Policy Forum

DOI: 10.5582/irdr.2019.01090

Marketing of drugs for rare diseases is speeding up in China: Looking at the example of drugs for mucopolysaccharidosis

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Summary **In May 2019, China National Medical Products Administration approved the marketing of an elosulfase alfa injection (brand name: Vimizim) from BioMarin Pharmaceutical for the treatment of patients with mucopolysaccharidosis (MPS) type IVA. This is the first drug to treat MPS in China, and it has ended the "dearth of medicines" to treat MPS in China, a situation that has persisted for many years. One can reasonably say that the drug has benefited from the continuous reform of the drug review and approval system in China and the increasing attention paid to rare diseases. At present, China has implemented a series of preferential policies for the review and approval of drugs for rare diseases, mainly including priority review and approval, accelerated review and approval, special review and approval (mainly simplified review and approval), data protection, and communication. Moreover, China now has a specific reference for the review and approval of drugs for rare diseases with the creation of China's First List of Rare Diseases and the publication of two batches of the List of Overseas New Drugs Urgently Needed in Clinical Settings. Drug review and approval has been significantly accelerated, as has marketing. The two batches of lists of new drugs, issued in November 2018 and May 2019, include 43 drugs for rare diseases (58.1% of all drugs in the lists), 37 of which were included in China's First List of Rare Diseases. The lists also include three other drugs for MPS. As of July 1, 2019, four drugs for rare diseases from the first batch of new drugs have been approved for marketing. In order to further improve the review and approval of drugs for rare diseases in China, a special department should be established for the evaluation of drugs for rare diseases, research on and management of drugs in the post-approval phase should be enhanced, international cooperation in research on use of drugs to treat rare diseases should be enhanced, and the incentive policy for marketing drugs for rare diseases should be improved.**

Keywords: Rare disease, drugs for rare diseases, drug review and approval, China, mucopolysaccharidosis

1. Introduction

Rare diseases are a group of diseases with very low incidence and prevalence. Currently, less than 10% of patients with rare diseases have access to specific treatments (*1*). The limited number of patients means that limited attention is paid to those diseases, and few clinical trials of drugs are conducted. This reality has greatly hindered the timely marketing of drugs for rare diseases, and it has delayed effective and timely treatments for patients with rare diseases. The situation is even worse in China. Statistics indicate that prior to December 2018 only 83 drugs for rare diseases had been marketed in China (according to China's First List

Released online in J-STAGE as advance publication August 20, 2019.

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of Rare Diseases, hereinafter referred to as the Chinese Rare Diseases List, or CRDL); these drugs account for only 51% of orphan drugs around the world (*2*).

Fortunately, continuous reform of the drug review and approval system and increasing public attention paid to rare diseases has accelerated the review and approval process for drugs to treat rare diseases in China. In May 2019, the National Medical Products Administration (NMPA) authorized the marketing of an elosulfase alfa injection (brand name: Vimizim) from BioMarin Pharmaceutical for the treatment of mucopolysaccharidosis (MPS) type IVA. This is the first drug to treat MPS in China, having ended the "dearth of medicines" to treat MPS in China for many years. The drug was included in *the List of the First Batch of Overseas New Drugs Urgently Needed in Clinical Settings* (hereinafter referred to as the First New Drug List, FNDL) issued by the Center for Drug Evaluation (CDE) of the NMPA in November 2018 and authorized for marketing in May 2019, indicating that the drug review and approval process has accelerated (*3*).

2. Mucopolysaccharidosis

2.1. *Basic features*

MPS is a complex, progressive, and multi-system lysosomal disease caused by a lack of enzymes that degrade glycosaminoglycans. Mucopolysaccharides that cannot be completely degraded are stored in lysosomes, which leads to facial abnormalities, nervous system involvement, skeletal deformities, enlarged liver and spleen, heart disease, corneal opacity, *etc*. (*4*). MPS is classified into 7 types that involve 11 lysosomal enzymes encoded by 11 genes (I, II, IIIA, IIIB, IIIC, IIID, IVA, IVB, VI, VII, and IX).

Table 1. Incidence of different types of MPS

Type	Asian (*10-16*)	Global (*10*)
I	1/100,000	1/100,000
II	1/100,000	1/140,000-160,000
III	A:1/100,000	1/70,000-90,000
	B:1/200,000	
	C:1/1,500,000	
	D:1/1,000,000	
IV	A:1/201,000	1/200,000
	B:1/76,000-640,000	
VI	1/240,000-400,000	1/240,000-300,000
VII	1/400,000	<1/250,000
IX	Only 4 reported cases	Extremely rare

MPS, mucopolysaccharidosis.

