

Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives

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Summary

Rare diseases are an important public health issue and a challenge to medical care. Specific legislation to encourage research of rare diseases and development of orphan drugs has been adopted in the United States (US), the European Union (EU), and elsewhere. In recent years, much progress has been made in some parts of Asia, including Japan, South Korea, and Taiwan, with the enactment of legislation and accompanying regulation of rare diseases and orphan drugs. China is also actively promoting the regulation of rare diseases and orphan drugs. We describe the current status of the regulation of rare diseases and orphan drugs in Asia and we comparatively analyze the regulation of rare diseases and orphan drugs worldwide in order to examine the challenges to and future perspectives on promoting research on rare diseases and development of orphan drugs in China and other Asian countries.

Keywords: Orphan diseases, orphan drugs, legislation, incentives, reimbursement

1. Introduction

Rare diseases are rare and often debilitating or even life-threatening diseases or conditions with a prevalence of 0.65‰-1‰, as defined by the World Health Organization (WHO). Eighty percent of rare diseases have identified genetic origins, 50% of rare diseases affect children, and 30% of patients with rare diseases die before the age of 5 (1). The conventional view is that rare diseases together affect around 10% of individuals worldwide, but the definition and categorization of rare diseases differ slightly by region. The combined number of people suffering from rare diseases in the European Union (EU) and United States (US) is estimated to exceed 55 million and 5,000-7,000 rare diseases are thought to exist, with approximately 250 new diseases being described on an annual basis (2,3).

The features of rare diseases and the increasing number of identified rare diseases make these diseases

a priority for policymakers, researchers, legislators, and health care professionals (4). Currently, orphan drugs – the medicinal products intended for the diagnosis, prevention, or treatment of rare diseases – are a major facet of how rare diseases are dealt with. In the past three decades, many countries have recognized that orphan drugs would not lead to substantial sales under normal market conditions because of the high costs and risks of drug development, insufficient knowledge of pathophysiological mechanisms of rare diseases that the drugs diagnose or treat, and difficulties in conducting clinical trials with small patient populations and a small potential market. Therefore, specific legislation to encourage the discovery and development of orphan drugs was enacted in many countries and regions, including the US in 1983, Japan in 1993, Australia in 1997, the EU in 1999, Taiwan in 2000, and South Korea in 2003 (5-7). Incentives include financial subsidies, market exclusivity, tax credits, fee waivers, fast track approval, and protocol assistance, resulting in substantial improvements in the treatment of patients with a range of rare diseases.

In Asia, Japan, South Korea, and Taiwan have established systematic economic and regulatory incentives to encourage the development of drugs for rare diseases. China is also actively promoting the regulation of rare diseases and orphan drugs. Here,

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Japan, South Korea, China, and Taiwan are cited as examples to describe the current status of the regulation of rare diseases and orphan drugs in Asia. The regulation of rare diseases and orphan drugs worldwide has also been comparatively analyzed (Table 1). These two steps should help examine the challenges to and future perspectives on promoting research on rare diseases and development of orphan drugs in China and other Asian countries.

2. The current regulation of rare diseases and orphan drugs in Asian

The regulation of rare diseases and orphan drugs in Japan: *i) Definition of rare diseases.* Originally, rare diseases were known as "intractable diseases (Nanbyo)" in Japan. There was no concept of "rareness" until 1995, when the Ministry of Health and Welfare revised the definition of intractable disease (Nanbyo) to "a disease of unknown etiology with no effective treatment that presents a major financial and psychological burden and that is rare (fewer than 50,000 total patients)". Currently, rare diseases are termed "rare and intractable diseases" in Japan. *ii) Incentives for orphan drugs.* Revised orphan drug regulations (amendment of the Pharmaceutical Affairs Act and Drug Fund for Adverse Reaction Relief and Research Promotion Act) were established in 1993 and regulates the incentives, which include financial subsidies for up to 50% of expenses for clinical and non-clinical research during the entire research process, exclusive marketing rights for 10 years (compared to 6 years for other medications), 15% tax credits on research costs excluding financial subsidies and up to a 14% reduction in corporate tax, priority review and fast track approval, free protocol assistance, and user fee waivers. *iii) Support system.* Support measures include grants-in-aid for research programs (10 billion yen was allocated for the studies of 130 diseases in 2010), price-control policies negotiated by Japanese National Health Insurance (NHI) and pharmaceutical companies, and medical expense reimbursement for 56 diseases. *iv) Public awareness.* The Intractable Disease Information Center (<http://www.nanbyou.or.jp>) was established in 1997 and provides vast information on rare and intractable diseases, a list of experts, and contact addresses of rare disease patients' support organizations throughout Japan.

