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Current progress in the management of rare diseases and orphan drugs in China

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Summary **Currently, the issues of how to treat rare diseases and to improve accessibility to orphan drugs are arousing more and more concerns in China. Here we describe the push and pull incentive policies for rare diseases and orphan drugs and analyze the coverage and reimbursement level of rare diseases in the current Chinese medical insurance system. Three key obstacle factors that hinder Chinese patients' accessibility to timely drug treatment are summarized. Based on a comprehensive analysis, the measures of orphan drugs legislation, incentive mechanism, supply mechanism, and reimbursement mechanism are urgently expected to be established with the purpose of improving healthcare for patients with rare diseases in China.**

Keywords: Rare diseases, orphan drugs, accessibility, management strategies

1. Introduction

In recent decades, there were a series of events concerning the shortage of drug medication for patients suffering from rare diseases reported by the mass media of China. These drugs are always in the literature termed orphan drugs, which most frequently include *Clostridium botulinum* antitoxin type A, alglucerase injection (Ceredase®), imiglucerase (Cerezyme®), ceramide trihexosidase/ α-galactosidase A (Fabrazyme®), zinc acetate, coagulation factor VIII, coagulation factor IX, iron(III)-hexacyanoferrate(II) (Radiogardase®), busulfan, *etc*. It is also known now that various types of rare diseases exist in China, *e.g.* osteogenesis imperfecta, neuromuscular diseases, Wilson's disease, Fabry's disease, Gaucher's disease, phenylketonuria, acromegaly, hemophilia A and B, hereditary angioedema, chronic myeloid leukemia, Pompeii disease, mucopolysaccharidosis, lymph-angioleiomyomatosis, albinism, growth hormone deficiency, pulmonary arterial hypertension, botulism caused by type A *C. botulinum*, and internal contamination with thallium.

Currently, rare disease is defined as an incidence rate of less than 0.65‰ or 1‰ of the disease or symptoms by the World Health Organization (WHO). In terms of WHO's definition of rare diseases, at least 10 million people are suffering from rare diseases in China, given a population of at least 1.3 billion (*1*). Unfortunately, most of the Chinese patients with such diseases are bearing a deadly physical, psychological, and economic burden due to lack of proper health care and supportive policy or health care insurance. In addition, shortage of orphan drugs has also become a major problem.

Management of rare diseases and orphan drugs has attracted wide attention in recent years in China. Patients and patients' families, patients' advocacy groups, health care professionals, pharmaceutical policy scholars, lawyers, and representatives of The National People's Congress are advocating establishing some protective measures for rare disease, such as rare diseases prevention and treatment law, medical insurance system of rare diseases or medical assistance system

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for rare diseases. In recent times, many changes that favor patients with rare diseases are emerging in China as compared to previously. In our study, we describe three key aspects including incentive policies, medical insurance policies and social supportive activities, with the purpose of exploring current progress in management of rare diseases and orphan drugs in China.

2. Incentive policies for rare diseases and orphan drugs in China

For incentive strategies for global health research and development, funders and advocates have considered solutions of two types: "push" mechanisms and "pull" mechanisms (*2*). "Push" mechanisms aim to reduce the developer's risks and initial costs, thereby lowering barriers to entry and increasing investment in research at the start of the innovation pathway. In contrast to push mechanisms, "pull" mechanisms are designed to create or secure a market, thereby improving the likelihood of a return on investments. They motivate investment by guaranteeing a reward for the product after completion of its development phase (*3*). Push mechanisms subsidize research inputs, while pull mechanisms reward research output.

Push mechanisms can take many forms, such as public innovation funding/grants in basic research, subsidies for research, tax credits on research and development, product development partnerships (public-private partnerships), expedited drug regulatory review, facilitation mechanisms, liability protection, and so on. Pull incentive measures include market guarantees, purchase funds, prizes for successful research, improved market information, tax credits on sales, intellectual property incentives, and patent buyouts. For example, advance purchase commitment to buy a new drug, extension of patent term or market exclusivity on a new drug, or transferable patent extension of an alternative drug (*2,3*).

