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Determinants For Approval And Reimbursement Of Orphan Products In China

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Abstract

Rare disease definition varies among countries/regions. China has published *The First National List of Rare Diseases*, including 121 kinds of rare diseases in 2018. It was the first time that China has defined rare diseases officially. China has also started releasing a range of encouraging regulations regarding orphan drug development and approval in recent years. Nevertheless, the FDA has introduced Orphan Drug Act in the 1980s, Japan has launched a government-led support initiative in the 1990s, and the European Parliament has adopted the Orphan Regulation in 2000. Among the 121 rare diseases, 58 of them have approved treatments in the US, the EU, or Japan, with 124 drugs in total. Until 2020, only 68 drugs have been approved in China, meaning many remaining rare diseases have no treatment yet in China, and there is still a long way to go for orphan drug approval. Also, as orphan drugs usually have dramatically high prices, being listed in the National Reimbursement Drug List (NRDL) would help decrease the economic burden for patients significantly. However, among the 68 approved drugs, only 38 have been included in the NRDL. This study showed that successful orphan drug approval in China is associated with two significant characteristics, registration status in the National Rare Diseases Registry System, and the sponsor size. Orphan drug reimbursement is associated with orphan drug substances. The information may help drug developers and regulators in future orphan drug market access programs in China.

Keywords: Rare disease, Orphan drug, drug approval, drug reimbursement,

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Table 1: Rare disease definition in the US, EU, Japan, and China

	The US[5]	**EU[6,7]**	**Japan[8]**	**China[9]**	**Russia[10]**
Prevalence or affected population	<200,000 or <1/1500	<1/2000	<50,000 or 1/2500	/[a]	<1/10,000
Number of rare disease patients in total[b]	3 million	30 million	/[a]	/[a]	/[a]
Number of rare diseases [b]	>7000	6000-8000	123	121	261

[a] / means no data available

[b] Number of rare disease patients in total and number of rare diseases are estimated numbers

Table 2. Current effective national policies about rare diseases since 2015

Effective time	**Policy & regulation (official titles [a])**	**Contents about rare disease**
2015	Opinions of the State Council on Reform of the System of Evaluation, Review and Approval of Drugs and Medical Devices 21	Accelerated evaluation and approval process for treatment of rare diseases
2017	Opinions on Deepening the Reform of the Evaluation and Approval Systems and Encouraging Innovation on Drugs and Medical Devices[22]	Establishing rare disease patient registration system in China Reduced number or exempting clinical trials application could be submitted, and the Center for Drug Evaluation (CDE) would make evaluation opinion based on the actual situation of the Chinese patients Orphan drugs that have been approved overseas may be approved conditionally. The sponsor shall be responsible for risk management and research as required
2018	Announcement on Matters Concerning the Optimization	Orphan drugs that do not have ethnic disparities after research

	of Drug Registration Review & Approval[23]	could be approved by submitting overseas clinical trial data
2018	First Official Chinese Orphan Drug List[9]	121 recognized rare diseases
2018	Announcement on Matters Related to Clinical Urgent Needed for Overseas New Drug Review and Approval [24]	Drug approval evaluation should be completed within three months for listed orphan drugs (six-month for non-orphan drugs) from the reception of the dossiers. The National Medical Products Administration (NMPA) must deliver the examination and approval decision within ten days after receiving the review outcomes from CDE (20 days for other drugs that are not urgently needed)
2018	List of Urgently Needed New Drugs in Clinical Settings (the first batch)[25] The second batch of the Urgently Needed Drugs in Clinical Settings was published in 2019[26] The third batch of the Urgently Needed Drugs in Clinical Settings was published in 2020[27]	Including 34 orphan drugs in total
2019	Announcement of Reducing Import Tariffs on Drugs[26]	The added value tax for 21 orphan products and 4 active pharmaceutical ingredients was reduced from 16% to 3% upon import
2020	Evaluation and Approval for Breakthrough Therapies[27]	Accelerated approval of innovative therapies which possibly have beneficial outcomes based on first and second stages clinical trial evidence

[a] English translation of these policy titles are from the Chinalawinfo database[18]

Table 3. Variable category, specific characteristics, inclusion criteria, and data sources of orphan drugs targeting diseases in CRDL