The regulation of rare diseases and orphan drugs in South Korea: *i) Definition of rare diseases.* In Korea, rare diseases are defined as diseases that affect fewer than 20,000 people or diseases for which an appropriate treatment or alternative medicine has yet to be developed. *ii) Incentives for orphan drugs.* The Orphan Drugs Guideline was established in 2003 and stipulates exclusive marketing rights for 6 years to encourage the research and development of orphan drugs. *iii) Support*

system. Support measures include medical expense reimbursement and nationally funded research programs along with support from the Ministry of Family Affairs, Health and Welfare and the Korean Centers for Disease Control and Prevention. *iv) Public awareness.* The Korean Rare Disease Information Database (<http://helpline.cdc.go.kr>) and Korean Organization for Rare Diseases (<http://www.kord.or.kr>) provide vast information on rare diseases for patients, researchers, pharmaceutical companies, and administrators.

The regulation of rare diseases and orphan drugs in Taiwan: *i) Definition of rare diseases.* In Taiwan, a disease is classified as a rare disease if it is prevalent in fewer than 1/10,000 population, has a genetic origin, and is difficult to diagnose and treat. *ii) Incentives for orphan drugs.* The Rare Disease Control and Orphan Drug Act was established in 2000, and incentives include financial subsidies, awards to special contributors from the central competent authority, exclusive marketing rights for 10 years (compared to 5 years for other medications), fast track approval, and protocol assistance. *iii) Support system.* Support measures include a reporting system for patients with rare diseases, "Genetic Counseling Centers" to counsel patients and other individuals, an "Orphan Drug Distribution Center" and a "Special Nutritional Supplement Supply Center" to facilitate the distribution of drugs, and 70% reimbursement for patients with rare diseases (which is expanded to 100% reimbursement for low-income families). *iv) Public awareness.* The Taiwan Foundation for Rare Disorders (TFRD) (<http://www.tfrd.org.tw>) was established in 1999 and provides general information and support to patients with rare diseases with regard to medication, education, employment, and long-term care.

The regulation of rare diseases and orphan drugs in China: *i) Definition of rare diseases.* Recognition of the concept of rare diseases may date back to the Drug Registration Regulation in 1999, but rare diseases have not been clearly defined by legislation until now. A consensus on the definition of rare disease is emerging according to the Expert Seminar on the Definition of Rare Diseases in China held in 2010, which proposed that a disease be classified as a rare disease if it is prevalent in fewer than 1/500,000 or has a neonatal morbidity of fewer than 1/10,000 (8). *ii) Incentives for orphan drug.* Many regulations – the New Drug Approval Regulation (1999), Drug Registration Regulation (2007), and Special Review and Approval Procedures for Drug Registration (2009) – implemented by the State Food and Drug Administration (SFDA) have set forth general criteria to accelerate the registration and approval of orphan drugs, but detailed rules have yet to be implemented and further incentives have not been proposed until now. *iii) Support system.* Support measures have been provided mainly from special organizations dealing with rare diseases –

Table 1. Comparison of the regulation of rare diseases and orphan drugs worldwide*

