



# Market Access of Orphan Drugs in China

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## Overview

Market access of orphan drugs in China involves many challenges, including the absence of official legislation for orphan diseases; the lack of impactful incentives for manufacturers to develop orphan drugs; and limited resources available for funding high-cost orphan drugs. This report is based on secondary research and primary research from interviewing payers (national, regional, and local) and key opinion leaders, and provides insights to the challenges faced by manufacturers and the actions that manufacturers can take to support the market access of orphan drugs in China in the short, medium, and long term.

## Market access environment for orphan drugs in china

### Absence of official legislation

#### Lack of official definition of orphan diseases in China

Compared to other Asian markets and major Western markets, China's policies around orphan conditions and drugs are not well developed. There is no official definition of the prevalence of orphan diseases that is recognized by the Chinese government.<sup>1</sup>

Among clinical experts, there is a consensus on a working definition of orphan disease emerging. In a Clinical Expert Seminar on the Definition of Rare Diseases held in 2010, orphan disease is defined as having a prevalence of less than 1 patient per 500,000 people or a neonatal morbidity of less than 1 patient per 10,000 people, which is more restrictive than the World Health Organization (WHO) definition of 0.65-1 patients per 1,000 people.<sup>1,2</sup>

### First treatment centers established to better understand orphan diseases

Faced with the challenge of serving the world's largest orphan disease population, China launched its first pilot project in 2013 to frame the health policy situation and to better understand the epidemiology and treatment guidelines for 20 rare diseases.<sup>1</sup>

The focus of this pilot program is to develop medical guidelines and clinical pathways for rare diseases; establish a rare disease patient registry and data repository system; and promote molecular testing for rare genetic disorders. It also aims to build close links among collaborative networks: clinicians on the front lines of basic medical services institutions and rare disease patient organizations. A national network including about 100 provincial or municipal medical centers has been established in order to enable collaboration on rare diseases across China.<sup>1</sup>

### Absence of impactful incentives

#### Lack of enforced fast track approval channel

The market authorization approval process in China is generally quite lengthy. After the application is submitted by manufacturers, it can take up to a year to get an approval from the State Food and Drug Administration (SFDA) and the Center for Drug Evaluation (CDE) in order to be able to start a clinical trial in China. After the trial, it can take another year or more for SFDA/CDE to approve the registration of the drug.

In principle, a fast track regulatory approval channel exists for certain new drugs, including those that demonstrate clinical effectiveness for rare diseases. However, in practice, the approval time for orphan drugs is not reduced, mainly due to staff shortages. As a result, the approval process for orphan drugs can take as long as non-orphan drugs.

### Lack of financial incentives

Some countries provide financial incentives to encourage manufacturers to develop orphan drugs. In Japan, for example, the government covers up to 50% of the development costs for orphan drugs, grants a 6% tax reduction for research and development, and allows additional price premiums for orphan drugs. However, in China, there are no financial incentives or special pricing policies for orphan drugs.<sup>3</sup>

### High rate of misdiagnosis

There is no special diagnostic or treatment center for orphan diseases in China. As for other serious diseases, patients are often diagnosed at local hospitals or community clinics, and then go to large hospitals for confirmation and treatment. Patients also have the option of going directly to large hospitals since no referral is required. Due to limited clinical expertise in orphan diseases, the rate of misdiagnosis is high. Overall, nearly half (48.3%) of patients with orphan diseases have been wrongly diagnosed.<sup>4</sup> Therefore, even when orphan drugs are approved and available on the market in China, they may not reach the right patients.

### Limited funding for high cost orphan drugs

High-cost orphan drugs are often excluded from reimbursement drug lists (RDLs), since price is a key driver for reimbursement decisions. As a result, the patients' out-of-pocket payment is significant, and the use of high-cost orphan drugs is limited by patients' ability to pay. The sources of funding for orphan drugs are discussed below.

### Future market access environment

While efforts are being made in China to better understand orphan diseases, the changes in the government legislation and policies will likely take

a long time. In the next five years, there are no significant changes expected, and the market access environment for orphan drugs will likely remain challenging.

### Funding sources for orphan drugs

Three main sources of funding exist for orphan drugs in China: (1) funding through government (at national, regional or local level), (2) funding through charity, and (3) funding by patients' out-of-pocket (OOP) payment. While these multiple funding channels exist, provincial/local government funding and patients' out-of-pocket payments are currently the most important sources of funding for high-cost orphan drugs.

### Funding through government

#### National reimbursement drug list (national RDL)

As for non-orphan drugs, it can take several years for orphan drugs to be included on the national RDL after market authorization by the SFDA, and the criteria for inclusion on the national RDL are broadly the same for both orphan and non-orphan drugs. Efficacy and price are the two key drivers for reimbursement decisions. As a result, high-cost orphan drugs are often excluded from the national RDL.

Drugs for orphan diseases that are reimbursed at 100% on the national RDL are often low-cost and generally produced by local manufacturers. Higher cost drugs are either partially reimbursed or not covered at all.