The orphan drug policies in the United States of America (USA), the European Union (EU) and Japan use the push and pull incentive strategies. The most common push strategies included in the existing orphan drug programs are: research grants, protocol assistance for clinical trials (automatic or on request), fast-track procedures (or high priority), tax credits (mainly for clinical research expenses), and exemption from drug registration fees. In this respect, the Orphan Drug Act in the USA offers particularly favorable conditions with tax credits that can reach up to 50% of clinical costs. Pull strategies in the existing orphan drug programs from the USA and EU have a long market exclusivity for orphan drugs and authorization criteria for orphan drug designation according to clinically superior values. It means orphan drug programs protect the first drug sponsor's benefits (*4*).

In China, on the one hand, push stimulating policies for orphan drugs allow reduction of sample size of clinical trials and entrance into fast-track procedures. But currently Chinese government does not design special funding/grants or subsidies or priority grants for rare diseases or orphan drug research. On the other hand, the pull stimulating policies for rare diseases and orphan drugs include administrative market protection for traditional Chinese medicine preparations, and an information management system for hemophilia (as a form of improved market information). There are further details as follows.

2.1. *Incentive push policies*

2.1.1. *Provisions for drug registration*

This regulation was implemented originally on May 1, 1999, which was called the Chinese New Drug Registration Regulation. Article 27 in the old edition stipulates that if a new drug which could have an effective clinical therapeutic value for life-threatening or difficult critical illness (such as AIDS, cancer, rare diseases, *etc*.), and was made as the first domestic application, then the review process should be sped up. The latest edition of this provision was carried out on October 1, 2007, and named Provisions for Drug Registration (*5*). In the latest edition, Article 32 of the provision indicates that the clinical sample size of rare or special diseases can be reduced or can get a clinical trial exemption. Article 45 regulated that State Food and Drug Administration of China (SFDA) may implement special review and approval in case of the following applications: new drugs with significant clinical advantage for the treatment of diseases such as AIDS, malignant tumors, and rare diseases, *etc*. For drugs specified in the above-mentioned causes, applicants may apply for special review and approval in the process of drug registration. The Center for Drug Evaluation of SFDA shall organize expert meetings to discuss and determine whether or not to conduct special review and approval for the drugs. In 2010, SFDA approved the import of ambrisentan tablets (Volibris®) as an orphan drug and conditionally approved imatinib mesylate tablets (Glivec®) for the treatment of dermatofibrosarcoma protuberans sarcoma (DFSP). The soluble guanylate cyclase (SGC) agonist and long-term non-prostaglandin class of prostacyclin receptor (IP receptor) agonist were also approved to enter clinical trials by SFDA (*6*).

2.1.2. *Requirements for special approval of new drug registration*

This requirement was formally issued and implemented as of January 7, 2009 (*7*). Article 2 points out that new drugs for the treatment of diseases such as AIDS, malignant tumors, and rare diseases, *etc*. with a significant clinical advantage may apply to enter the

special review and approval procedure in the stage of marketing approval, excluding the stage of clinical trial approval. The requirements follow the general principles for special approval of new drug registration, namely "early intervention, priority review, multi-channel communication, and dynamic data supplement". When a new drug enters the special approval procedure, the marketing approval time of a new drug is about 120 work days. Generally, the standard marketing approval time of a new drug is at least 150 work days. At the same time, the sponsor of the new drug with special approval has a chance to attend the communication meeting and gain protocol technical assistance from the Center for Drug Evaluation of SFDA. In 2010, tinib hydrochloride tablets (Conmana®) as an original new drug in China got special approval. Conmana treats advanced non-small cell lung cancer (*6*).