Variable category	**Specific characteristics**	**Inclusion criteria and data sources**
Characteristic related to the drug substance	Small molecule or biologics	Small molecule has a low molecular weight (<900 Da)[42,50]
	Molecule been used for other indications	Data collected through several open databases[41,42,43,44,45]
Characteristics related to the indication	Indication category	The indications were classified as cardiovascular and respiratory, endocrinology and metabolic, hematology, immunology, infectious diseases, musculoskeletal and nervous system, oncology, and Other[2]. Since each of the indication category of the drugs comprised a small proportion of the total dataset, they were grouped together when doing regression analysis.
	Multiple drugs available on the market	Data collected through several open databases[41,42,43,44,45]
	Registration data available in NRDRS	The National Rare Diseases Registry System of China (NRDRS)[40] has started registering rare disease patients since 2019. However, the system uses a broader list of rare diseases (i.e., the system has registered more rare diseases than the original list of 121 kinds), 166 kinds of diseases have registered patients, with 63301 patients have already been registered in total.
	Prevalence data available in the Chinese population	The prevalence of the diseases in China was collected from the Rare Disease Guidelines[51,52] published by National Health Commission. However, some diseases do not have available prevalence data in China, then Asia or worldwide data were used instead[3,51]. Also, not every epidemiology study has done national-wide research. Many of them were only done in partial regions in certain countries, so the prevalence data may not represent the true rate.
	Prevalence	The prevalence was classified as less than 5 per 100,000, 5-10 per 100,000, and more than 10 per 100,000[2].
Characteristics related to the prior approval status	Number of regions that have given the drug marketing authorization	Some drugs have received marketing authorization from more than one country/region among the US/EU/Japan. Data collected through several open databases[41,42,43,44,45]

	Orphan designation in any country	Some drugs have received Orphan Designation before in the US/EU/Japan. Both the drug and disease or condition must meet certain criteria set by the Orphan Drug Act and FDA's regulation to receive the orphan status in the US[53]. Similar in the EU, drugs can receive such designation if meeting the criteria made by EMA[54]. Data collected through several open databases[41,42,43,44,45]
Characteristics related to the sponsor	Sponsor nationality	The sponsor information was collected from the mentioned databases[41,42,43,44,45] and official websites of each company. Company regions are classified as the USA, the EU (including UK and Switzerland), Japan, and others (including Korea, Hongkong, Israel, Australia, and Canada).
	Sponsor size (number of employees)	A company with 0-100 employees is considered a small-size business, with 100-999 employees is considered a medium-sized business, with 1000-9999 employees is considered a large-sized business, and more than 10,000 employees are considered top-large companies[55]. Yet some drugs were claimed specifically from a certain bureau of the global company, then the size of the company was also adjusted to the size of the certain bureau.
	Experience in orphan drug development	Different countries have defined orphan drugs differently, so the definition of orphan drugs used in the data analysis section is the 124 drugs targeting diseases from CRDL.

Table 4. Association between determinants and having available orphan drugs in China (univariate and multivariate regression analysis)

Characteristic	**Total (n=58)**	**N (%) of having approved drugs in China (n=29)**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Multiple drugs available on the market				
No	36(62.1)	15(41.7)	1.00	N/A[b]
Yes	22(37.9)	14(63.6)	2.45(0.82, 7.30)	
Registration data available in NRDRS				

No	40(67.0)	15(37.5)	1.00	1.00
Yes	18(31.0)	14(77.8)	5.83(1.62,21.03)	5.83(1.62,21.03)[a]
Prevalence data available in the Chinese population				
No	42(72.4)	18(42.9)	1.00	N/A[b]
Yes	16(27.6)	11(68.8)	2.93(0.87,9.94)	
Prevalence				
<5 per 100,000	41(70.7)	17(41.5)	1.00	N/A[b]
5-10 per 100,000	7(12.1)	5(71.4)	3.53(0.61,20.38)	
>10 per 100,000	10(17.2)	7(70.0)	3.29(0.74,14.59)	

[a] the result of the univariate regression and multivariate are identical because this is the only variable left after the backward elimination

[b] N/A, not applicable after the backward elimination of the multivariate analysis

Table 5. Association between determinants and orphan drugs approval status in China (univariate and multivariate regression analysis)

