Policy Forum

DOI: 10.5582/irdr.2023.01030

Analysis of marketed orphan drugs in China

Wei Zhi, Meilin Liu, Dan Yang, Shanshan Zhang, Yanqin Lu*, Jinxiang Han*

Key Laboratory for Biotech Drugs of the National Health Commission, Key Laboratory for Rare & Uncommon Diseases of Shandong Province, Biomedical Sciences College & Shandong Medicinal Biotechnology Centre, Shandong First Medical University & Shandong Academy of Medical Sciences, Ji'nan, Shandong, China.

SUMMARY In recent years, China has increased attention on the issue of rare diseases, and the government has promulgated rare disease–related policies to gradually improve rare disease diagnosis, treatment, drug marketing, and patient burden. Orphan drugs were added to the medical insurance directory in 7 batches, of which 22 drugs were first included in the 2004 medical insurance directory and 8, 16, 12, 7, 8, and 7 were included in the 2009, 2017, 2019, 2020, 2021, and 2022 versions, respectively. Currently, 106 orphan drugs are marketed in China, which are suitable for treating 53 rare diseases such as hematologic diseases, congenital metabolism disorders, neuropathies, and digestive system diseases and for other treatment fields. The drugs are mainly manufactured in 15 countries such as China, Switzerland, and the USA, of which 10 drugs can be used to treat different rare diseases. At the same time, there are multiple treatments available for 25 rare diseases. In this paper, we examined the manufacturers, marketing status, indications, and inclusion of orphan drugs in the National Basic Medical Insurance Directory to describe and analyze the current status of 106 orphan drugs that are currently marketed in China to provide a reference for rare disease policy formulation and drug development.

Keywords marketed orphan drugs, rare diseases, medical insurance, indications for medication

1. Introduction

Rare diseases refer to rarely encountered diseases with low prevalence and are also known as orphan diseases. The World Health Organization defines rare diseases as diseases with an incidence of 0.65‰–1‰ (*1*). Currently, 6,000–8,000 unique rare diseases have been identified, of which 80% are genetic in origin and 50% occur in children (*2*). Rare diseases are often chronic and progressive diseases that have significant incidence and mortality rates (*3*). The issue of orphan drugs was first mentioned by rare disease groups in the USA. In other countries, rare disease security policies mainly include formulating marketing laws for orphan drug marketing, encouraging the research and development of orphan drugs, and accelerating the marketing review and approval of orphan drugs, such as the Orphan Drug Act passed in the USA in 1983 (*4*) and the Orphan Drug Regulation promulgated and implemented in the European Union in which orphan drugs recognized in the European Union can enjoy scientific recommendations, expedited review and approval, and 10-year postmarketing market monopoly by the European Medicines Agency (*5*).

In recent years, China has focused increasing attention on rare disease medical insurance, and rare disease medical insurance policies in China have been formulated from scratch. On the one hand, the Chinese government has promulgated a series of policies to encourage the development and marketing of orphan drugs, which has achieved some progress in increasing the number of orphan drugs. These policies include supporting companies in research and development of orphan drugs and encouraging the exploration of new rare disease indications for marketed drugs in the area of encouraging the development of orphan drugs (*6*) and providing expedited review and approval for orphan drugs in the area of priority review and approval (*7*) and corresponding policies for clinical trial exemption and tax reduction. On the other hand, as rare diseases are prone to misdiagnosis and missed diagnosis, a national diagnosis and treatment cooperative network was established by China's healthcare system to construct a rare disease case information registration and management system. In October 2019, the National Health Commission promulgated the China Rare Disease Diagnosis and Treatment Service Information System Working Management Protocol requiring

member hospitals in the cooperative network to perform diagnosis and treatment information registration for rare disease cases and set up an information system to collect relevant data (*8*). In addition, local governments have actively explored rare disease administration security mechanisms. After many years of practice, local rare disease administration security mechanisms have gradually become the "project fund" model represented by Zhejiang and Jiangsu (*9*), the "major disease insurance" model represented by Shandong and Chengdu (*10*), and "medical relief" represented by Foshan (*11*). Overall, the rare disease security attempts and practices of some provinces and cities resulted in the "expansion from a point" development of rare disease policies and healthcare security and accumulated practice experience for rare disease security policies at the national level.

The *Notice on First Batch of Rare Disease Directory* released in May 2018 included a total of 121 rare diseases (*12*). The 2020 Opinions on *Deepening the Reform of the Medical Security System* by the State Council of the People's Republic of China explored rare disease administration security mechanisms, strengthening basic medical insurance, major disease insurance, and medical relief security systems, and encouraged the development of commercial health insurance and social charity relief (*13*). In June 2022, the National Healthcare Security Administration released the 2022 National Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance Drug Directory Adjustment Working Plan. The plan clearly stated prioritizing rare disease patients, removed application time limits for orphan drugs, and supported inclusion into the national generic drug directory at the same time (*14*). On January 18, 2023, the National Healthcare Security Administration printed the National Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance Drug Directory (2022) notice and encouraged active exploration of using "dual-channel" to improve the supply and security levels of orphan drugs (*15*).