2.1.3. *Provisions for in vitro diagnostic reagents registration*

This Provision of *in vitro* diagnostic reagents registration was run on July 1, 2007 by the Chinese SFDA (*8*). Article 31 points out that new *in vitro* diagnostic reagents for rare diseases and special diseases or other conditions may be allowed to reduce the number of cases required for clinical trials or be exempt from clinical trials, but the applicant needs to submit a registration dossier to apply for a waiver of clinical trials, in which detailed reasons should be provided. Besides, in January 2012, the 2011-2015 plan of national drug safety from the State Council of China clearly indicates encouragement for research and development of orphan drugs (*9*).

2.2. *Incentive pull policies*

2.2.1. *A protection system for certain traditional Chinese medicine preparations*

The State Council of China issued regulations for protection for certain traditional Chinese medicine preparations on October 14, 1992 (*10*). Thereafter, SFDA released the protection guidelines for certain traditional Chinese medicine preparations in 2009 (*11*). Article 2 in the protection guideline emphasizes that if a traditional Chinese medicine preparation can make a significant improvement on the critical end point of clinical outcomes (mortality, disability, *etc*.) for severe or rare diseases (such as phenylketonuria, thalassemia, *etc*.), it may apply for first-level national protection. A traditional Chinese medicine preparation which gained first-level protection can get a duration of administrative market protection for thirty years, twenty years, or ten years respectively, based on different situations. During the period of protection, the other pharmaceutical companies which also have the same medicine as that of the traditional Chinese medicine protected will be required to stop producing a similar pharmaceutical product, otherwise the market approval of the medicine of any other pharmaceutical company shall be suspended by SFDA.

2.2.2. *An information management system of hemophilia cases in China*

It is estimated that China has about 60,000-130,000 hemophilia patients, who are in great need of coagulation factor VIII. The Ministry of Health of China released a bulletin board on the establishment of an information management system of hemophilia cases on November 17, 2009. This notice requires that a medical institution in every province should be designated as a provincial information management center of hemophilia patients, which is responsible for collecting and reporting the information of patients with hemophilia including the basic conditions of patient, disease detection, diagnosis, the supply and demand situation of coagulation factors, and other information. Currently, Ministry of Health designated the Department of Blood Diseases Hospital of Chinese Academy of Medical Sciences as a national information management center for hemophilia patients and also announced 31 hospitals from 31 provinces as treatment and information centers for hemophilia. Up to April 6, 2012, there are 10,164 treatment cases of hemophiliacs in the information management system (*12*). Besides, in 2010, the Ministry of Health launched hemophilia diagnosis and replacement therapy training. The country's leading experts on hemophilia were invited to give lectures on the basics, diagnosis and treatment of hemophilia, hemophilia treatment-related blood transfusion and blood products by video conference, or other means, in order to improve the diagnosis and treatment level of hemophilia by the clinical doctors across the country. As a consequence, the training taught more than 8,500 doctors. Meanwhile, the domestic supply of coagulation factor VIII has markedly improved over the past two years with an annual total production of coagulation factor VIII of 39.7 million bottles (based on 200 units per bottle), meeting the basic clinical needs of patients with hemophilia (*13*). But still there is a big supply gap for coagulation factor VIII in rural regions of China. Furthermore, many hemophiliacs can not afford to pay high drug costs for a long treatment (*14*).

3. The medical insurance policies of rare diseases and orphan drugs in China

Haffner studied the changing nature of approved orphan products and disease indications by the Food and Drug Administration (FDA) of the USA from 1983 to 2003 (*15*), which showed there were approximately 85% orphan designations for the treatment of serious and/or life-threatening diseases, the highest percentage (31

%) of orphan designations are for rare forms of cancer, while metabolic disorders represent the second largest group of orphan designations (11%); the majority of rare diseases are chronic, however a small number of products have been developed for single-occurrence diseases or emergency medicine for such conditions as acute smoke inhalation or lead poisoning.

The Chinese medical insurance system generally consists of the basic social medical insurance system, public medical insurance and commercial health insurance. Although the Chinese medical insurance system still does not establish special insurance programs for rare diseases and orphan drugs, it has covered some major diseases or specific diseases which include rare diseases.