Characteristic	**Total (n=124)**	**N (%) of been approved (n=68)**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Small molecule				
No	52(41.9)	28(53.9)	1.00	N/A[a]
Yes	72(58.1)	40(55.6)	1.07(0.52, 2.19)	
Molecule been used for other indications before				
No	85(68.6)	49(57.7)	1.00	N/A[a]
Yes	39(31.5)	19(48.7)	0.70(0.33, 1.49)	
Number of regions that have given the drug marketing authorization				
1	67(54.0)	32(47.0)	1.00	1.00
>=2	57(46.0)	36(63.2)	1.88(0.91, 3.86)	1.99(0.89, 4.46)
Orphan designation in any country				
no	25(20.2)	16(64.0)	1.00	N/A[a]
yes	99(79.8)	52(52.5)	0.62(0.25, 1.54)	
Sponsor nationality				
Other	6(4.8)	4(66.7)	1.00	N/A[a]
USA	67(54.0)	31(46.3)	0.43(0.07, 2.51)	
EU	47(37.9)	30(63.8)	0.88(0.15, 5.33)	
Japan	4(3.2)	3(75.0)	1.50(0.09, 25.39)	
Sponsor size (number of employees)				
<100	16(12.9)	2(12.5)	1.00	1.00
100-999	30(24.2)	16(53.3)	8.00(1.54, 41.49)	8.64(1.63, 45.69)
1000-10,000	35(28.2)	20(57.1)	9.33(1.84, 47.44)	8.07(1.56, 41.68)
>10,000	43(34.7)	30(69.8)	16.15(3.20, 81.48)	16.75(3.27, 85.88)
Experience in orphan drug development				
No	41(33.1)	19(46.3)	1.00	N/A[a]

Yes	83(66.9)	49(59.0)	1.67(0.79, 3.55)	

[a] N/A, not applicable after the backward elimination of the multivariate analysis

Table 6. Association between determinants and being included into NDRL in China (univariate and multivariate regression analysis)

Characteristic	**Total (n=68)**	**N (%) been listed into NDRL (n=38)**	**Univariate OR (95% CI)**	**Multivariate OR (95%CI)**
Small molecule				
No	28(41.2)	8(28.6)	1.00	1.00
Yes	40(58.8)	30(75.0)	7.50(2.53, 22.27)	7.50(2.53,22.37)[a]
Molecule been used for other indications before				
No	49(72.1)	27(55.1)	1.00	N/A[c]
Yes	19(27.9)	11(57.9)	1.12(0.38, 3.27)	
Number of regions that have given the drug marketing authorization				
1	32(47.1)	21(65.6)	1.00	N/A[c]
>=2	36(52.9)	17(47.2)	0.47(0.18, 1.25)	
Orphan designation in any country				
No	16(23.5)	12(75.0)	1.00	N/A[c]
Yes	52(76.5)	26(59.0)	0.33(0.10, 1.17)	
Sponsor nationality				
Other	4(5.9)	1(25.0)	1.00	N/A[c]
USA	31(45.6)	15(48.9)	0.70(0.13, 3.68)	
EU	30(44.1)	19(63.3)	1.30(0.24, 6.89)	
Japan	3(4.4)	3(100.0)	N/A[b]	
Sponsor size (number of employees)				
<100	2(2.9)	2(100.0)	N/A[b]	N/A[c]
100-999	16(23.5)	7(43.8)	1.00	
1000-10,000	20(29.4)	8(40.0)	0.67(0.18, 2.41)	
>10,000	30(44.1)	21(70.0)	2.33(0.70, 7.82)	
Experience with orphan drug development				
No	19(27.9)	13(68.4)	1.00	N/A[c]
Yes	49(72.1)	25(51.0)	0.48(0.16, 1.47)	

[a] the result of the univariate regression and multivariate are identical because this is the only variable left after the backward elimination

[b] N/A, not applicable (deleted because of quasi-complete separation)

[c] N/A, not applicable after the backward elimination of the multivariate analysis

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Figure 1. The market status of therapeutic drugs for rare diseases in the CRDL