Items	United States	European Union	Australia	Japan	South Korea	Taiwan	China
Criterion for prevalence of rare diseases (%)	0.75	0.5	0.11	0.4	0.4	0.1	prevalent < 1/500,000, or neonatal morbidity < 1/10,000**
Affected population	25-30 million	27-36 million	1.2 million	N	N	more than 2,000	16.8 million**
Administrative bodies involved	FDA/OOPD	EMA/COMP	TGA	MHLW	KFDA	DOH	SFDA
Legal framework	Orphan Drug Act (1983), Rare Diseases Act of 2002 (2002)	Regulation (EC) No. 141/2000 (1999)	Orphan Drug Policy (1997)	Revised orphan drug regulations (1993)**	Orphan Drugs Guideline (2003)	Rare Disease Control and Orphan Drug Act (2000)	No
Financial subsidies	government grants for clinical research	framework programs plus national measures	N	governmental grants for clinical and non-clinical research	N	government grants and awards from the central competent authority	NSFC research grants
Market exclusivity (years)	7	10	5 (similar to other drugs)	10	6	10	N
Tax credits	up to 50% for clinical expenses	managed by member states	N	15% tax credits, up to 14% corporate tax reduction	N	N	N
Fast track approval	Yes	Yes (centralized approval)	Yes	Yes	N	Yes	Yes
Protocol assistance	Yes	Yes	Yes	Yes	N	Yes	N
Regulatory fee waivers	Yes	Yes	Yes	Yes	N	N	N
Pharmaceutical pricing	market-driven	depending on member states	same as general drugs	price negotiation	N	N	N
Medical expense reimbursement	Yes	Yes	Yes	for 56 diseases	Yes	70% for patients, up to 100% for low-income families	N
Public awareness	NORD	EURORDIS	AGSA	IDIC	KRDID, KORD	TFRD	Chinese Rare Disease Net, and others

* Data are from references 2, 3, 5-12, 20, 24-26.

** Has not being defined by legislation according to the Expert Seminar on the Definition of Rare Diseases in China.

*** Revised orphan drug regulations (amendment of the Pharmaceutical Affairs Act and Drug Fund for Adverse Reaction Relief and Research Promotion Act) (1993).

N, no information; FDA, Food and Drug Administration; OOPD, Office of Orphan Products and Development; EMA, European Medicines Agency; COMP, Committee of Orphan Medicinal Products; TGA, Therapeutic Goods Administration; MHLW, Ministry of Health, Labor and Welfare; KFDA, Korean Food and Drug Administration; DOH, Department of Health; SFDA, State Food and Drug Administration; NSFC, National Natural Science Foundation of China; NORD, National Organization for Rare Disorders; EURORDIS, European Organization for Rare Diseases; AGSA, Association of genetic support of Australasia; IDIC, Intractable Disease Information Center; KRDID, Korean Rare Disease Information Database; KORD, Korean Organization for Rare Diseases; TFRD, Taiwan Foundation for Rare Disorders.

the Committee Specializing in Rare Diseases of the Shenzhen Medical Association, the Committee Specializing in Rare Diseases of the Chinese Medical Association, the Committee Specializing in Rare Diseases of the Shanghai Medical Association, and the Rare Disease Association of Shandong Province – to promote the research on rare diseases and development of orphan drugs. *iv) Public awareness.* The Rare Disease in China Network (<http://www.hanjianbing.org>), the Chinese Rare Disease Academic Network (<http://www.chinards.com>), and many patients' advocacy groups, such as the China-Dolls Care and Support Association, the Haemophilia Home of China (HHC), the Neuro-Muscular Disease Association of China, and the Chinese Lymphangiomyomatosis Organization (LAM-China), are devoted to providing information and improving patients' access to healthcare.

3. Comparative regulatory aspects of rare diseases and orphan drugs worldwide

3.1. Definition and classification of rare diseases

There is no internationally accepted definition of rare diseases. In the US, rare diseases are defined as diseases that affect fewer than 200,000 Americans (prevalence of < 0.75‰), while stipulated prevalence rates in other regions were < 0.5‰ in the EU, fewer than 2,000 patients (prevalence of < 0.11‰) in Australia, fewer than 50,000 patients (prevalence of < 0.4‰) in Japan, fewer than 20,000 patients (prevalence of < 0.4‰) in South Korea, and prevalence of < 0.1‰ in Taiwan (9-11). The number of patients affected by rare diseases could be about 27-36 million in the EU, 25-30 million in the US, and 1.2 million in Australia (2,3,12), but the true burden of rare diseases in the EU and elsewhere is difficult to estimate since epidemiological data for most rare diseases are not available. The primary reasons why such epidemiological data are often lacking could be due to *i)* the absence of proper classification and coding for rare diseases and the absence of registration of patients suffering from rare diseases and *ii)* the absence of appropriate biochemical and genetic diagnostic data.

