ, Chen C, Wang DW, Dong XY, Yuan JJ, Li B. Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy. EBioMedicine. 2016; 10:258-268.
19. Pearson S, Jia H, Kandachi K. China approves first gene therapy. Nat Biotechnol. 2004; 22:3-4.
20. National Health and Family Planning Commission of the PRC. Major Rare Diseases in China. *http://www.chinadaily.com.cn/m/chinahealth/2014-09/22/content_18639787.htm* (accessed August 11, 2016).
21. Gao F, Shen XZ, Jiang F, Wu Y, Han C. DNA-guided genome editing using the Natronobacterium gregoryi Argonaute. Nat Biotechnol. 2016; 34:768-773.
22. Cyranoski D, Reardon S. Chinese scientists genetically modify human embryos. *http://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378* (accessed August 11, 2016).
23. Callaway E. Second Chinese team reports gene editing in human embryos. *http://www.nature.com/news/second-chinese-team-reports-gene-editing-in-human-embryos-1.19718* (accessed August 11, 2016).
24. Cyranoski D. China embraces precision medicine on a massive scale. Nature. 2016; 529:9-10.

(Received April 17, 2016; Revised September 1, 2016; Accepted September 2, 2016)

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 fulfil 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.