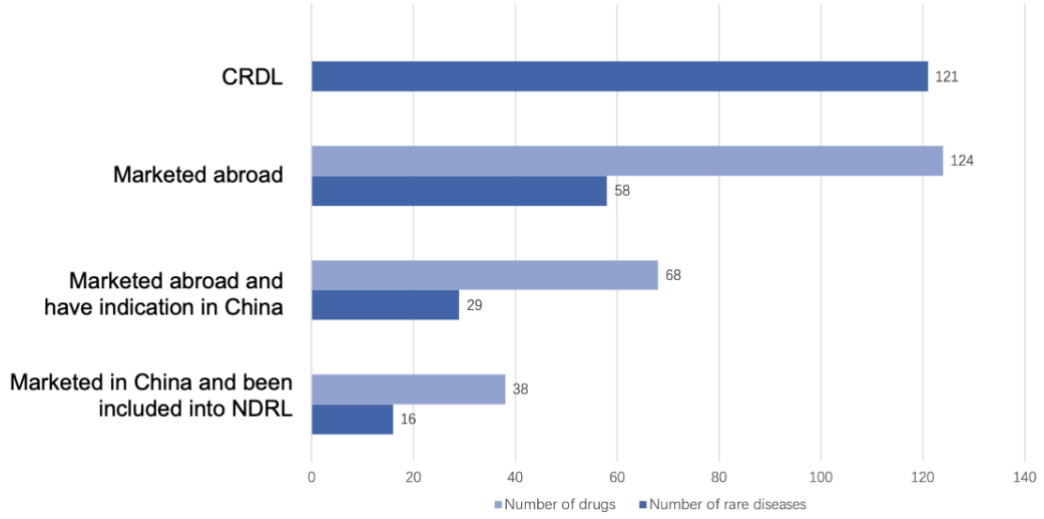
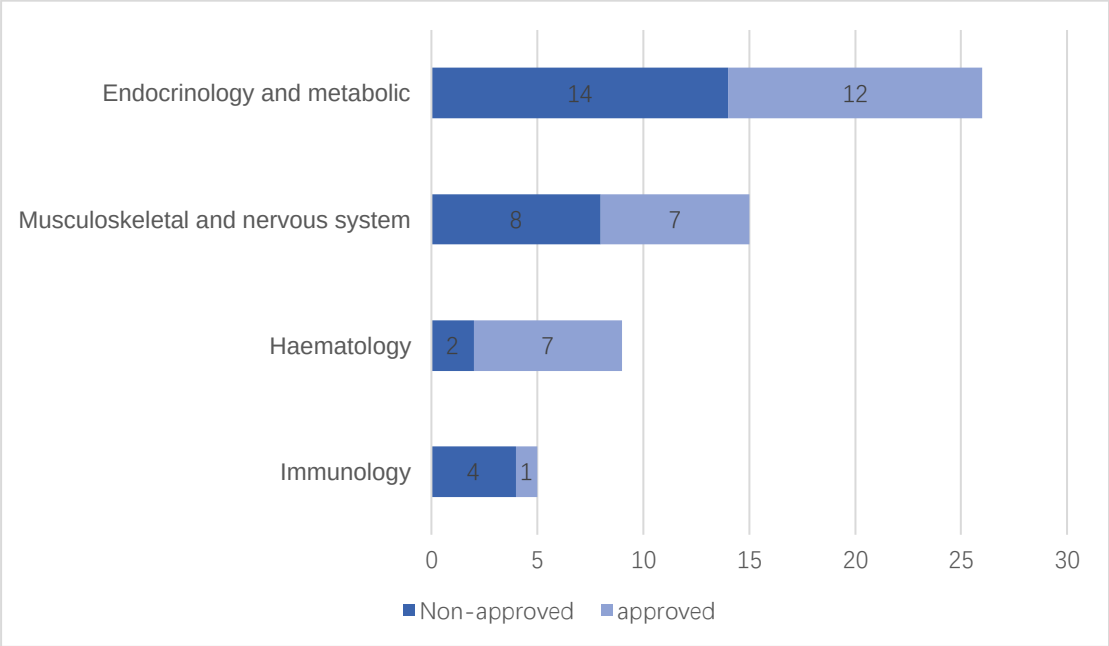


Figure 2: Proportion of approved and non-approved orphan drugs in China per indication category



Introduction

Study objectives

The objective of the study is to 1. Summarize characteristics of orphan drugs that have been approved in China, 2. Find determinants for orphan drug approval in China by comparing orphan drugs that have been approved elsewhere in the world but not in China with orphan drugs that have been approved in China, and 3. Find determinants for orphan drug

reimbursement in China by comparing orphan drugs approved and reimbursed to those approved but not reimbursed.

Previous studies done in other countries have shown drug characteristics associated with successful approval of orphan drugs, including characteristics related to indications, characteristics related to drug substance, characteristics related to prior approval status, and characteristics related to the sponsor[1,2,3]. However, no existing studies have analyzed the characteristics and determinants of the approved and the National Reimbursement Drug List (NRDL) listed orphan drugs in China. The US, the EU, and Japan are mainly used for reference and comparison. These are countries/regions that are more experienced in orphan drug development and approval, and they are the leading pharmaceutical markets in the world[3]. This study would provide information for drug developers and regulators in China in future orphan drug market access projects by accomplishing these objectives.