2. Existing orphan drugs and drug manufacturers

In recent years, the National Healthcare Security Administration has exerted efforts in improving the affordability of orphan drugs. Since 2017, when the National Health Insurance Directory was routinely adjusted and examined, the National Healthcare Security Administration has appropriately aimed at orphan drug declaration and attention. After enquiring the National Healthcare Security Administration and searching the Wuwang Database and Yaozhi Database, the number of approved drugs for treating rare diseases in China (Table 1) was calculated. It was found that 106 drugs could be used to treat 53 rare diseases, such as hematologic diseases, congenital metabolism disorders, neuropathies, and digestive system diseases. From Table 1, it can be observed that 83 orphan drugs were included in the National Health Insurance Directory as of March 2023, of which 22 drugs were first included in the 2004 medical insurance directory and 8, 16, 12, 7, 8, and 7 were included in the 2009, 2017, 2019, 2020, 2021, and 2022 versions, respectively. These 80 drugs cover a total of 40 rare diseases, of which 13 are under class A reimbursement in the National Health Insurance Directory and used to treat 10 rare disease indications without requiring patient self-pay and 67 drugs are under class B reimbursement, which requires patients to pay a specific proportion of the drug fees on the basis of the provincial medical insurance policy and in which part of the cost is reimbursed. The reimbursement ratio differs according to local policies and drugs.

There are 106 orphan drugs, and all are Western medicines. From Figure 1, it can be observed that manufacturers are located in 15 countries, of which 26 drugs were developed by 23 Chinese companies such as Zhaoke Pharmaceutical Co. Ltd. and Shandong Taibang Biological Products Co. Ltd. The remaining 67 drugs are manufactured in 14 other countries, mainly Switzerland, the USA, and Germany. From the statistical analysis in Table 1, it can be observed that Novartis AG from Switzerland developed 11 drugs, which are used to treat six rare diseases. Among them, four are used to treat multiple sclerosis. Furthermore, Actelion from Switzerland developed three drugs for idiopathic pulmonary hypertension. In the USA, the main pharmaceutical companies that developed drugs for rare diseases are Merck Sharp & Dohme, Biogen, and Pfizer. There are 11 drugs that were developed in Germany, of which six were developed by Bayer. Sanofi in France developed seven drugs, Takeda in Japan developed five drugs, and AstraZeneca and GSK in the UK developed six drugs.

3. Current status of marketed orphan drugs in China

After searching the Orphanet database, it was found that 73.5% of these 53 rare diseases are inherited, such as idiopathic pulmonary hypertension and spinal muscular atrophy. These rare diseases include immune disorders, hematologic diseases, tumors, congenital metabolic disorders, nervous system diseases, respiratory diseases, and endocrine disorders. At present, 42.5% of the drugs can be used to treat 21 different neurological disorders such as Parkinson's disease (young-onset, early onset) and multiple sclerosis, and 24% of the drugs can be used to treat 19 congenital metabolic disorders such as primary carnitine deficiency and Fabry disease (Supplementary Table 1).

From Table 2, it can be observed that there are many drugs for 25 rare diseases and that some drugs have the same mechanisms of action for treating

Table 1. The list of 106 marketed drugs approved in China for the treatment of rare diseases