2.2. *Epidemiological features*

The prevalence of MPS is approximately 1/100,000 (*4*). The incidence of MPS is shown in Table 1. In Asian countries like South Korea and Japan, about 50% of patients have MPS type II, while the incidence of MPS type I is higher than that of MPS type II in Western countries (*5*). Prior to January 31, 2019, 176 patients with MPS were identified in Taiwan, China (*6*). Although there is a lack of epidemiological data on MPS in mainland China with only individual studies of clinical cases, the disease has been included in many rare disease catalogues in China, including the CRDL (*7*), *the List of Major Rare Diseases in Shanghai (2016 edition)* from the former Shanghai Municipal Health and Family Planning Commission (now called Shanghai Municipal Health Commission) (*8*) and *China's Rare Diseases Reference List (Revised Edition)* from a non-profit organization (*9*).

2.3. *Treatments and drugs*

The most common treatments for MPS are hematopoietic stem cell transplantation and enzyme replacement therapy (*17*). Many of the drugs for enzyme replacement therapy are already on the market in the US, the EU or Japan, and some came on the market in the US 10 years ago, including laronidase (2003), idursulfase (2006) and galsulfase (2005). Some drugs have also been marketed in the US in recent years, including elosulfase alfa (2014) and vestronidase alfa (2017). Table 2 shows the global

Table 2. The status of global marketing of drugs for MPS (*2,3,18-21*)

General name	Brand name	Indication	Marking status			
			USA	EU	Japan	China
Laronidase	Aldurazyme	MPS I	2003/04	2003/09	2006/10	Included in the SNDL (2019/05).
Idursulfase	Elaprase	MPS II	2006/07	2007/01	2007/10	Included in the SNDL (2019/05).
Dursulfase beta	Hunterase	MPS II	South Korea (2012/07)			Pharmaceutical companies signed an agreement on exclusive licensing in China (2019/01). An application for marketing approval has been received by the NMPA (2019/07).
Elosulfase alfa	Vimizim	MPS IV	2014/02	2014/04	2014/12	Included in the FNDL (2018/11). Approved (2019/05).
Galsulfase	Naglazyme	MPS VI	2005/05	2006/01	2008/03	—
Vestronidase alfa	MepseVII	MPS VII	2017/11	2018/06	—	Included in the FNDL (2018/11).

MPS, mucopolysaccharidosis; FNDL, First New Drug List, *the List of the First Batch of Overseas New Drugs Urgently Needed in Clinical Settings*; SNDL, Second New Drug List, *the List of the Second Batch of Overseas New Drugs Urgently Needed in Clinical Settings*.

marketing of drugs for MPS.

However, these drugs have yet to be approved in China. Hence, symptomatic treatment is often provided in China, with the goal of treating respiratory and cardiovascular complications, deafness, hydrocephalus, along with surgery and rehabilitation in order to improve the quality of life of patients with MPS (*4*). The review and approval of drugs for rare diseases in China has been significantly accelerated by the reform of the drug review and approval system and the introduction of policies on rare diseases in recent years. Elosulfase alfa for the treatment of MPS type IVA and vestronidase alfa for the treatment of MPS type VII were included in the FNDL (*3*). Laronidase for MPS type I and idursulfase for MPS type II were included in *the List of the Second Batch of Overseas New Drugs Urgently Needed in Clinical Settings* (hereinafter referred to as the Second New Drug List, SNDL) issued in May 2019 (*18*). Elosulfase alfa, which treats MPS type IVA, was officially approved by the NMPA in May 2019.

3. The development of review and approval policies of drugs for rare diseases in China

3.1. *Early stage (Before 2015)*

Provision for Drug Registration, which were formulated in accordance with the *Pharmaceutical Administration Law of the People's Republic of China*, are the fundamental policy for drug review and approval. The *Provision* mentioned how new drugs for rare diseases with obvious clinical advantages could be specially approved (*22*). The *Regulations to Manage the Special Approval of New Drugs* were issued in 2009 (*23*), and they included three main mechanisms: dynamic supplementation of materials through multiple channels, multi-channel communication, and a reduced approval time. However, a study indicated that the average time for review of drugs for rare diseases was 351 days (*24*).