Background introduction and policy review

Rare disease definition

Rare diseases are generally severe, chronic, and life-threatening, and 80% of rare diseases are generic origins[4], yet the definition varies across countries and regions, as shown in Table 1. China did not have an exact definition of rare diseases until May 2018. In 2018, China National Health Commission, Ministry of Science and Technology, Ministry of Industry and Information Technology, National Medical Product Administration, and National Administration of Traditional Chinese Medicine had co-posted the First National List of Rare Diseases (hereinafter referred to as China Rare Disease List, CRDL)[9], included 121 kinds of

diseases. The definition of rare diseases in China remained controversial before the establishment of the CRDL. They were defined as diseases with prevalence less than 1/500,000 or neonatal morbidity of less than 1/10,000, as recommended by the Genetics Branch of the Chinese Medical Association[11]. The current CRDL is based on actual conditions of diseases, derived from opinions of the *Expert Committee on the Diagnosis, Treatment, and Care for Rare diseases*[12]. Like Russia, both countries are "disease-centered" by directly defining a list of diseases[13]. The Russian rare disease list was published in *Federal Law on the Foundation of Health Protection in Russia* in 2011[10]. The list consisted of three categories of rare diseases, including rare diseases that are extremely expensive to treat and are uniformly purchased by the federal government; life-threatening diseases; and common rare diseases[10,13]. Though no study or explanatory document clarifying how China identified the CRDL exactly, it is suggested China has referred from Russia to define rare diseases[13]. In conclusion, publication of the CRDL would be expected to help in the management of rare disease patients. The CRDL would be also be used as a reference by government agencies and ministries[12].

Orphan drug overview

Orphan drugs treat rare diseases and conditions, yet not all of the rare diseases have adequate medication[4]. The FDA has introduced the Orphan Drug Act in 1983[5], Japan launched a government-led support initiative in 1993 about orphan drug designation[14], and the European Parliament has adopted Regulation (EC) No 141/2000 (the Orphan Regulation) in 2000[15]. All

these programs had the purpose of promoting pharmaceutical companies to develop drugs for rare diseases through both the regulatory and economic incentives[13].

European Medicines Agency (EMA) has authorized over 160 orphan medicines since 2000[16]. FDA has approved more than 770 orphan medicines since 1983[17]. Japan has approved more than 300 orphan drugs[18].

It was not until recent years that China has started releasing a range of encouraging regulations regarding orphan drug development and approval. Until 2020, among the 121 rare diseases, 58 of them have approved treatments in the US, or the EU, or Japan. 124 drugs are used to treat the 58 diseases, and 68 of 124 drugs have been approved in China. This means many remaining rare diseases have no treatment yet in China, and there is still a long way to go for orphan drug approval[13].

Orphan drug policy progress in China

In the 2010s, it has been proposed several times from the national level to address the importance of universal health care. In 2015, *Healthy China 2030 Planning Outline*[19] was published officially by China's Central Party Committee and the State Council, which was the first strategic plan in the health sector since the founding time of PRC. This means health has been put at the center of the entire policymaking machinery in China[20].

Since 2015, several regulations have been promoted to incentivize orphan drug development and approval, as shown in Table 2. It is worth noting that the official CRDL was not published until 2018, so rare disease definition before 2018 mentioned in any regulations was

based on the recommended definition by the Genetics Branch of the Chinese Medical Association[11].

In summarization, these policies focus on 1. The accelerated approval process for orphan drugs, i.e., shorter evaluation time than non-orphan drugs; 2. Conditional approval for orphan drugs from overseas without all-stage clinical trial data; 3. Tax credits for imported orphan drugs.

These policies share many common points with the policies of some other countries. Particularly, the US, as the first country to officially promulgate orphan drug legislation, and as the leading pharmaceutical market globally, it has already formed a complete set of incentive policies and approval procedures[29]. Therefore, China has borrowed many experiences from the US[29]. The Orphan Drug Act has created incentives, including 1. A 7-year market exclusivity period for orphan drugs; 2. Tax credits for drug development spending; 3. Financial aid for drug research and development; 4. Fast-track development and approval pathway ("a process to facilitate development and expedite the review of drugs to treat serious conditions and fill an unmet medical need"[30]); 5. Waiver for drug application fees; and 6. Investigational New Drug Program and pre-approval pathway[31]. Comparing these two regulatory systems, we could tell that both regulatory systems have focused on the accelerated approval process and tax incentives. However, they two still vary in several aspects. Instead of focusing more on incentives for research, China pays more attention to providing convenience for drug importation from overseas. This could be because most drugs are developed originally overseas[13]. Specifically, the US has provided market exclusivity for orphan drug developers, tax credits for development fees and research grants. In contrast,

China has provided tax credits for imported orphan drugs, and reduced or exempting clinical trials when importing orphan drugs.