3.1. *The basic social medical insurance system*

The basic social medical insurance system is jointly composed of Urban Employees' Basic Medical Insurance Scheme (UEBMIS, initiated in 1998), Urban Residents' Basic Medical Insurance Scheme (URBMIS, 2007), and New Rural Cooperative Medical Insurance Scheme (NRCMIS, 2003), respectively covering urban employees, urban non-employees, and the rural population (*16*). In 2008, the Fourth National Health Services Survey (NHSS, 2008) was conducted all over China. A total of 56,456 households or 177,501 people were investigated. Based on the NHSS result, as of June 2008, 87.1% of residents investigated were covered by government or collectively-run health insurance. In urban areas, coverage rates of basic medical insurance for urban employees and urban residents were 44.2% and 12.5%, respectively. The coverage rate of the NRCMIS for rural residents reached 93.0% (*17*). In 2010, the three schemes of basic social medical insurance covered over 1.2 billion people according to the China Human Resources and Social Security Yearbook (working volume).

We analyzed the national policies and implementing rules of 25 local governments for the three basic social medical insurance schemes. The common characteristics of the operations of the three schemes have three aspects. First, the three schemes require those eligible people to pay a premium; second, they design the deductible and the ceiling and reimbursement rates; last, they generally cover inpatient care and outpatient care. However, unlike the mandatory UEBMIS, URBMIS and NRCMIS have been running on a voluntary basis.

The three schemes function independently, differing in aspects related to financing, reimbursement, and expansion (*16*). In the UEBMIS and URBMIS, the social pooling fund mainly pays for inpatient costs in a ratio of reimbursement within a pre-defined band (above the deductible line but below the ceiling) and outpatient's expenditures incurred in the treatment of specific diseases or serious chronic or major diseases. The NRCMIS fund pays for inpatient costs in a ratio of reimbursement within a pre-defined band (above the deductible line but below the ceiling) and high outpatient expenditures. For the outpatient reimbursement of specific diseases or serious chronic diseases or major diseases, there are several ways for payment of the social pooling fund in the three schemes, which include the ceiling for a single major disease (without the deductible), the deductible line and the ceiling, reimbursement rate or in accordance with the local inpatient reimbursement policy.

Meanwhile, the central government gave a certain degree of autonomy to local governments in the implementation of the three schemes. The local governments also have the autonomy to determine the deductible, ceiling, and reimbursement ratio according to local economic and demographic status (*16*). As a result, the reimbursement level for eligible enrollees in every scheme varies greatly by region in China.

The UEBMIS requires enrollment of all urban employers and employees, who share in the responsibility of paying premium contributions. Premiums equivalent to 8% of employees' monthly payroll are contributed to medical insurance, with the employee contributing 2% and the employer providing the remaining 6%. All the premiums are divided into two parts, namely social pooling and individual accounts (*16*). In 2010, the average monthly payroll of urban employees at their posts is about 3,096 RMB. Namely the average annual premium *per capita* in the UEBMIS is about 248 RMB in China. For example, in 2011, the ceiling of the inpatient costs which are paid by the social pooling fund of Urban Employees in Beijing is 100,000 RMB per year, while it is 54,000 RMB per year in Urumqi. With regard to the premium in the URBMIS, every city has a different standard. In 2011, an unemployed adult urban resident who lives in Beijing needs to pay 600 RMB per year for the local pooling fund of the URBMIS in contrast to 372 RMB per year in Urumqi.

As for outpatient reimbursement for specific diseases in the NRCMIS fund, Guangzhou's policy for 15 specific diseases is to comply with inpatient reimbursement policy in 2012 (*18*), while Lanzhou's policy is that the ceiling of a single major disease is defined without the deductible. For instance, in Lanzhou city, the outpatient ceiling of hemophilia is 20,000 RMB per year, while the outpatient ceiling of arsenic poisoning or malaria is 1,000 RMB per year in 2012 (*19*). In Wuhan city (Hubei province), the ceiling of outpatient costs is 5,000 RMB per year in 2012.