Rare Disease	Drug	R&D Country	R&D Manufacturer	Time to market (abroad)	Time to market (China)	Medical insurance type (insurance period)
21-Hydroxylase Deficiency	Hydrocortisone	China	Henan Lihua Pharmaceutical Ltd	N.A.*	2001	Class-A (2004)
	Hydrocortisone Acetate	China	Meyer Pharmaceuticals Ltd	N.A.	1979	-**
Amyotrophic Lateral Sclerosis	Riluzole Oral Suspension	China	Zhaoke Pharmaceutical (Hefei) Ltd	2022	2022	Class-B (2022)
	Edaravone Injection	China	Jiangsu Zheng Dafeng hai pharmacy Ltd	N.A.	2019	Class-B (2020)
	Riluzole Tablets	France	Sanofi	1996	1998	Class-B (2017)
Atypical Hemolytic Uremic Syndrome	Eculizumab Injection	Britain	AstraZeneca Pharmaceutical Ltd	2007	2018	-
Beta-ketothiolase Deficiency	Levocarnitine	Italy	AlfasigmaS.p.A.	1990	1999	Class-B (2009)
Biotinidase Deficiency	Compound Vitamin B Tablets	Germany	Bayer Schering Pharma AG	1986	1999	Class-B (2004)
Carnitine Deficiency	Levocarnitine	Italy	AlfasigmaS.p.A.	1990	1999	Class-B (2009)
Castleman Disease	Siltuximab for Injection	America	Johnson&Johnson Pharmaceuticals Ltd	2004	2021	-
Citrullinemia	Sodium Phenylbutyrate Powder	China	Zhaoke Pharmaceutical (Guangzhou) Ltd	1996	2021	-
Congenital Adrenal Hypoplasia	Hydrocortisone	China	Henan Lihua Pharmaceutical Ltd	N.A.	2001	Class-A (2004)
	Hydrocortisone Acetate	China	Meyer Pharmaceuticals Ltd	N.A.	1979	-
Fabry Disease	Agalsidase Alfa Concentrated Solution for Infusion	Japan	Takeda Pharmaceutical Ltd	2001	2021	Class-B (2021)
	Agalsidase Beta for Injection	France	Sanofi	2001	2018	-
Gaucher's Disease	Velaglucerase Alfa for Injection	Japan	Takeda Pharmaceutical Ltd	2014	2021	-
	Imiglucerase for Injection	France	Sanofi	1994	2008	-
Generalized Myasthenia Gravis	Pyridostigmine Bromide Tablets	China	Shanghai Shangyao Traditional Chinese and Western Pharmaceutical Ltd	1955	2003	Class-A (2004) -
Glycogen Storage Disease (Type I, II)	Alglucosidase Alfa for Injection	France	Sanofi	2006	2015	-
Hemophilia	Human Coagulation Factor IX	China	China Biologic Products Holdings, Inc	N.A.	2020	Class-B (2021)
	Desmopressin Acetate	Netherlands	Ferring Pharmaceuticals Ltd	1972	2001	Class-A (2004)
	Human Prothrombin Complex	China	Shanghai Xinxing Medicine Ltd	N.A.	2002	Class-B (2004)
	Human Coagulation Factor VIII	China	Tonrol Bio-pharmaceutical Ltd	N.A.	2018	Class-A (2017)
	Recombinant Human Coagulation Factor VIII	Germany	Bayer Schering Pharma AG	1992	2007	Class-B (2009)
	Recombinant Human Coagulation factor IX	America	Pfizer Inc	1977	2012	Class-B (2017)
	Recombinant Human Coagulation Factor VIIa	Denmark	Novo Nordisk Biotechnology Ltd	1999	2002	Class-B (2017)
	Eftrenonacog alfa for Injection	France	Sanofi	2016	2021	-
	Emicizumab Injection	Switzerland	Roche Pharmaceutical Ltd	2017	2018	-
Hepatolenticular Degeneration	Penicillamine Tablets	China	Hainan Honghui Pharmaceutical Ltd	N.A.	1999	Class-A (2004)
	Sodium Dimercaptosuccinate	China	Shanghai Fudan Fuhua Pharmaceutical Ltd	N.A.	2002	Class-A (2004)
	Dimercaptosuccinic Acid	America	Recordati Rare Diseases Inc.	1991	1999	Class-A (2004)
	Zinc Sulfate	China	Shanghai Pharmaceutical Xinyi Pharmaceutical Ltd	1970	2004	Class-B (2009)
Hereditary Angioedema	Danazol Capsules	China	Baiyunshan Zhengqing Pharmaceutical Ltd	N.A.	1999	Class-B (2004)
	Icatibant Acetate Injection	Japan	Takeda Pharmaceutical Ltd	2011	2021	Class-B (2021)
	Lanadelumab Injection	Japan	Takeda Pharmaceutical Ltd	2018	2020	Class-B (2022)
Hereditary Hypomagnesemia	Magnesium Gluconate	China	Beijing Jialin Pharmaceutical Ltd	N.A.	2020	-

Table 1. The list of 106 marketed drugs approved in China for the treatment of rare diseases (continued)

