Commentary

DOI: 10.5582/ddt.2013.v7.3.126

Rare disease patients in China anticipate the sunlight of legislation

Jianjun Gao[1,2], Peipei Song[1], Wei Tang[1,2,*]

[1] *Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;*
[2] *Shandong University China-Japan Cooperation Center for Drug Discovery & Screening, Ji'nan, Shandong, China.*

ABSTRACT: It is estimated that there are over ten million rare disease patients in China currently. Due to a lack of effective drugs and reimbursement regulations for medical expenses the diseases bring most patients enormous physical suffering and psychological despair. Past experience in other countries such as the United States, Japan, and the European Union have shown that legislation is the critical step to improve the miserable situation of rare disease patients. Laws and regulations for rare diseases in these countries prescribe a series of incentives for research and development of orphan drugs which turn out to obviously allow these drugs to flourish. Legislation has also established a drug reimbursement system to reduce the medical burden of the patients. These measures effectively protect the rights and interests of patients with rare diseases. In China, legislation for rare diseases has begun to attract the attention of authorities. It is anticipated that relevant laws and regulations will be established as early as possible to provide safeguards for rare disease patients in China.

Keywords: Rare disease, orphan drugs, laws and regulations, medical reimbursement

A rare disease is referred to as any disease that affects an extremely small percentage of the population. The World Health Organization (WHO) defines a disease as a rare disease when its incidence ranges approximately from 0.65-1‰ in the whole population. In different countries, identification standards of a rare disease varies based on their specific legislation. For example, a rare disease is identified in the United States (US), Japan, and Australia when it afflicts less than 200,000 (approx. 0.75‰ of the population), 50,000 (approx. 0.4‰ of the population), and 2,000 (approx. 0.1‰ of the population) people, respectively (*1*). In China, the definition of a rare disease is not officially established due to a lag in legislation. Expert consensus indicates that a rare disease could be identified in China when the incidence of the disease in adults or neonates is less than 1 in 500,000 and 1 in 10,000, respectively (*2*). Although each specific disease affects a limited number of patients because of its rarity, the total number of patients with rare diseases represents a striking proportion of the total population because it is estimated that there are 5,000-7,000 distinct rare diseases worldwide (*3*). In the US and European Union (EU), it is estimated that 30 million people suffer from rare diseases in each of these regions (*4,5*). In China, this figure may be over 10 million according to the definition of rare diseases by WHO and the number of cases of rare diseases patients in other countries. These statistical data suggest that the overall incidence of rare diseases is far from rare either in China or in other regions of the world.

Missed or delayed diagnosis, shortage of effective drugs, and the high cost of currently available drugs are three features in treatment of rare diseases. In China, the latter two are particularly prominent since lack of incentive measures for the development of so called 'orphan drugs' and absence of drug reimbursement for the high price tag of these medicines. Thus far, no orphan drugs have been successfully developed and marketed by the domestic pharmaceutical companies in China. Patients with rare diseases are faced with the situation that they are nearly dependent on imported drugs. However, there are two hindrances that limit the availability of these orphan drugs to the patients. First, it takes a long time to obtain imported drug licenses in China. The result is that orphan drugs cannot be approved for marketing in China in a timely fashion. Thus, rare disease patients have difficulty getting suitable treatments in a short time period although the effective drugs have been approved and used in clinics in other countries. The delayed treatment leads to irreversible pathological changes and thus causes lifelong suffering for patients. Second, the government has not established a specific national healthcare system for rare disease patients, which leads to poor affordability of treatment costs for general families. The complicated research process, high expenses for pre-clinical and clinical trials, and the small targeted population decide the high prices

**Address correspondence to:*
Dr. Wei Tang, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan.
E-mail: TANG-SUR@h.u-tokyo.ac.jp

of successfully developed orphan drugs. Since 80% of rare diseases have genetic origins and 50% occur in childhood, most of these patients must receive therapies for a lifetime (*6*). Without strong support from the drug reimbursement system, most patients feel powerless and frustrated in obtaining effective but expensive treatments. In brief, rare diseases bring patients in China substantial physical suffering and psychological despair due to the lack of therapeutic hope and the absence of practical support for everyday life. Since these kinds of diseases require a significant amount of labor for the patient's care, they also cause a heavy burden on other family members, both financially and mentally. The helpless state of patients with rare diseases in China should be of concern to the entire society.