Currently, in many Chinese cities, the UEBMIS and URBMIS define the kinds of specific diseases or serious chronic diseases or major diseases for outpatients, which mainly includes malignant tumors using chemotherapy or radiotherapy, severe uremic poisoning requiring hemodialysis, organ transplant requiring anti-rejection therapy, leukemia, hemophilia, aplastic anemia, systemic lupus erythematosus, Parkinson's disease, myasthenia gravis, ankylosing

spondylitis, *etc*. The specific diseases in the NRCMIS mainly include malignant tumors using chemotherapy or radiotherapy, severe uremic pisoning requiring hemodialysis, hemophilia, aplastic anemia, systemic lupus erythematosus, myasthenia gravis, thalassemia (Guangdong province), phenylketonuria and chronic C-viral hepatitis (Putian City, Fujian province), Keshan disease, Kashin-Beck disease, brucellosis, kala azar, cretinism, hydatid disease, skeletal fluorosis, arsenic poisoning, and malaria (Gansu province).

An interesting case study emerged in Tongling city (Anhui province) in 2011, located in central China. Tongling's government took some new measures for rare diseases in the UEBMIS and URBMIS. If an enrollee suffered from a rare disease, the reimbursement of his outpatient expenses was the same as the inpatient reimbursement. The orphan drug used will be reimbursed as a "Yi" tier drug in the UEBMIS. The medical expenses of the treatment of his rare disease which costs in other cities will be treated as local treatment expenses and get reimbursement (*20*).

What are our reimbursement policies for excess expenses above the ceiling? In order to further alleviate the persistent phenomenon of poverty resulting from catastrophic diseases, the central government and local governments encourage people to participate in the social insurance scheme for major or catastrophic diseases. For example, the urban enrollee also needs to pay a premium for the supplementary social pooling fund of major disease or the medical mutual pooling fund for huge medical inpatient costs. In 2009, Ministry of Health of China launched the children's medical insurance pilot plan for major diseases in rural areas. This pilot plan is a part of the NRCMIS. The major diseases of children have six types, including acute lymphoblastic leukemia, acute promyelocytic leukemia, congenital atrial septal defect, congenital ventricular septal defect, congenital patent ductus arteriosus, and congenital pulmonary valve stenosis. In 2011, this pilot plan covered over 7,200 children with leukemia who got 65% reimbursement and 22,600 children with congenital heart diseases who got 78% reimbursement (*21*).

In the early months of 2012, Ministry of Health of China began to build a major disease security pooling fund of the NRCMIS in a provincial or municipal pooling level. This fund will pay for the medical expenses of 12 major diseases, such as hemophilia, chronic myeloid leukemia, esophageal cancer, gastric cancer, colon cancer, rectal cancer, *etc*. Currently, hemophilia is covered by the UEBMIS and URBMIS from 18 provinces and is reimbursed by the NRCMIS from 16 provinces (*21*).

3.2. *The public medical insurance program*

The public medical insurance program (state-funded public medical program) is provided by the government to employees working in state agencies, such as civil services. This program is a kind of Free Medical Service program which is financed by the central and local governments according to the number of eligible enrollees. If the public medical insurance expenses in a state agency exceed the allocated funding, the excess medical expenses will be borne by the state agency. In the public medical insurance program, eligible enrollees in the state agencies do not have to pay a premium and a deductible. Meanwhile, they can get about 80% reimbursements without a ceiling (*22*). This program has low out-of-pocket costs and a high reimbursement rate.

The diseases covered in the public medical insurance program are decided by patient work agencies and the local administrative department. As a matter of fact, this insurance program covers some rare diseases, but public medical insurance only accounts for a small proportion in the Chinese medical insurance system. The coverage rate of the public medical insurance was 1.0% based on the data of NHSS in 2008. It is gradually being replaced by the basic medical insurance for urban employees (*22*).