However, in 2018, CDE has published *Implementation Measures for the Protection of Drug Test Data (draft for Solicitation of Comments)*[32], exploring possibilities of providing data exclusivity period of 6 years for innovative drugs and 12 years for innovative biologics in the near future. This policy has not been officially approved, yet it acted as an essential sign of incentivizing future domestic new drug R&D in China in the future[32].

The payment system in China

In China, public insurance covers over 90% of medical insurance, including national and provincial level[13], yet huge disparities remain in coverage scope and depth. Three insurance schemes exist, including insurance for rural residents, insurance for unemployed urban residents, and insurance for urban employed residents[33]. Urban employed residents have far more resources than the other two kinds of residents[33]. Also, covered scope, co-payment levels, deductibles, and reimbursement ceiling vary hugely. Even within the same scheme, coverage extent would rely on local financial support. Generally, even though public medical insurance coverage has increased to 95% of the general population, there is a long way to go to reach free medication[33].

Though many orphan drugs have dramatically high value, covering orphan drugs to national and local reimbursement funds could be feasible[34]. A study estimated that orphan drug expenditure would only account for 0.5%-2% of the country's overall medical insurance budget, which could be considered controllable[34].

Some cities in China have pioneered exploring medical insurance for rare disease patients, yet these policies still have revealed some underlying issues. Qingdao city has started digging a payment system in 2005. First, the officials of Qingdao city would negotiate with manufacturers to get a price reduction in drugs. Second, the government funds would guarantee the bulk in the payment, while patients take a small amount of cost-sharing. Third, the remaining part would be covered by charity funds from the donation of pharmaceutical companies and the whole society[35]. However, such local policies have exacerbated the inequality in distributing public health resources[13].

Another remaining issue is the lack of systematic and concrete design of the whole payment system. Even in Shanghai, the leading city in exploring the orphan drug payment system, charity NGOs and the local government are still disjointed. The patient information of the two systems could not be connected and transferred in time. Problems such as repeated reimbursement both by the government and social charity funds are prone to occur. Also, different functional departments have not yet formed clear boundaries of the rights and responsibilities[13].

Furthermore, both Qingdao and Shanghai still highly rely on the motivation of individuals, not by the government[36]. In the future, we should be expecting a reform coming down from the national level to form a more comprehensive system[13,36].

In general, national legislation should be developed more quickly to satisfy the emerging need for orphan drug access. Luckily, in more recent years, more and more orphan drugs have been taken into the National Drug Reimbursement list[13,34]. Hopefully, as promoted by the National People's Congress members, all drugs targeting the CDRL will be reimbursed eventually[37].

Possible accessibility barriers

Besides high prices, some other factors have also decreased accessibility. 1. In hospitals, the total number of drugs, the total amount of medical insurance budget used, and drug sales as a share of the total revenue are all under control. Although these policies were originally intended for health care spending control, public hospitals may hesitate in purchasing orphan drugs due to these restrictions[13]; 2. Physicians' prescriptions are also restricted, because they are also under such control. They might be very cautious about their prescriptions[13]; 3. Most rare diseases do not require long-term inpatient treatment. Patients mostly rely on outpatient visits[13]. However, outpatient reimbursement is limited and has complicated restrictions; 4. Due to the limited number rare disease patients, especially in smaller cities, local hospitals are unlikely to offer orphan drugs. Not every patient could afford the traveling fee to larger cities for treatment[13,34].

In general, China has also started increasing the accessibility and affordability of orphan drugs. Nevertheless, it is currently still at the stage of expanding coverage, instead of focusing more on further cost control, but it is expected that price reduction and cost control are the next steps[13].

Possible determinants of orphan drug approval

Previous studies have been done in the US, the EU, and Japan, looking at determinants for orphan drug approval.

A study in the US[1] has concluded that sponsor size and sponsor experience in orphan drug development have shown clear associations with orphan drug approval. Small and medium

companies have shown a higher probability of rejection[1]. Also, less experienced companies in orphan drug development might face extra challenges when designing and conducting clinical trials, such as statistical design challenges due to limited patient numbers, and difficulty in recruiting a sufficient number of participants[38]. Besides, this study indicated that new molecules that have never been used in any other clinical practice have an eightfold higher chance of non-approval[1].

Another study done in the EU[2] has found that oncological and metabolic-related products have a higher chance of receiving marketing authorization. Also, drugs been previously used in other countries were more likely to be approved in the EU. Besides, small molecule products were more likely to receive marketing approval than biologics due to safety concerns. Also, in EU, the urgent and high medical need seems to be considered to be more important than scientific evidence due to a clear association between lack of alternative therapy and successful approval[2].