Rare Disease	Drug	R&D Country	R&D Manufacturer	Time to market (abroad)	Time to market (China)	Medical insurance type (insurance period)
	Potassium Aspartate and Magnesium Aspartate	Hungary	Gedeon Richter Plc	1962	1989	Class-B (2004)
Homozygous Hypercholesterolemia	Evolocumab Injection	America	Amgen Inc.	2015	2018	Class-B (2021)
	Rosuvastatin Calcium Tablets	Britain	AstraZeneca Pharmaceutical Ltd	2002	2006	Class-B (2009)
	Ezetimibe Tablets	America	Merck Sharp & Dohme	2002	2012	Class-B (2017)
Huntington Disease	Deutetrabenazine Tablets	Israel	Teva Pharmaceutical Industries Ltd	2017	2020	Class-B (2020)
	Tetrabenazine	France	Recipharm Fontaine SAS	2008	2021	-
Hyperphenylalaninemia	Sapropterin Dihydrochloride Tablets	Germany	Excella GmbH & Co.KG	2007	2010	-
Hypophosphatemic Rickets	Burosumab Injection	Japan	Kyowa Kirin Inc.	2019	2021	-
Idiopathic Cardiomyopathy	Tafamidis Meglumine	America	Pfizer Inc	2019	2020	Class-B (2021)
Idiopathic Hypogonadotropic	Gonadorelin for Injection	China	Maanshan Fengyuan Pharmaceutical Ltd	N.A.	1996	Class-B (2004)
Hypogonadism	Menotrophins for Injection	China	Maanshan Fengyuan Pharmaceutical Ltd	N.A.	2010	Class-B (2004)
	Chorionic Gonadotrophin for Injection	China	Penglai Huatai Pharmaceutical Ltd	N.A.	2001	Class-A (2004)
Idiopathic Pulmonary Arterial	Treprostinil Injection	China	Zhaoke Pharmaceutical (Hefei) Ltd	2005	2013	Class-B (2022)
Hypertension	Ambrisentan tablets	Britain	GlaxoSmithKline	2007	2010	Class-B (2020)
	Bosentan Tablets	Switzerland	Actelion Pharmaceuticals Ltd	2001	2006	Class-B (2019)
	Riociguat Tablets	Germany	Bayer Schering Pharma AG	2013	2017	Class-B (2019)
	Macitentan Tablets	Switzerland	Actelion Pharmaceuticals Ltd	2013	2017	Class-B (2019)
	Selexipag Tablets	Switzerland	Actelion Pharmaceuticals Ltd	2018	2018	Class-B (2019)
	Sildenafil Citrate Tablets	America	Pfizer Inc	1998	2000	-
	Iloprost	Germany	Bayer Schering Pharma AG	2003	2018	-
Kallmann Syndrome	Gonadorelin for Injection	China	Maanshan Fengyuan Pharmaceutical Ltd	N.A.	1996	Class-B (2004)
	Menotrophins for Injection	China	Maanshan Fengyuan Pharmaceutical Ltd	N.A.	2010	Class-B (2004)
	Chorionic Gonadotrophin for Injection	China	Penglai Huatai Pharmaceutical Ltd	N.A.	2001	Class-A (2004)
Idiopathic Pulmonary Fibrosis	Nintedanib esilate soft capsules	Germany	Boehringer Ingelheim Pharma GmbH & Co. KG	2014	2019	Class-B(2020)
	Pirfenidone Capsules	China	Beijing Cantiny Pharmaceutical Ltd	2008	2013	Class-B(2017)
Inborn Errors of Bile Acid Synthesis	Sodium Cholate Tablets	China		N.A.	2002	-
Mucopolysaccharido-sis	Laronidase concentrated solution for infusion	France	Changzhou Qianhong Biochemical Pharmaceutical Ltd Sanofi	2003	2020	-
	Elosulfase alfa injection	Germany	Vetter Pharma-Fertigung GmbH & Co.KG	2014	2019	-
	Idursulfase beta Injection	Korea	Green Cross Corporation	2012	2020	-
Multiple Sclerosis	Fampridine	America	Biogen, Inc.	2010	2021	Class-B (2021)
	Fingolimod Hydrochloride Capsules	Switzerland	Novartis Pharma Schweiz AG	2010	2019	Class-B (2020)
	Siponimod Tablets	Switzerland	Novartis Pharma Schweiz AG	2019	2020	Class-B (2020)
	Teriflunomide Tablets	France	Sanofi	2012	2018	Class-B (2019)
	Baclofen Tablets	Switzerland	Novartis Pharma Schweiz AG	1977	1994	Class-B (2004)
	Dimethyl Fumarate Enteric Capsules	America	Biogen, Inc.	2013	2021	Class-B (2022)
	Ofatumumab Injection	Switzerland	Novartis Pharma Schweiz AG	2020	2021	Class-B (2022)
	Interferon beta-1b	Germany	Bayer Schering Pharma AG	1993	2018	-
	Recombinant human interferon beta-1b for injection	Germany	Bayer Schering Pharma AG	1993	2018	-

Table 1. The list of 106 marketed drugs approved in China for the treatment of rare diseases (continued)