3.3. *Commercial health insurance*

Commercial health insurance in China serves as a supplement to social medical insurance, targeting mainly the upper class. These plans have high premiums and reimbursement rates (*16*). According to the result of NHSS in 2008, the coverage rate of commercial health insurance was 6.9% in the investigated people. The *per capita* premium for commercial health insurance was 858 RMB, compared with 16 RMB for the NRCMIS and 186 RMB for the URBMIS (*17*). Commercial health insurance categories mainly cover particular critical illness, medical cost reimbursement insurance, and medical allowance insurance for accommodation fees related to hospitalization (*16*). As an illustration, there is a medical insurance plan for lifetime major diseases in Taikang Life Insurance Co., Ltd., Beijing, China. A male enrollee in the plan for lifetime major diseases may have a choice to pay a premium of 60,000 RMB once or 3,000 RMB/year up to 20 years. The ceiling of the medical cost of a lifetime major disease is 100,000 RMB.

Currently, there are more than 100 commercial insurance companies in China, offering around 200 kinds of insurance for patients with critical illness. In 2007, China Insurance Association issued "The Operating Regulation of the Insurance for Critical Illness". This regulation defined 25 types of major diseases such as Parkinson's disease, primary pulmonary hypertension, aplastic anemia, motor neuron disease, cancer, *etc*. Meanwhile, it also stated that the commercial insurance companies may exclude genetic diseases, congenital malformations, deformation or chromosomal abnormalities diseases and chronic lymphocytic leukemia, and Hodgkin's disease (*23*).

4. The rapid development of social supportive activities for rare diseases or orphan drugs in China

From 2003 to present, there has taken place a series of charity or academic activities focusing on rare diseases or orphan drugs in China. In 2003, Glivec® International Patient Assistance Program (GIPAP), a disease relief program, was launched by the China Charity Federation and Novartis Pharmaceuticals in China. Novartis Pharmaceuticals donated Glivec (imatinib mesylate tablets) to patients with chronic myelogenous leukemia (CML) or gastrointestinal stromal tumor in China. Currently, the price of Glivec (60 Capsules/box, 0.1g) is around 12,000 RMB. Generally, a CML patient needs to take 2 boxes of Glivec every month, namely 24,000 RMB/month, and 288,000 RMB/year. If a CML patient is supported by GIPAP, he or she may pay 72,000 RMB to buy 6 boxes of Glivec for the first 3 months, followed by free payment of Glivec for the next 9 months. For urban residents with low-incomes below the local poverty line or rural destitute family members, they may apply to get all free Glivec through this program. In July 2009, the China Charity Federation launched the charitable donation program of Cerezyme® (imiglucerase for injection). Genzyme Corporation donated Cerezyme (valued at 200 million RMB) to help Chinese patients with Gaucher's disease. Cerezyme received SFDA approval to market in November 2008 in China. The China Charity Federation built an assistance foundation for rare diseases in 2009 and started the β-thalassemia patient assistance project of deferasirox (Exjade®) in 2010. In 2011, Qingdao Municipal Charity Federation and Bayer jointly launched the "Little Sunflower Hemophilia Charity Fund". This fund has 1 million RMB to support children with hemophilia who need to use Kogenate® FS (recombinant coagulation factor VIII for injection) (*24*).

Meanwhile, some Chinese patient organizations for rare diseases were also set up one by one, *e.g.*, the Home of Babies of the Moon − the China Albinism Association (*http://www.albinism.org.cn*), Beijing Rare Disease Care Center of the Hemophilia Home of China (*http://www.xueyou.org*), the Neuro-Muscular Disease Association of China, LAM-China (Lymphangio leiomyomatosis, *http://www.lamchina.org*), China TSC Together (tuberous sclerosis complex, *http://www.tscchina.org*) and the China-Dolls Care and Support Association (osteogenesis imperfecta, *http://www.chinadolls.org.cn*). The China-Dolls Care and Support Association was founded in 2007, which is a non-profit, non-governmental organization for people with osteogenesis imperfecta. The word "china" here has a dual meaning. One is porcelain, signifying that these patients are as fragile as porcelain. The other is the country China, emphasizing those with this disease are also Chinese citizens, and cannot be ignored and should not be discriminated against (*1*).