Legislation has proven to be the critical step to improve the miserable situation of rare disease patients. In fact, the development of orphan drugs for treatment of rare diseases had not been the focus of the pharmaceutical companies in the world for a long time due to worries of small market demand for a certain kind of disease and expensive research and development costs. Owing to the relentless work of patient and parent organizations, the neglected status of orphan drug development has attracted the attention of public health authorities and policy makers in recent decades. Since 1983 when the first law on rare disease in the world, *i.e.* Orphan Drug Act, was enacted in the US, thus far over 30 countries and regions such as Japan, the EU, Australia, and South Korea have passed laws and regulations to stimulate research and development of orphan drugs and help build a health care system for rare disease patients. Legislation has provided incentives for orphan drug development such as, new drug exclusivity, tax credits, subsidies for research, fast government evaluation, and drug reimbursement to a variable extent (Table 1) (*7*). With the aid of legislation, the number of approved orphan drugs has substantially increased. In the US, since the mid-1990s there has been a near tripling in the annual number of orphan drug designations for drugs in development, from 57 in 1996 to 165 in 2008 (*8*). In the 29 years (1983-2011) since the Orphan Drug Act was established, a total of 398 orphan drugs have been approved (*8*). On the contrary, only less than 10 orphan drugs were marketed in the US for a long time period before the law was enacted. Orphan drugs also represent a growing proportion of Food and Drug Administration (FDA) approvals, accounting for 30% in the most recent five-year period. In 2011, 35 new molecular entities were approved, in which 11 are for patients with rare

Table 1. Outline of laws and regulations for rare diseases in different countries

Items	US	Japan	Australia	EU	South Korea
Laws or regulations	Orphan Drug Act	Pharmaceutical Affairs Law (Article 77-2)	Orphan Drug Policy	Regulation(EC) No 141/2000	Orphan Drugs Guideline
Issue year	1983	1993	1998	2000	2003
Population size	305,000,000	127,000,000	21,000,000	500,000,000	48,000,000
Disease identification	< 7.5 in 10,000	< 4 in 10,000	< 1.1 in 10,000	< 5 in 10,000	< 4 in 10,000
Application range	Drug, biological products, medical device, medical foods, parenteral nutrition	Drug, biological products, medical device	Drug, biological products (including vaccine and in vivo diagnostic reagents)	Drug, biological products (including vaccine and in vivo diagnostic reagents)	Drug, biological products, medical device
New drug exclusivity	7 years	10 years	5 years	10 years	6 years
Tax credit	Yes; 50% of clinical trial expense	Yes; 6% of total drug development expense and 10% of corporate tax (Maximum)	No	Encourage member countries to offer tax favors	No
Subsidy for research	Yes; clinical trials	Yes; the entire process	No	Yes	No
Technical support for preparing application documents	Yes	Yes	No	Yes	No
Fast review program	Yes	Yes	Yes	Yes	No
Re-review after marketing	No	Yes	Yes (every 12 months)	Yes (6 years after marketing)	Unknown
Medical reimbursements	National health insurance, commercial health insurance	National health insurance plus 10% discount of drug price	Life Saving Drugs Program	Unique in each member country	Reimbursing two-thirds of medical expense

Data are from China Rare Disease Manual (*http://www.chinararedisease.cn*).

diseases such as the genetic defect of congenital factor XIII deficiency, several cancers, and scorpion poisoning (*9*). The flourishing of development of orphan drugs is largely ascribed to the stimulation effect of the laws and regulations that have been established in the orphan disease area.

It is worth noting that the laws and regulations that have been issued prescribe terms on the assurance or reimbursement of medical expenses for rare diseases. In the US, rare disease patients are not only covered by the national basic medical care system, they can also be accepted as insured by commercial health insurance. In Japan, the National Health Insurance System covers everyone who lives in this country and will reimburse 70% of medical costs in general cases. For rare disease patients, another 10% discount of drug prices is offered. In South Korea, the insurance system undertakes two-thirds of medical expenses for the patients. These measures provide powerful financial security for rare disease patients to obtain essential health care. In addition, they also offer economic security for pharmaceutical industries to cover costs and profits from the product.