3.2. *The reform of drug review and approval (2015-)*

The *Opinion on Reform of the Review and Approval System of Drugs* and Medical Devices was published by the State Council in August 2015 (*25*), marking the beginning of a new round of reform of the drug review and approval system in China. The reform is of great significance since it seeks to improve the quality of review and approval, reduce the backlog of applications for registration, improve the quality of generic drugs, encourage research and development of new drugs, and improve the transparency of drug review and approval. Accelerating the review and approval of innovative drugs for rare diseases was mentioned in the *Opinion*. Since then, a number of specific policies on drug review and approval have been introduced. In October 2017, the Central Office of the Communist Party of China and the General Office of the State Council issued their *Opinion on Further Reform of the Review and Approval System and Encouraging Innovation in Drugs and Medical Devices*, signaling further reform (*26*). One specific section mentioned supporting the development of drugs and medical devices for rare diseases. The aforementioned reform has created a good external policy environment to accelerate the marketing of drugs for rare diseases in China.

3.3. *Publication of the CRDL (2018-)*

Although the review and approval of drugs for rare diseases has benefited from a series of policies, these policies cannot be effectively implemented since China lacks a clear definition or scope of rare diseases. Social security for patients with rare diseases in China has a clear and priority range, as identified by the publication of the CRDL in May 2018 (*27*). Moreover, arrangements to accelerate the approval of overseas new drugs were made by Premier Li Keqiang at the Executive Meeting of the State Council on June 20, 2018. Simplification of the marketing requirements for drugs to treat rare diseases has been proposed, and applications for marketing approval can be submitted with research materials from overseas. Regulatory authorities should conclude review of an application within three months (*28*). In October 2018, *Procedures for the Review and Approval of Overseas New Drugs Urgently Needed in Clinical Settings* were issued by the NMPA and National Health Commission (*29*). Drugs for rare diseases that have been marketed in the US, the EU, or Japan for ten years can directly receive marketing approval and would be included in special channels for review and approval. Since the *Procedures* were issued, the review and approval of drugs for rare diseases in China has really sped up. Material requirements for drugs in different stages are shown in Table 3.

In general, the current preferential policies for the review and approval of drugs for rare diseases in China include prior review and approval, accelerated review and approval, special review and approval (mainly simplified review and approval), and data protection and communication, as shown in Table 4.

4. Recent approval and review of drugs for rare diseases in China

The FNDL includes a total of 48 types of drugs, with 25 drugs for rare diseases (not including rare tumors); 20 of those drugs are to treat diseases in the CRDL. Prior to July 1, 2019, 4 of the 20 drugs had been approved for marketing, 2 were under review, 4 were preparing for application, 6 were not scheduled for marketing approval, and 4 had no contact (*35*). The SNDL includes a total of 26 types of drugs, with 18 drugs for rare

Table 3. Material requirements for an application for marketing approval of overseas new drugs urgently needed in clinical settings (*29*)

Drug status	Application for marketing approval
Drugs that have not yet been submitted for clinical trials or marketing approval	Submit an application for marketing approval.
Drugs that have been submitted for clinical trials but that have not completed technical review	Adjust the clinical trial application to the application for marketing approval. Supplement all research materials from overseas and supporting materials indicating no ethnic differences in action.
Drugs undergoing clinical trials	Submit an application for marketing approval and continue the clinical trial. After completing the clinical trial, submit a research report in the form of a supplementary application.
Drugs that have submitted for marketing approval	Supplement all research materials from overseas and supporting materials indicating no ethnic differences in action.
Drugs that have been marketed in Japan or Chinese Hong Kong, Macau, Taiwan with abundant cases	Provide research reports on drug utilization in the aforementioned countries or regions and perform relevant analysis; may not need to provide research materials on ethnic differences in action.

Table 4. The main preferential policies for the review and approval of drugs for rare diseases in China

Type of Policy	Main contents
Prior review and approval	Establish a special channel of review and approval for drugs that have been included in the List of New Drugs (*27*). Examine classified review and approval of drugs for rare diseases, children, and the elderly (*30*).
Accelerated review and approval	CDE should complete the technical review of drugs in the List of New Drugs within 3 months of acceptance (excluding the time taken for the applicant's supplementary materials), and NMPA should make a decision in 10 working days after receiving the review materials from CDE (*27*).
Specialized/Simplified review and approval	When applying for a clinical trial, the applicant can apply to reduce the number of subjects or to receive an exemption from clinical trials (*22,31*) . An application for marketing approval of drugs that have been listed overseas and that are believed to have no ethnic differences in action can be submitted with clinical trial data from overseas (*32*). Still soliciting opinions: real-world data from natural disease cohorts could be used as external controls, and external controls are mainly used for non-random single-arm trials, which can be historical or parallel (*33*).
Data Protection	A certain period of protection should be provided to data acquired by the applicant and undisclosed trial data. During the period of data protection, an application for similar marketing approval by another applicant should not be approved except in situations where the applicant obtained the data or the applicant received the consent of a company marketing the drug (*26*). Still soliciting opinions: 6 years of data protection should be provided starting from approval in China (*34*).
Communication	CDE should establish a mechanism for communicating with applicants to enhance its guidance of drug development (*29,32*).