Moreover, academic activities and organizations for rare diseases were launched. In April 2010, the China Charity Federation, China Health Education Center and Tsinghua University in Beijing sponsored "2010 Symposium on Rare Diseases". In October 2010, China's first rare disease control association was established in Shandong Academy of Medical Sciences, namely Shandong Rare Disease Prevention Association. In February 2011, a rare disease specialist Medical Association Shanghai Branch was established. In 2010 and 2011, China Central Television (CCTV) broadcasted a series of programs about the painful situation of patients with rare diseases and the shortage of orphan drugs in the "Economy 30 Minutes", "Focus" program. Public awareness of rare diseases and orphan drugs is increasing fast.

5. Obstacle factors of access to orphan drugs in China

"Orphan drugs" are medicinal products intended for diagnosis, prevention or treatment of rare diseases. These drugs are called "orphan" because the pharmaceutical industry has little interest or is reluctant to invest in developing and marketing products intended for only a small number of patients suffering from very rare conditions. For the drug companies, the cost of bringing a rare disease medicinal product to the market would not be recovered by the expected sales of the product (*25*). Although Chinese pay more attention to rare diseases and orphan drugs, there are three key obstacle factors which affect improving accessibility of orphan drugs for patients with rare diseases.

5.1. *No definition of rare diseases and orphan drugs*

Currently, there is not a clear definition of rare diseases and orphan drugs in China. In this case, it is very difficult for people including many health providers that can clearly identify a rare disease or a common disease and an orphan drug or a general drug. Certainly, efficiency and effectiveness of medical demand and supply information communication of rare diseases and orphan drugs between the different market players will be weakened. An appropriate example can be founded in many hospitals in China. The hospitals do not establish the orphan drug formulary or alternative formulary of orphan drugs and special management system for rare diseases and orphan drugs, so that the shortage of orphan drugs and high medical risk of rare diseases are very likely to occur (*23*). Fortunately, the Ministry of Health in China is aware of the treatment problems and begins developing a clinical treatment pathway for some rare diseases, such as myelodysplastic syndrome, chronic myeloid leukemia, chronic lymphocytic leukemia, diffuse large B cell lymphoma, hemophilia, autoimmune hemolytic anemia, children with acute lymphoblastic leukemia, children with acute promyelocytic leukemia, and muscularamyotrophic lateral sclerosis (*26*).

5.2. *Lack of effective incentive policies for orphan drugs*

Compared with the orphan drug policies of the USA, EU and Japan, the Chinese incentive policies for rare diseases and orphan drugs which can be seen in the above chapter seem to lack a dynamic system. For push incentive policies, China is short of the direct cash investment in science research for rare diseases or orphan drugs, like special financial subsidies of the government for research grants, or tax credits for clinical research. For pull incentive policies, China does not set up useful market protection and assurance policies for orphan drugs, like market exclusivity, and a special market information network. Meanwhile, the supply and stockpile of orphan drugs have a low use frequency and high cost, so the drug wholesale and pharmacy also lack enough motivation to supply orphan drugs under no incentive policy. As a result, the output of orphan drugs is much less in China.

The Orphan Drug Act was passed in January 1983 in the USA, with lobbying from the National Organization for Rare Disorders and many other organizations. Under the law, companies that develop such an orphan drug (an orphan drug for a disorder affecting fewer than 200,000 people in the USA) may sell it with marketing exclusivity for 7 years, and may get tax credit for clinical research and research grants. From 1983 to May 2010, the FDA approved 353 orphan drugs and granted orphan designations to 2,116 compounds. As of 2010, 200 of the roughly 7,000 officially designated orphan diseases have become treatable (*27*). In contrast, the decade prior to 1983 saw fewer than ten such products come to market.