Legislation on rare diseases has begun to attract the attention of government in China. In the National People's Congress (NPC) and Chinese People's Political Consultative Conference (CPPCC) of 2009, several NPC and CPPCC delegates proposed that legislation on rare diseases in China should be established as early as possible (*10,11*). Their suggestions include *i*) establishing an authentic and scientific definition of rare diseases; *ii*) constructing a reasonable drug reimbursement system; *iii*) simplifying the registration process for imported orphan drugs; *iv*) promoting research and development of orphan drugs through intensified policy support; *v*) building-up national health service institutes for rare disease patients. Although these proposals have been admitted by the Legislative Affairs Commission of the Standing Committee of the National People's Congress, it may take quite a long time (3-10 years) for the whole process from the motion to the final legislation. Fortunately, some districts in China have introduced policies that could reduce the medical care burdens of rare disease patients. In Shanghai, twelve kinds of rare diseases such as, phenylketonuria, maple syrup urine disease, and tyrosinemia have been covered by the city medical insurance (*12*). In addition, the Medical Mutual-Aid Foundation for Hospitalized Children, which is affiliated with the Shanghai Branch of the Red Cross Society of China, has announced that drugs against four rare diseases including: Gaucher's disease, Fabry's disease, Mucopolysaccharidosis, and Pompe's disease are covered by the mutual-aid funds for hospitalized children in Shanghai (*12*). According to this policy, one child with a rare disease could receive a maximum of 200,000 RMB per school year as reimbursement for treatment costs. The experiences of these districts will provide beneficial lessons for the final foundation of nationwide laws and regulations on rare diseases.

Rare disease patients are vulnerable groups in current China. They are suffering from a series of difficulties including disease treatments, attending school, and surviving for daily life. Parents could not take care of these children for a lifetime, but the laws and regulations can. Since every individual has the possibility to develop a rare disease, the final enacted legislation will be a safeguard for the whole society. This is the hope of rare disease patients and the direction of legislation in the future.

Acknowledgements

This study was supported by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan.

References

1 Song PP, Gao JJ, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. Intractable Rare Dis Res. 2012; 1:3-9.
2. Ma D, Li DG, Zhang X, He L. Opportunities and challenges of rare diseases treatments in China. Chin J Evid Based Pediatr. 2011; 6:81-82.
3. Tang W, Makuuchi M. Intractable and rare diseases research. Intractable Rare Dis Res. 2012; 1:1-2.
4. EURORDIS. Rare Diseases: Understanding this Public Health Priority. *http://www.eurordis.org/publication/rare-diseases-understanding-public-health-priority* (accessed May 6, 2013).
5. National Organization for Rare Disorders (NORD). *http://www.rarediseases.org/docs/NewsletterFall2010.pdf* (accessed May 6, 2013).
6. EURORDIS. About rare diseases. *http://www.eurordis.org/about-rare-diseases* (accessed June 1, 2013).
7. Rare Disease Manual. Rare Disease Aid Office, China Charity Federation. *http://www.chinararedisease.cn* (accessed May 10, 2013).
8. PhRMA 2012 Pharmaceutical Industry Profile. *http://www.phrma.org/* (accessed June 1, 2013).
9. Jenkins JK. "CDER New Drug Review: 2011 Update" presentation at the FDA/CMS Summit (Washington, DC), 8 December 2011, *http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM282984.pdf* (accessed June 1, 2013).
10. News. *http://www.caijing.com.cn/2009-03-09/110115538.html* (accessed June 3, 2013).
11. News. *http://www.people.com.cn/h/2012/0302/c25408-3807063986.html* (accessed June 3, 2013).
12. News. *http://sh.eastday.com/m/20120301/u1a6394800.html* (accessed June 6, 2013).

(Received June 15, 2013; Accepted June 21, 2013)