Rare Disease	Drug	R&D Country	R&D Manufacturer	Time to market (abroad)	Time to market (China)	Medical insurance type (insurance period)
Multiple System Atrophy	Droxidopa Capsules	China	Chongqing Shenghuaxi Pharmaceutical Ltd	1989	2012	Class-B (2017)
Neonatal Diabetes Mellitus	Insulin Detemir Injection	Denmark	Novo Nordisk Biotechnology Ltd	2004	2009	Class-A (2009)
	Glibenclamide Tablets	China	Zhicheng Pharmaceutical Ltd	1966	1999	Class-A (2004)
Neuromyelitis Optica	Inebilizumab Injection	Britain	AstraZeneca Pharmaceutical Ltd	2020	2022	Class-B (2022)
Niemann-Pick Disease	Miglustat Capsules	Switzerland	Actelion Pharmaceuticals Ltd	2009	2016	Class-B (2019)
Ornithine Transcarbamylase Deficiency	Sodium Phenylbutyrate	China	Zhaoke Pharmaceutical (Guangzhou) Ltd	1996	2021	-
Parkinson Disease (Young-onset , Early-onset)	Entacapone,Levodopa and Carbidopa Tablets	Finland	Orion Corporation	1998	2016	Class-B (2019)
	Rasagiline	Israel	Teva Pharmaceutical Industries Ltd	2005	2017	Class-B (2019)
	Carbidopa and levodopa Tablets	America	Merck Sharp & Dohme	1975	1991	Class-B (2004)
	Droxidopa Capsules	China	Chongqing Shenghuaxi Pharmaceutical Ltd	1989	2012	Class-B (2017)
	Amantadine Hydrochloride Tablets	China	Northeast Pharmaceutical Group Ltd	1966	1971	Class-A (2004)
	Ropinirole Hydrochloride Tablets	Britain	GlaxoSmithKline	1996	2018	Class-B (2017)
	Pramipexole Dihydrochloride Tablets	Germany	Boehringer Ingelheim Pharma GmbH & Co. KG	1999	2005	Class-B (2009)
	Selegiline Hydrochloride Tablets	Finland	Orion Corporation	1995	2004	Class-B (2004)
	Levodopa Tablets	Switzerland	Roche Pharmaceutical Ltd	1973	1997	Class-A (2004)
	Rotigotine Patches	Belgium	UCB Pharma S.A.	2006	2018	-
Paroxysmal Nocturnal Hemoglobinuria	Eculizumab Injection	Britain	AstraZeneca Pharmaceutical Ltd	2007	2018	-
Primary Combined Immune Deficiency	Human Immunolobulin (pH4) for Intravenous Injection	China	Guanfeng Biological Products Ltd	2006	2018	Class-B (2017)
Primary Light Chain Amyloidosis	Daratumumab Injection	America	Janssen-Cilag International NV.	2015	2019	Class-B (2021)
Severe Congenital Neutropenia	Mecapegfilgrastim Injection	China	Jiangsu Hengrui Pharmaceuticals Ltd	N.A.	2018	Class-B (2019)
	Lenograstim	Japan	Chugai Pharmaceutical Ltd	1991	1993	-
Sitosterolemia	Ezetimibe Tablets	America	Merck Sharp & Dohme	2002	2012	Class-B (2017)
Spinal Muscular Atrophy	Nusinersen Sodium Injection	America	Biogen, Inc.	2016	2019	Class-B (2021)
	Risdiplam Powder for Oral Solution	Switzerland	Roche Pharmaceutical Ltd	2020	2021	Class-B (2022)
Tetrahydrobiopterin Deficiency	Sapropterin Dihydrochloride Tablets	Germany	Excella GmbH & Co.KG	2007	2010	-
Tuberous Sclerosis Complex	Everolimus Tablets	Switzerland	Novartis Pharma Schweiz AG	2003	2013	Class-B (2017)
Tyrosinemia	Nitisinone	Switzerland	Swedish Orphan Biovitrum AB	2002	2021	-
X-linked Agammaglobulinemia	Human Immunolobulin (pH4) for Intravenous Injection	China	Guanfeng Biological Products Ltd	2006	2018	Class-B (2017)
Lennox-Gastaut syndrome	lamotrigine Tablets	Britain	GlaxoSmithKline	1994	1999	Class-B (2009)
Mediterranean Anemia	Desferrioxamine Mesylate for Injection	Switzerland	Novartis Pharma Schweiz AG	1975	2005	Class-A (2004)
	Deferasirox Dispersible Tablets	Switzerland	Novartis Pharma Schweiz AG	2005	2010	Class-B (2019)
Myelofibrosis	Ruxolitinib Phosphate Tablets	Switzerland	Novartis Pharma Schweiz AG	2011	2017	Class-B (2019)
Myelodysplastic syndrome	Decitabine for Injection	America	Janssen-Cilag International NV.	2006	2009	Class-B (2017)
	Azacitidine for Injection	Germany	Baxter Oncology GmbH	2004	2017	Class-B (2017)
Crohn disease	Infliximab for Injection	America	Merck Sharp & Dohme	1998	2006	Class-B (2019)
Respiratory distress syndrome	Poractant Alfa Injection	Italy	Chiesi Farmaceutici S.p.A	N.A.	2001	Class-B (2017)
Acromegaly	Bromocriptine Mesilate Tablets	Switzerland	Novartis Pharma Schweiz AG	1978	2001	Class-B (2004)

Table 1. The list of 106 marketed drugs approved in China for the treatment of rare diseases (continued)

Rare Disease	Drug	R&D Country	R&D Manufacturer	Time to market (abroad)	Time to market (China)	Medical insurance type (insurance period)
	Octreotide Acetate Microspheres for Injection	Switzerland	Novartis Pharma Schweiz AG	1998	2003	Class-B (2017)
	Lanreotide Acetate Sustained-release Injection	France	Ipsen Pharma Biotech	1995	2019	Class-B (2020)
Multiplemyeloma	Bortezomib for Injection	America	Janssen-Cilag International NV.	2003	2005	Class-B (2017)
	Lenalidomide	America	Celgene Corporation	2005	2013	Class-B (2017)
	Thalidomide	Switzerland	Novartis Pharma Schweiz AG	1957	2008	Class-B (2004)
	Ixazomib Citrate Capsules	Japan	Takeda Pharmaceutical Company Limited	2015	2018	Class-B (2017)