#### Provincial/local reimbursement drug list (provincial/local RDL)

Drugs that are not included on the national RDL can be reimbursed in some provinces or cities through inclusion on the provincial/local RDL. Healthcare budgets are managed at the provincial/local level; therefore, depending on the local needs and ability to

**Table 1: Examples of high-cost drugs for orphan diseases that are included on provincial/local RDLs, but not the national RDL**

Disease Name	Drug Name	Reimbursement Level	Price (RMB)	Maker
Non-Hodgkin's lymphoma	Rituximab	Partial in some provinces	3,980 (100mg/10ml)	Roche
Neonatal respiratory distress syndrome	Poractant Alfa Injection	Partial in some provinces	8,084 (3ml; 0.24 g)	Chiesi Farmaceutici S.p.A.
Chronic myelogenous leukemia and gastrointestinal stromal tumors	Imatinib	Partial in some provinces	25,500 (100mgx120)	Novartis
Advanced non-small cell lung cancer	Gefitinib	Partial in Guang Zhou City	5,000 (0.25gx10)	AstraZeneca

pay, some provinces or cities may include some high-cost drugs in their RDL (which are not on the national RDL), or increase the level of reimbursement to 100% for the drugs that are only partially reimbursed on the national RDL (See Table 1). Consequently, provinces and cities are driving the reimbursement for high-cost orphan drugs.

### **Serious disease coverage**

For diseases that are considered a high-cost burden on patients and families, serious disease coverage provides additional reimbursement, on top of basic medical insurance, to patients with limited financial resources. While the numbers of diseases covered under the serious disease coverage has expanded recently and includes certain orphan diseases such as hemophilia and chronic myeloid leukemia, the level of coverage is still quite low due to limited funding. For the serious disease coverage to be of relevance to high-cost orphan drugs funding, substantial cash injections will be needed.<sup>5</sup>

### **Funding through charity**

#### **Drug donation via charity**

Some high-cost orphan drugs that are not reimbursed are provided by manufacturers free of charge to patients through charitable organizations. China Charity Federation (CCF) is one of the most influential charity organizations in China. High-cost orphan drugs donated by manufacturers through CCF include Cerezyme by Genzyme for Gaucher's disease, Gleevec by Novartis for chronic myeloid leukemia, and Exjade by Novartis for beta-thalassemia.

Charity donations by manufacturers can help in raising awareness of the orphan disease and the drug of interest among key stakeholders, which could lead to reimbursement in the future, as seen in this Cerezyme case study:

Over 10 years ago, Genzyme began donating Cerezyme free of charge to patients with severe Gaucher's disease in China, first through the World Health Foundation, and then through the CCF beginning in 2008. As well as donating drugs for free, the manufacturer worked closely with the CCF to increase public awareness of the disease and promote research into policy and insurance coverage for orphan diseases. Possibly as a result of these efforts, Cerezyme has recently been reimbursed in the city of Qingdao.

#### **Fundraising via charity**

Public fundraising through charitable organizations provides another route of funding for orphan drugs, as seen with the recent success of the ice bucket challenge for Amyotrophic Lateral Sclerosis (ALS), which was introduced in China in August 2014 and spread rapidly.<sup>8</sup>

As the people in China have more disposable income and have become more involved in charitable activities, public fundraising could represent an increasingly important source of funding for high-cost orphan drugs. Currently, the fundraising right is restricted to only a few charities, which are often large and linked to the government. For public fundraising to have a greater impact on orphan drug funding, the current restrictions on fundraising rights need to be addressed to allow more charitable organizations to be able to fundraise.

### **Out-of-pocket payment by patients**

Because of limited funding currently available, patients' out-of-pocket payments for orphan drugs is significant. Overall, almost 80% of patients with orphan diseases have less than 10% of their total treatment costs reimbursed, and only approximately 10% of patients have more than 50% of the total treatment cost reimbursed. High OOP payments impose a significant burden for the patient and family, with more than 70% of families expressing concern for their ability to afford their treatment.<sup>4</sup>

### **Qingdao City as an example**

The city of Qingdao has been leading the way for orphan drug funding in China, with the local government actively providing coverage for orphan diseases. In 2012, the local government issued a policy to cover two orphan diseases together with other major diseases, and provided direct funding for these diseases. In 2014, the coverage was expanded to include six additional orphan diseases, with several high-cost orphan drugs reimbursed (See Table 2). The orphan diseases covered in Qingdao include hemophilia, tetrahydrobiopterin deficiency (BH4 deficiency), Gaucher's disease and acromegaly.

With the funding from the Qingdao local government and charitable donations, the treatment cost to patients with orphan diseases can be as low as 10 to 15%.<sup>7</sup>

While the drivers for the Qingdao government's progressive stance toward orphan diseases funding are uncertain, it is clear that its local government considers funding for major diseases and orphan diseases to be a public health priority. The ability of Qingdao to fund high-cost orphan drugs is also helped by its strong financial resources. For manufacturers with high-cost orphan drugs, the city of Qingdao could represent a gateway to market access in China.

### **Future funding sources for orphan drugs**

In the next five years, provinces/cities will likely continue to drive the reimbursement for high-cost orphan drugs, and charity will become increasingly important for providing funding for them and also for raising awareness. As a result, patients' out-of-pocket payment levels could be reduced, but overall will still remain significantly high in the short term.