Similar to the USA, EU, Australia, Singapore, Japan, South Korea, and Taiwan also set up legislation for rare diseases. For example, the Regulation on Orphan Medicinal Products was passed by the European Council in 1999. European Parliament and Council Regulation (EC) No 141/2000 came into force in April 2000. It also provided incentives for the development of orphan drugs (or other medical products for rare disorders) in the EU. Orphan drug status granted by the European Commission gives marketing exclusivity in the EU for 10 years after approval. The EU's legislation is administered by the Committee on Orphan Medicinal Products of the European Medicines Agency (EMA). In May 2010, EMA had received more than 1,100 applications for orphan medicines. Out of these, 720 orphan designations have been granted, a success rate of 65%. A total of 62 orphan designated medicines have now been approved for use in the EU, giving treatment options for 53 different rare diseases (*28*).

5.3. *Limited insurance coverage and reimbursement levels for rare diseases and orphan drugs*

In the Chinese medical insurance system, the number of rare disease types covered is about 10-15, and the difference of disease coverage is obvious between different provinces. Currently, the central government of China claims the ceiling of inpatient expense for the social pooling fund in the three social insurance schemes is capped at six times of the local average payroll of urban employees or six times of the average disposable income of urban residents or eight times of the average net income of rural residents and is at least 60,000 RMB per year in 2012 (*21*). As an example of NRCMIS, it covered 0.836 billion people in 2011. The current issue is that the NRCMIS increases the enrollees' access to medical service and stimulates their service utilization, but the enrollees' medical expense burden of major disease was not alleviated significantly (*29*). As for the patients with hemophilia, they favor receiving outpatient treatment of hemophilia as opposed to inpatient treatment (*14*). Generally speaking, an average medical cost of 10-year-old children with hemophilia is about 60,000 RMB per year (*30*). The ceiling of outpatient expense for the social pooling fund in the three social insurance schemes is from 2,000 RMB per year (Shijiazhuang, Hebei province) to 45,000 RMB per year (Fushun, Guangdong province) in the different regions in China. As for CML, the medical expense burden of CML is still huge for the patient, although the medical costs can be paid partly by the social insurance schemes.

In a previous study, our group reported that the inpatients' average medical cost of 11 rare diseases in the public hospital is 6,405.69 RMB and the average duration of stay in the hospital is 11.15 days, based on an analysis of the data released in China Health Statistics Yearbook from 2004 to 2008. In the corresponding period, the average *per capita* disposable income of an urban resident was 12,248.14 RMB, and the average *per capita* net income of rural households was 3,735.86 RMB. For a disease, if the household's financial contribution index (Foc_i) is $\geq 40\%$, the medical expense is regarded as a catastrophic health expenditure for the patient's family. Consequently, the average hospital medical cost of a patient with a brain tumor in a public hospital is a catastrophic health expenditure for urban and rural middle-income families. The average hospital medical cost of patients with spina bifida, acute leukemia, or bladder cancer is a catastrophic health expenditure for rural middle-income families. The price and income elasticities of medical care demand of 11 rare diseases were 1.253 and 1.805 respectively (*31*).

As a matter of fact, the current Chinese medical insurance system is characterized by low premiums and large coverage, but its reimbursement for rare diseases and orphan drugs is limited.

6. Conclusion

Everyone should have equal rights of accessibility to basic health care opportunities. Under the condition

of a market economy, it is critical that the government should enact economic incentives to encourage drug companies to develop and market medicines for the many neglected and "orphaned" rare disease patients and ensure rare disease patients access to drugs and medical care.

All things considered, to raise the accessibility of orphan drugs in China, it is necessary to define basic concepts, list rare diseases and orphan drugs and build a systematic incentive mechanism for orphan drugs, design a special response system for orphan drugs in the medicine and health system supply, and establish a collaboration model of economic support between such parties as the government, enterprise, non-governmental organizations, and patients to reduce the patients' economic burden.

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