N.A.[*] : Not available; -[**] : none medical insurance drugs.

the same disease. For example, the greatest number of drugs (*10*) are available for treating Parkinson's disease (young-onset, early onset), of which ropinirole hydrochloride tablets and pramipexole hydrochloride tablets are dopamine agonists of the non-ergoline class, and rasagiline and selegiline hydrochloride tablets are monoamine oxidase B inhibitors. This is followed by nine drugs for treating multiple sclerosis, of which fingolimod hydrochloride capsules and siponimod tablets are both sphingosine-1-phosphate receptor modulators. There are eight drugs for treating idiopathic pulmonary hypertension, which are endothelin receptor antagonists such as ambrisentan, bosentan, and macitentan. The drugs used to treat thalassemia are deferoxamine and deferasirox dispersible tablets, and both drugs are oral iron chelators. A total of 11 orphan drugs such as droxidopa capsules, ezetimibe tablets, and hydrocortisone can be used to treat two rare diseases and that there are many drugs for treating four rare diseases, such as 21-hydroxylase deficiency and idiopathic hypogonadotropic hypogonadism (Table 3).

4. Outlook

Currently, the orphan drug landscape in China can be summarized as follows: drugs not available in China but available overseas, drugs available in China but not included in medical insurance, and drugs included in medical insurance but not available in hospitals. Although major progress has been achieved in the rare disease medical insurance system in China, it is mainly based on basic medical insurance, and charity and other security systems do not play a supplementary role. In addition, there are still a large number of orphan drugs that have not been included in the basic medical insurance directory, placing immense burdens on patients. Because of this, we formulated national rare disease security policies and directed the process of rare disease legislation. Systematic special laws should be passed for orphan drug development, review and approval, security, and services. In addition, modifications to the rare disease directory should be accelerated by refining the dynamic updating of the rare disease directory on the basis of disease prevalence, medical technology level, disease burden, and security level of China. Furthermore, we recommend the improvement of the multilayered healthcare security system for rare diseases on the basis of basic medical insurance supplemented by commercial health insurance, charity donations, and patient self-pay and the identification of the limits and responsibilities of various security entities. The government should guide social forces to set up a rare disease–related fund, lead in establishing a negotiating platform for pharmaceutical companies and commercial insurance, promote the creation of a discussion platform for inclusive commercial insurance, and include more

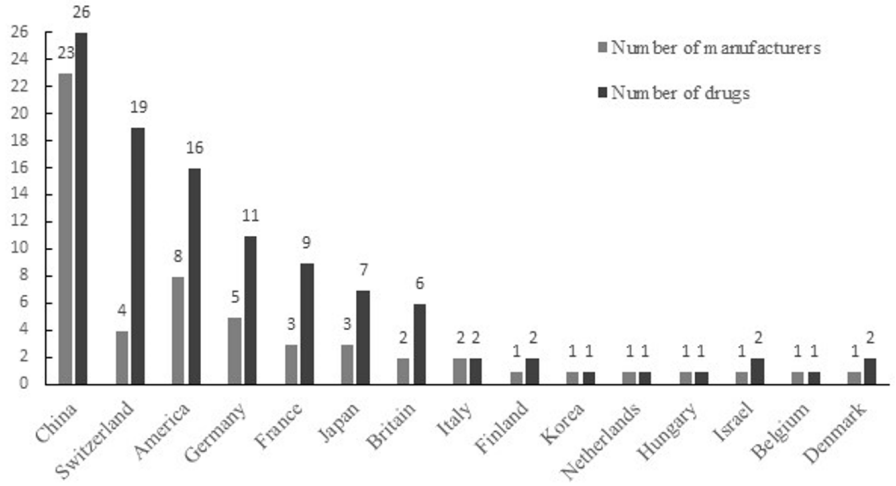

Figure 1. Distribution of R&D manufacturers for marketed 106 orphan drugs.