**Table 2: Examples of orphan diseases and high-cost orphan drugs that are covered by the Qingdao government**

Disease Name	Drug Name	Price (RMB)	Maker
Hemophilia	BeneFIX (recombinant human coagulation factor IV)	6800 (1000IU)	Pfizer
Tetrahydrobiopterin deficiency (BH4 deficiency)	Kuvan (saprotein dihydrochloride tablets)	Not available	Merck
Multiple sclerosis	Betaferon, recombinant human interferon beta – 1b	13,000 (800IU)	Schering
Primary pulmonary hypertension	Bosentan tablets	31,630 (125mg*56)	Actelion
Acromegaly	Somatuline	4,260 (40mg)	Ipsen
Gaucher's disease	Cerezyme (imiglucerase)	29,741 (400 units/bottle)	Genzyme

### Key stakeholders for market access of orphan drugs

Currently, the most important stakeholders for high-cost orphan drug funding are regional policy makers and regional pricing and reimbursement bodies. National level pricing and reimbursement bodies are less important in terms of access of high-cost orphan drugs. Charity also plays an important role in funding, raising awareness and potentially providing a bridge to reimbursement in the long term (as was the case for Cerezyme). Other organizations, such as patient advocacy groups, medical organizations and manufacturer organizations have limited influence.

In the next five years, provincial/regional stakeholders will remain important for funding high-cost orphan drugs. Charity will likely become increasingly important for providing funding and raising awareness.

### Implications, action plans and key considerations for manufacturers

#### Implications

As mentioned earlier, multiple challenges exist (and are expected to remain in place for the next five years) for the market access of orphan drugs in China, all of which can impact the bottom line for manufacturers.

- The lack of legislation and incentives means there is a lack of public health recognition among key stakeholders for orphan drugs, which could negatively impact priorities among policy makers and budget allocation for orphan drugs at the national, regional, and local levels.

- The slow market authorization for drugs, including orphan drugs, means there will be a delay in revenue generation and return on investment.
- The price control of reimbursed drugs means that there is pressure on the manufacturers to reduce price in order for high-cost orphan drugs to be reimbursed.
- The limited reimbursement for orphan drugs means that there is a high-cost burden on patients and their families, and the market uptake will be limited by the patients' ability to afford the drugs.
- The high rate of misdiagnoses means that even when orphan drugs do reach the market, it is difficult for them to reach the right patients and for meaningful real-world evidence to be gathered.

#### Action plans

##### Short term: Work with charitable organizations

Many of the challenges in the market access of orphan drugs in China are driven by the lack of awareness and subsequent lack of priority among the key stakeholders for orphan diseases. Charity provides a valuable pathway for fundraising, as well as building relationships with and influencing key stakeholders, since most of the large charitable organizations are linked to the government.

##### Medium term: Seek reimbursement at the provincial and local levels

The goal for manufacturers in a medium term is to seek reimbursement at provincial/local levels. This will require continued effort in order to support funding allocation and reimbursement decisions, including working with

senior sponsors in government, key opinion leaders, and charities, as well as educating and influencing key stakeholders on the importance of orphan disease funding and the value of the orphan drugs of interest.

### **Long term: Continue efforts to drive policy changes leading to a more favorable environment**

For long-term change, manufacturers need to continuously work with charities, senior sponsors, and key opinion leaders to influence policy makers in order to support changes in legislation and policy and promote a more favorable market access environment for orphan drugs in China.

### **Considerations**

#### **Should an orphan drug be launched at all, given the challenges?**

The current environment is not likely to change in the short term. Delaying launch could lead to missed opportunities, particularly in out-of-pocket payments. Whether to launch an orphan drug in China or not would depend on a number of factors, including 1) the level of the unmet need in the orphan disease of interest in China, 2) how well the drug addresses the unmet need, 3) the size of the eligible patient population in China, and, 4) the size of the out-of-pocket payment market if the drug is not reimbursed on the RDL.

#### **When should an orphan drug be launched? Should it wait until the market environment is more favorable?**

Given that the market access environment is not likely to change in the short term, having the drug on the market early will help manufacturers start raising awareness for the orphan drug of interest early and increase market presence of the product. It will also help gain physician confidence in using the product and support from key opinion leaders, who can then influence budget holders. Furthermore, for a drug to be reimbursed, it has to be on the market in China for a certain period of time, typically two years or more.

#### **What is the best way to prepare for the launch?**

Work with key opinion leaders to educate payers as early as possible on the severity of the disease, the value of the orphan drug of interest, and the importance of funding. Manufacturers can also work with the relevant charities to raise funding, increase public awareness, and indirectly influence payers in order to support reimbursement in the long term.

#### **What can be done once the product is on the market?**

To optimize market uptake, continue to work with local and regional payers, charities, and key opinion leaders to support reimbursement. Work with physicians to gain support, as they play a key role in treatment choice. Working with patient organizations to increase patient awareness of the product is also valuable. This is particularly important if the drug is not reimbursed, in which case the patients themselves are the payers.

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