In Japan, 74.4% of orphan products have already been previously approved in other countries/regions, such as the US[39]. Another analysis[33] also showed that successful orphan drug development in Japan was associated with prior approval status in the US. Besides, some other factors were also positively associated with successful marketing approval, such as sponsor size, sponsor experience in orphan drug development, and unmet clinical needs [3].

In conclusion, variables that are considered related to marketing approval include 1. Characteristic related to the drug substance, including whether it has been used in other clinical therapies before, and small molecule or biologics; 2. Characteristics related to the indication, including registration status in the National Rare Diseases Registry System of China (NRDRS)[40], indication category, disease prevalence and existing epidemiology studies in China, and alternative treatments availability for the disease; 3. Characteristics related to prior approval status, including prior approval status in other countries/regions, and whether it has received orphan designations in other countries/regions; 4. Characteristics of the sponsor, including the company nationality, company size, and prior experience with orphan drug development[1,2,3,7,13].

Thus, this study is going to 1. Summarize characteristics of the approved orphan drugs in China, and those that have not been approved yet (the drugs that have been approved successfully in other countries/regions, yet not approved yet in China), using characteristics mentioned above; 2. Find determinants for orphan drug approval in China in comparing orphan drugs that have been approved elsewhere in the world but not in China with China-approved ones, and 3. Find determinants for orphan drug reimbursement in China by comparing orphan drugs approved and reimbursed to those approved and not reimbursed.

Methods

Data collection

The list of the 121 kinds of rare diseases was derived from the National Health Commission[1]. Available treatments targeting the 121 diseases are derived from the US/EU/Japan drug approval data in several open data bases[41,42,43,44,45]. Drugs that are only recognized as on-label use for specific indications have been included in the analysis, i.e., if a drug that was only approved to treat disease A but was prescribed by physicians to treat rare disease B off-label, was not included in the dataset[48]. Also, only drugs that have received marketing authorization in the US/EU/Japan, i.e., have been officially registered, were included in the analysis[49]. The inclusion criteria have yielded 124 drugs in total, targeting 58 diseases as of March 2021.

The choice of study variables was based on the analysis of past relevant studies[1,2,3], including four major categories mentioned in the last section. Table 3 shows detailed inclusion criteria and data sources.

The list of orphan drugs which have been listed in the NDRL was obtained from the official National Drug Catalog for Basic Medical Insurance, Work-Related Injury Insurance, and Maternity Insurance (2020 Edition)[56], which included 38 orphan drugs.

Data analysis

This study has done three sets of comparisons. The first one was to compare diseases that currently have available drugs in China and those do not yet. Explanatory variables used are characteristics related to the indication. The second one was to compare the characteristics of orphan drugs currently available in China and those not yet. Explanatory variables used are characteristics related to drug substance, the prior approval status, and the sponsors. The third comparison was made between drugs that in the NDRL and those that do not, using the same variables mentioned above in the second comparison group.

Univariate regression was conducted first. Multivariate logistic regression analysis was done at the next step. The backward elimination strategy was used to derive the most parsimonious model. All the independent variables are entered into the equation first, and the least significant variable will be deleted at each step[57]. The reason for choosing this strategy is that the number of variables is smaller than the sample size, and the full model gives us the chance to consider the effects of all variables simultaneously first[58]. Both the odds ratios (OR) and 95% confidence intervals (95% CI) were calculated in both models. SAS (SAS 9.4 TS1M5, Rev. 940_18w08) is used in the analysis process.

Results

The market status of therapeutic drugs for rare diseases in the CRDL is displayed in Figure 1. Out of the 121 diseases, 58 of them have therapeutic drugs (in the US/EU/Japan). 124 drugs

are available for the 58 kinds of diseases. 68 of 124 drugs are available now in China, targeting 29 diseases. 38 of 68 drugs have been reimbursed, targeting 16 diseases.

Determinants for orphan drug approval in China

Characteristics related to the indication

The Proportion of approved and non-approved orphan drugs in China per indication category is displayed in Figure 2. 12 of 26 drugs for endocrinology and metabolic diseases have been approved. By contrast, only 1 of 8 drugs for immunology diseases have been approved. The result has revealed a similar outcome with the EU study[2]. None of the 58 diseases are classified as oncology or infectious diseases. This may be because that only one oncology disease is included within the CRDL (Retinoblastoma), and no infectious disease is within CRDL.