Currently, there is no special coding system for rare diseases. The International Classification of Diseases (ICD) code that is used in most countries is not suitable for rare diseases. The absence of a universally recognized coding system is an obstacle for reliable registration of patients in national or international databases, preventing assessment of the economic and social effects of rare diseases. However, the good news is that the European Rare Disease Task Force of the Health and Consumers Protection Directorate General of the European Commission has set up a working group to collaborate with the WHO on the ICD-10 and is considering all other existing classifications to provide the rare disease community with a uniform

system (13). Worldwide, major mutation databases include Online Mendelian Inheritance in Man (OMIM), the Human Gene Mutation Database (HGMD), and the Human Genome Variation Society (HGVS). Recently, country-specific databases have also been developed, such as the Singapore Human Mutation/Polymorphism Database (SHMPD) and Korean Mutation Database (KMD) (14). Advances in genetic research and establishment of additional databases could facilitate the diagnosis of patients with rare diseases.

Thus, a legislative definition and classification of rare diseases and accurate data on the epidemiology of rare diseases are urgently needed at the national and international levels in order to support health management policies and studies aimed at developing and assessing treatments.

3.2. Incentives for orphan drug research and development

Orphan drugs are less likely to be developed by pharmaceutical companies because the market is small and research and development costs are usually too high to make the drugs profitable. Given this context, orphan drug legislation has been adopted in several countries around the world in the past three decades to encourage manufacturers to develop orphan drugs. The primary incentives can be broken down into three types: *i)* marketing exclusivity for the orphan drug, whereby sponsors of this drug are granted a given period of marketing exclusivity during which no other drug will be approved to treat the disease in question; *ii)* the setting up of tax credits and financial subsidies for research; and *iii)* simplification of and preference in drug authorization, including fast track approval, fee waivers, and protocol assistance.

Regulatory systems have both similarities and differences. With regard to financial subsidies, for example, only expenses in clinical research activities are subsidized in the US, while expenses in clinical and non-clinical research during all research can be subsidized in Japan. With regard to market exclusivity, Japan, the EU, and Taiwan offer market exclusivity for 10 years, while the US offers market exclusivity for 7 years. With regard to tax credits, credits can cover up to 50% of clinical expenses in the US, while Japan offered a 6% tax credit for research expenses excluding financial subsidies and up to a 10% reduction in corporate tax (since 1999, Japan has offered a 15% tax credit for research expenses excluding financial subsidies and up to a 14% reduction in corporate tax). Revised orphan drug regulations in Japan also require sponsors to pay a 1% sales tax to offset the subsidies they received from the government when their orphan drug annual profits exceed 100 million yen (15,16).

Evidence has shown that all of the incentives have successfully encouraged the development of new pharmaceutical products to treat rare diseases and have

resulted in an increasing number of licensed orphan drugs. Prior to 2010, 352 orphan drugs were approved in the US, helping an estimated 12 million Americans, compared to only 10 such drugs in the decade preceding the Orphan Drug Act (1983). Similarly, 720 drugs had received orphan drug designation from the European Medicines Agency (EMA) and 63 designated orphan medicinal products had received marketing authorization in the EU. Furthermore, data have shown that an average of 15 new orphan drugs are approved annually in the US and 10-12 new orphan drugs are approved annually in the EU (17-19).