Table 2. The list of 106 marketed drugs approved in China for the treatment of rare diseases

Rare disease	Number of drug	Marketed drug
Parkinson Disease (Young-onset , Early-onset)	10	Entacapone,Levodopa and Carbidopa Tablets, Rasagiline, Carbidopa and levodopa Tablets, Droxidopa Capsules, Amantadine Hydrochloride Tablets, Ropinirole Hydrochloride Tablets, Pramipexole Dihydrochloride Tablets, Selegiline Hydrochloride Tablets, Levodopa Tablets, Rotigotine Patches
Multiple Sclerosis	9	Fampridine, Fingolimod Hydrochloride Capsules, Siponimod Tablets, Teriflunomide Tablets, Baclofen Tablets, Dimethyl Fumarate Enteric Capsules, Ofatumumab Injection, Interferon beta-1b, Recombinant human interferon beta-1b for injection
Hemophilia	9	Human Coagulation Factor IX, Desmopressin Acetate, Human Prothrombin Complex, Human Coagulation Factor VIII, Recombinant Human Coagulation Factor VIII, Recombinant Human Coagulation factor IX, Recombinant Human Coagulation Factor VIIa, Eftrenonacog alfa for Injection, Emicizumab Injection
Idiopathic Pulmonary Arterial Hypertension	8	Treprostinil Injection, Ambrisentan tablets, Bosentan Tablets, Riociguat Tablets, Macitentan Tablets, Selexipag Tablets, Sildenafil Citrate Tablets, Iloprost
Hepatolenticular Degeneration	4	Penicillamine Tablets, Sodium Dimercaptosuccinate, Dimercaptosuccinic Acid, Zinc Sulfate
Multiplemyeloma	4	Bortezomib for Injection, Lenalidomide, Thalidomide, Ixazomib Citrate Capsules
Hereditary Angioedema	3	Danazol Capsules, Icatibant Acetate Injection, Lanadelumab Injection
Idiopathic Hypogonadotropic Hypogonadism	3	Gonadorelin for Injection, Menotrophins for Injection, Chorionic Gonadotrophin for Injection
Kallmann Syndrome	3	Gonadorelin for Injection, Menotrophins for Injection, Chorionic Gonadotrophin for Injection
Amyotrophic Lateral Sclerosis	3	Riluzole Oral Suspension, Edaravone Injection, Riluzole Tablets
Homozygous Hypercholesterolemia	3	Evolocumab Injection, Rosuvastatin Calcium Tablets, Ezetimibe Tablets
Acromegaly	3	Bromocriptine Mesilate Tablets, Octreotide Acetate Microspheres for Injection, Lanreotide Acetate Sustained-release Injection (a pre-filled syringe)
Mucopolysaccharidosis	3	Laronidase concentrated solution for infusion, Elosulfase alfa injection, Idursulfase beta Injection
Neonatal Diabetes Mellitus	2	Insulin Detemir Injection, Glibenclamide Tablets
Idiopathic Pulmonary Fibrosis	2	Nintedanib esilate soft capsules, Pirfenidone Capsules
Mediterranean Anemia	2	Desferrioxamine Mesylate for Injection, Deferasirox Dispersible Tablets
Myelodysplastic syndrome	2	Decitabine for Injection, Azacitidine for Injection
Spinal Muscular Atrophy	2	Nusinersen Sodium Injection, Risdiplam Powder for Oral Solution
Severe Congenital Neutropenia	2	Mecapegfilgrastim Injection, Lenograstim
Huntington Disease	2	Deutetrabenazine Tablets, Tetrabenazine
Hereditary Hypomagnesemia	2	Magnesium Gluconate, Potassium Aspartate and Magnesium Aspartate
Gaucher's Disease	2	Velaglucerase Alfa for Injection, Imiglucerase for Injection
Fabry Disease	2	Agalsidase Alfa Concentrated Solution for Infusion, Agalsidase Beta for Injection
21-Hydroxylase Deficiency	2	Hydrocortisone, Hydrocortisone Acetate
Congenital Adrenal Hypoplasia	2	Hydrocortisone, Hydrocortisone Acetate

Table 3. Marketed drugs for treatment of multiple rare diseases

Marketed drug	Rare disease
Droxidopa Capsules	Parkinson Disease (Young-onset , Early-onset), Multiple System Atrophy
Ezetimibe Tablets	Homozygous Hypercholesterolemia, Sitosterolemia
Sapropterin Dihydrochloride Tablets	Hyperphenylalaninemia, Tetrahydrobiopterin Deficiency
Human Immunolobulin (pH4) for Intravenous Injection	X-linked Agammaglobulinemia, Primary Combined Immune Deficiency
Eculizumab Injection	Atypical Hemolytic Uremic Syndrome, Paroxysmal Nocturnal Hemoglobinuria
Levocarnitine	Carnitine Deficiency, Beta-ketothiolase Deficiency
Hydrocortisone, Hydrocortisone Acetate	22-Hydroxylase Deficiency, Congenital Adrenal Hypoplasia
Gonadorelin for Injection, Menotrophins for Injection, Chorionic Gonadotrophin for Injection	Idiopathic Hypogonadotropic Hypogonadism, Kallmann Syndrome

orphan drugs in the commercial insurance directory. At the same time, secondary reimbursement can be carried out through major disease insurance or medical insurance reimbursement to further decrease the medication burden on patients.