CDE, Center for Drug Evaluation.

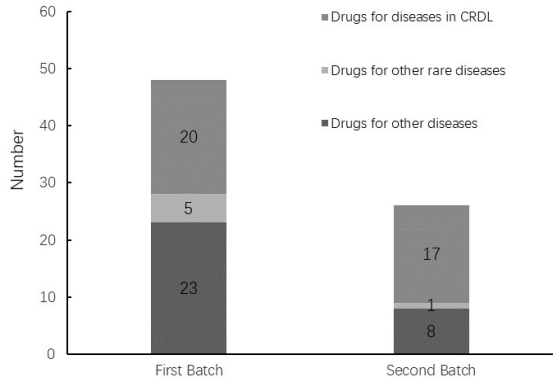

Figure 1. Drugs on the two lists of the First Batch and Second Batch of Overseas New Drugs Urgently Needed in Clinical Settings. CRDL, China's First List of Rare Diseases

diseases; 17 of those drugs are to treat diseases in the CRDL. Types of drugs on the two lists are shown in Figure 1.

5. Discussion and Suggestions

Despite the accelerated approval of drugs for rare diseases, the review and approval process still faces many challenges in China. There is still much work to do in order to further improve the marketing of drugs for rare diseases.

5.1. *Establishing a specialized department for the review and approval of drugs for rare diseases*

The current and future workload for the review and approval of drugs for rare diseases is relatively heavy, since only about half of the drugs for rare diseases are on the market in China. A specialized department in the CDE needs to be established to review and approve drugs for rare diseases. The Office of Orphan Products Development (OOPD) has been set up in the US FDA (*36*), and the Committee for Orphan Medicinal Products (COMP) has been set up in the EMA (*37*). This guarantees the effective review and approval of drugs for rare diseases and it also accelerates expert review and approval of those drugs. These benefits will play an important role in promoting the development and marketing of drugs for rare diseases in China.

5.2. *Enhancing the research and management of drugs for rare diseases after marketing*

Rapid or special approval of drugs for rare diseases is currently available. However, research on and management of rare disease drugs should be enhanced considering the possible risks of drug use and the great value of patient research. Both the US and the EU have implemented post-approval management for drugs to treat rare diseases (*38,39*). The FDA issued guidelines on post-marketing research and clinical trials in 2011. In addition, pharmaceutical companies are also obliged to inform doctors about information on drug usage and risks and to conduct risk management (*40*). Another urgent task is to establish and improve post-marketing research and management systems for drugs to treat rare diseases, such as enhancing physician training, establishing registries of drugs use, and collecting real-world data.

5.3. *Enhancing international cooperation in research on rare diseases*

With the accelerated marketing approval of drugs to treat rare diseases in China and the establishment of rare disease registries and patient organizations (*41*), information on patients with rare diseases and their medications in China has been fleshed out further. International cooperation on rare diseases, and especially on drugs used, should be coordinated. This will greatly promote the development, launch, and utilization of those drugs.

5.4. *Improving the incentive policy for marketing approval of drugs for rare diseases*

Although the review and approval of drugs for rare diseases has accelerated, many drugs for rare diseases still have yet to be approved, scheduled, or contacted for marketing in China despite their appearance in the List of New Drugs. In addition to the continuous improvement of the review and approval of drugs for rare diseases, appropriate incentive policies should be formulated to attract pharmaceutical companies. Detailed rules for the implementation of polices, like data protection for patients with rare diseases, need to be issued. Exclusivity of drugs for rare diseases could be implemented. More drugs for rare diseases need to be covered by social insurance.

6. Conclusion

The review and approval of drugs for rare diseases has been markedly accelerated in China. This was initially the result of reform of China's drug review and approval system and the publication of CRDL, though it could not have been achieved without further reform of the health care system, continued reform of social welfare, and optimization of the administrative review and approval system. Given the accelerated introduction of drugs for rare diseases, more patients with rare diseases will presumably have access to those medicines, and those medicines will gradually become more available to patients with rare diseases in China (*42*). However, this is just the first step to improving drug accessibility for patients with rare diseases, since affordability and rational use of medicines are essential as well. Medical care for patients with rare diseases in China still has a long way to go.

Acknowledgements

This study was supported by a grant from the Shanghai Municipal Health Commission for a Special Research Project related to Health Policies entitled "Study on the disease burden of and social security for the vulnerable population in Shanghai (Project number: 19Y04017)".

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(Received June 28, 2019; Received August 5, 2019; Accepted August 14, 2019)