In Asia, orphan drug legislation has been adopted in Japan, South Korea, and Taiwan, and incentives are playing an important role in encouraging manufacturers to develop orphan drugs. While China is actively preparing to regulate and encourage the development of orphan drugs, but it still lags far behind the US, the EU, Japan, and other countries and regions with orphan drug legislation. The current regulations only set forth general criteria to accelerate the registration and approval of orphan drugs, but detailed rules have not been implemented and further incentives have not been proposed until now. Thus, the pressing issue for China and other Asian countries without orphan drug legislation is to establish domestic legislative regulations and incentives to encourage the development of orphan drugs.

3.3. Support system for the development of rare disease and orphan drugs

Special regulatory authority: One of the similarities among the countries and regions with legislation on rare disease and orphan drugs is that they have a special regulatory authority, such as the Office of Orphan Products Development (OOPD) within the Food and Drug Administration (FDA) in the US and the Committee of Orphan Medicinal Products (COMP) within the European Medicines Agency (EMA) in the EU, with the main task of examining applications for orphan drug designation and planning and regulating the development of rare disease and orphan drugs. In Asia, this regulatory authority is the Ministry of Health, Labor, and Welfare (MHLW) in Japan, the Korean Food and Drug Administration (KFDA) in South Korea, and the Department of Health (DOH) in Taiwan. In Taiwan, the Rare Disease Control and Orphan Drug Act was promulgated in 2000, and the DOH has subsequently devised a series of accompanying regulations on the implementation of orphan drug approval, review, registration, supply, and awards (20). In China, orphan drugs and other drugs are all currently administered by the SFDA, and a special regulatory authority for rare diseases and orphan drugs has not been established.

Special research support: In the US and EU, special

research centers or projects have been established to support research on rare diseases and development of orphan drugs. In the US, the Office of Rare Diseases Research (ORDR) was established in 1993 within the National Institutes of Health (NIH) to coordinate and support rare disease research, explore opportunities to research rare diseases, and provide information on rare diseases. In EU, the Rare Disease Task Force (RDTF) was established in 2004 within the European Commission Public Health Directorate to provide evidence to support policymaking, provision of medical services, and community support for rare diseases and orphan drugs through European coordination. In Asia, the Specified Disease Treatment Research Program was established in Japan in 1972 with the support of MHLW, 130 diseases have been for the subject of special research programs and research grants from government sources expanded to 10 billion yen in 2010 (21). Recently, 214 diseases were selected for a second round of special research programs (22). In South Korea, the Research Center for Rare Diseases (RCRD) was established in 2008 with the support of the Ministry of Family Affairs, Health and Welfare. The Center oversees 3 collaborative research projects, 9 single-center research projects, and 7 clinical research networks in order to provide a foundation for research on rare diseases and orphan drugs. In China, research support comes mainly from the National Natural Science Foundation of China (NSFC). Data showed that 366 projects (involving 32 rare diseases) were funded by the NSFC from 1999 to 2007 with total funding of 89.358 million RMB and annual funding of about 10 million RMB, accounting for just 1/10th of similar funding in the US (23).

Access to Orphan Drugs: Pricing and reimbursement are the two major aspects that affect access to orphan drugs for patients with rare diseases. In the US, drug manufacturers negotiate with governmental programs such as Medicaid and Veterans Health Administration and Pharmacy Benefits but remain free to set their own introductory prices and there is little regulation of competition among manufactures in comparison to imposed price restrictions (24). In the EU, orphan designation and marketing authorization for orphan drugs are decisions made at the European level according to Regulation (EC) No 141/2000, but pricing and reimbursement decisions are a member state responsibility (25): some European countries, such as Belgium, France, Italy, and the Netherlands, compare the price requested by the pharmaceutical company to that in other countries; the United Kingdom has set up a system of profit control to constrain prices and Sweden uses a system of public procurement at the regional level in order to maximize price competition. In 2008, European drug prices averaged 40% less than American prices, with prices in Italy and Germany respectively averaging 55% and 70% of American prices (19).