Funding: This work was supported by a grant from Natural Science Foundation of Shandong Province (General program ZR2023MH276) and Academic Promotion Program of Shandong First Medical University (LJ001).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Lu J, Pan X. Current situation and future of rare diseases in China. China Tropical Medicine. 2023; 23:109-114. (in Chinese)
2. Chung CCY; Hong Kong Genome Project; Chu ATW, Chung BHY. Rare disease emerging as a global public health priority. Front Public Health. 2022; 10:1028545.
3. Gopal-Srivastava R, Kaufmann P. Facilitating clinical studies in rare diseases. Adv Exp Med Biol. 2017; 1031:125-140.
4. FDA Newsroom. Taking New Steps to Meet the Challenges of Rare Diseases — FDA Marks the 11th Rare Disease Day. *https://www.fda.gov/news-events/fda-voices/taking-new-steps-meet-challenges-rare-diseases-fda-marks-11th-rare-disease-day* (accessed March 14, 2023).
5. European Medicines Agency. Market exclusivity: orphan medicines. *https://www.ema.europa.eu/en/human-regulatory/post-authorisation/orphan-medicines/market-exclusivity-orphan-medicines* (accessed March 14, 2023).
6. National Medical Products Administration, China. Implementation Regulations of the Drug Administration Law of the People's Republic of China (Draft Revisions). *https://www.nmpa.gov.cn/xxgk/zhqyj/zhqyjyp/20220509220456183.html* (accessed March14, 2023). (in Chinese)
7. General Office of the State Council. Notice of the General Office of the State Council on Printing and Distributing the "14th Five-Year Plan" National Health Plan. *http://www.gov.cn/zhengce/content/2022-05/20/content_5691424.htm* (accessed March 14, 2023). (in Chinese)
8. National Health Commission, China. Notice of the General Office of the National Health Commission on Carrying out the Registration of Diagnosis and Treatment Information for Rare Disease Cases. *http://www.gov.cn/zhengce/zhengceku/2019-11/13/content_5451656.htm* (accessed March 14, 2023). (in Chinese)
9. Zhejiang Provincial Medical Insurance Bureau. Notice on Establishing a Drug Guarantee Mechanism for Rare Diseases in Zhejiang Province. *http://ybj.zj.gov.cn/art/2019/12/31/art_1229113757_601196.html* (accessed March 14, 2023). (in Chinese)
10. Chengdu Medical Security Bureau, Chengdu Municipal Finance Bureau, Chengdu Municipal Health Commission. "Notice on Issues Related to Drug Support for Rare Diseases" issued by Chengdu Medical Security Bureau, Chengdu Municipal Finance Bureau and Chengdu Municipal Health Commission. *http://cdyb.chengdu.gov.cn/ylbzj/c128998/2021-03/18/content_ebb0abea709e46999e3bddd5b24834d1.shtml* (accessed March14, 2023). (in Chinese)
11. The People's Government of Foshan Municipality. Notice of the Office of Foshan Municipal People's Government on Printing and Distributing the Medical Assistance Measures of Foshan City. *http://www.foshan.gov.cn/zwgk/rdzt/lwlb/zcjd/content/post_4516293.html* (accessd March 14, 2023). (in Chinese)
12. National Health Commission, Ministry of Science and Technology, Ministry of Industry and Information Technology, National Medical Products Administration, National Administration of Traditional Chinese Medicine. Notice on Publishing the First Batch of Rare Diseases Catalogue. *http://www.gov.cn/zhengce/zhengceku/2018-12/31/content_5435167.htm* (accessed March 14, 2023). (in Chinese)
13. Chinese Communist Party Central Committee, General Office of the State Council. Opinions of the Chinese Communist Party Central Committee and General Office of the State Council on Deepening the Reform of the Medical Security System. *http://www.gov.cn/zhengce/2020-03/05/content_5487407.htm* (accessed March 14, 2023). (in Chinese)
14. National Healthcare Security Administration. The National Healthcare Security Administration announcedon the "Work Plan for the Adjustment of the National Basic Medical Insurance, Industrial Injury Insurance, and Maternity Insurance Drug Catalog in 2022" and announcement of relevant documents. *http://www.gov.cn/zhengce/zhengceku/2022-06/30/content_5698559.htm* (accessed March 14, 2023). (in Chinese)
15. National Healthcare Security Administration, Ministry

of Human Resources and Social Security. Notice of the National Healthcare Security Administration and the Ministry of Human Resources and Social Security on Printing and Distributing the "Catalogue of National Basic Medical Insurance, Industrial Injury Insurance, and Maternity Insurance Drugs (2022)". *http://www.nhsa.gov.cn/art/2023/1/18/art_104_10078.html* (accessed March 14, 2023). (in Chinese)

Received April 13, 2023; Revised July 23, 2023; Accepted August 6, 2023.

**Address correspondence to:*
Yanqin Lu and Jinxiang Han, Shandong First Medical University & Shandong Academy of Medical Sciences, No. 6699 Qingdao Road, Ji'nan, 250117, China.
E-mail: yqlu@sdfmu.edu.cn (YL), jxhan@sdfmu.edu.cn (JH)

Released online in J-STAGE as advance publication August 12, 2023.