However, most orphan drugs are still expensive due to the high research costs and the small market and most patients will not be able to afford to pay for orphan drugs themselves. Given this context, both the US and EU have established financial support for patients with rare diseases. In Asia, the Japanese NHI negotiates prices with the pharmaceutical companies once a drug is approved for use, allowing a selling price of cost plus 10% for orphan drugs; nearly half of the orphan drugs on the Japanese market originated from the EU or US. Moreover, 56 of 130 designated diseases in Japan are subject to reimbursement of medical expenses, with 30% of expenses paid by insurance companies and the rest paid by national and prefectures governments (26). In 2010, reimbursements expanded to 28 billion yen and the number of recipients expanded to approximately 700,000 (22). In Taiwan, 77 approved orphan drugs and 40 special nutritional supplements can be imported, and the reimbursement cap is 70% of actual expenses but families that qualify for low-income status can receive reimbursement for up to 100% of drugs and nutritional supplements for patients (20). While in China, a sound supply mechanism and reimbursement system have not been established, hampering access to orphan drugs for patients with rare diseases (27). However, the good news is that patients with 12 rare diseases in Shanghai recently became eligible for partial reimbursement, and some special orphan drugs for children have been covered by insurance (28).

4. Public awareness, research, and global cooperation

In addition to the lengthy development of orphan drugs, the delay in diagnosis is also a huge challenge to cope with. A survey of 18,000 individuals found that 25% of patients waited for 5-30 years before being correctly diagnosed and 40% of patients were diagnosed incorrectly before correctly diagnosed (29). The challenge is the lack of quality information and a networking system to facilitate interaction among patients, clinicians, researchers, the pharmaceutical industry, and governmental bodies. In order to change this situation, many patients' advocacy organizations and networks, both nationally and internationally, have been established with or without governmental support. Major organizations in Western countries, such as the National Organization for Rare Disorders (NORD) in the US and the European Organization for Rare Diseases (EURORDIS) in Europe, can provide vast information on rare diseases and improve patients' access to healthcare. The "Rare Disease Day" initiated by EURORDIS in 2008 to raise public awareness started as a European event but has now become a world event, with the US joining in 2009 and patient organizations in 56 other countries participating in 2011(30). In Asia, patients' advocacy organizations and networks have also established in Japan, South Korea,

China, and Taiwan to provide vast information to patients with rare diseases and to promote research on rare diseases and development of orphan drugs.

In recent years, progress has been made in research on rare diseases and the dissemination of knowledge and information. However, existing research efforts are still scattered and fragmented research is being performed with little coordination between research laboratories. This hampers research on rare diseases and development of orphan drugs, especially with regard to clinical studies on orphan drugs that suffer from the small size of the trial population and the fact that patients are often geographically dispersed. Thus, there is a pressing need to increase international cooperation. In Western countries, some web-based resources have been established. For example, the Rare Diseases Clinical Research Network (RDCRN) was established in the US in order to facilitate collaboration amongst experts from 19 distinctive consortia and to create a platform for collaboration to identify biomarkers for disease risk, disease severity and activity, and clinical outcome (31). Orphanet was established in Europe and includes 1,673 organizations affiliated with EURORDIS that gather national expertise on rare diseases together and share reports of member states' assessments of the therapeutic or clinical added value of orphan drugs in order to minimize delays in access to orphan drugs for patients with rare diseases (32). Both RDCRN and Orphanet represent a good example for Asian countries to launch their own international collaborative projects to promote research on rare diseases and development of orphan drugs.

5. Conclusion

In conclusion, rare diseases are an important public health issue and a challenge to medical care. In recent years, much progress has been made in some parts of Asia, including Japan, South Korea, and Taiwan, with the enactment of legislation and accompanying regulation of rare diseases and orphan drugs. China is actively promoting the regulation of rare diseases and orphan drugs but still lags far behind the US, EU, Japan, and other countries and regions with orphan drug legislation. Comparative analysis of the regulation of rare diseases and orphan drugs worldwide has shown that public authorities should regard rare diseases as a public health priority and take definite action, including legislation to confirm the definition and classification of rare diseases, assembling accurate epidemiological data on rare diseases, incentives to encourage manufacturers to develop orphan drugs, an appropriate support system to ensure access to orphan drugs, and international cooperation in research on rare diseases and development of orphan drugs. "It is now time for action" (33), especially for China and other countries in Asia.

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