Descriptive statistics of the 58 rare diseases that have available orphan drugs are displayed in Table 4. 62.1% (36 of 58) diseases only have one available in-label treatment. For example, Idiopathic Pulmonary Arterial Hypertension has 11 on-label drugs, and hemophilia has 12 on-label drugs, and both of them have more than one approved drug in China. The reason why these diseases have multiple treatments could because, for example, drugs for pulmonary hypertension are not a cure for the disease, they help improve symptoms and slow disease progression. The mechanisms of these drugs vary[59]. As for the treatment of hemophilia, clotting factor concentrates could be injected into a person's vein to replace the missing blood clotting factor, so there is more than one choice of such concentrates[60].

The NRDRS[40] data showed that only 31% (18 of 58) of them have registered data in the system, consisting of over 60,000 cases in total. Yet 77.8% (14 of 18) of diseases with registered data in the system have treatment currently available in China. The 18 diseases are Fabry disease, Gaucher's disease, Glycogen Storage Disease (Type I, II), Wilson Disease, Hereditary Angioedema, Homozygous Hypercholesterolemia, Hyperphenylalaninemia, Idiopathic Pulmonary Arterial Hypertension, Mucopolysaccharidosis, Multiple Sclerosis, Generalized Myasthenia Gravis, Tuberous Sclerosis Complex, Leber Hereditary Optic Neuropathy，hemophilia, Porphyria, Retinitis Pigmentosa, Langerhans Cell Histiocytosis, and Lymphangioleiomyomatosis. Clearly, the number of rare disease patients is much greater than 60,000 in China, so more disease and patient data should be expected to be registered in the system in the future.

Only 27.6% (16 of 58) of the diseases have existing epidemiology studies in Chin. 70% (41 of 58) of the diseases have prevalence less than 5 per 100,000.

The outcome of the logistic regression is also presented in Table 5. Having registered patients in the NRDRS seems to be highly positively correlated with available treatments in China (OR=5.83; 95%CI=1.62-21.03), and this result is statistically significant, even after the multivariate analysis.

The other associations are not considered statistically significant yet may suggest possible relationships. Diseases that have multiple alternative therapies worldwide are numerically more likely to have approved drugs in China (OR=2.45; 95%CI=0.82-7.30), i.e., diseases with several available treatment plans are more likely to also have treatment plans in China. Diseases that have higher prevalence are numerically more likely to have available treatments

in China, 5-10 per 100,000 has an OR of 3.53 (95%CI=0.61-20.38), >10 per 100,000 has an OR of 3.29 (95%CI=0.74,14.59). Also, 68.8% of diseases with epidemiology studies done in China have available treatments in China, with an OR of 2.93 (95%CI=0.87-9.94).

In conclusion, having an exact number of registered patients in the NRDRS may be highly correlated with approving treatments in the Chinese population.

Characteristics related to the orphan drug substance

Descriptive statistics of the 124 orphan drugs targeting rare diseases from the CRDL are displayed in Table 5. Among all the 124 drugs, only 68 are currently approved for on-label use in China. 58.1% (72 of 124) of them are small molecule drugs. 68.6% (85 of 124) are used as the only on-label product for certain diseases.

According to the unadjusted model, small molecule and biologics have a numerically similar chance of approval (OR=1.07, 95%CI=0.52-2.19). Molecules that have also been used for other indications are numerically less likely to be approved (OR=0.7, 95%CI=0.33-1.49), yet both correlations are not considered statistically significant.

Characteristics related to the prior approval status

As shown in Table 5, 43.5% (54 of 124) of them have received marketing authorization in more than one country/region. 79.8% (99 of 124) of the drugs have received orphan designation in at least one of the regions mentioned above.

Regression analysis suggests drugs that have marketing authorization in more than one country/region are numerically more likely to be approved (ORadj=1.99, 95%CI=0.89-4.46), though the p-value is greater than 0.05 (p-value=0.074).

Characteristics related to the sponsor

As shown in Table 5, 54.0% (67 of 124) of the drugs were sponsored or developed by American companies, 37.9% (47 of 124) were from EU sponsors, the rest few were from companies of some other countries/regions, including Japan, Korea, Canada, and Israel. 34.7% (43 of 124) of the companies have employees over 10,000 worldwide, such as Pfizer, Novartis, Novo Nordisk, Eli Lilly, etc. While 12.9% (16 of 124) companies are small-sized businesses, with employees worldwide less than 100 people, such as Immedica Pharma, Recordati Rare Disease, Lucane Pharma, etc.

The outcome of the regression analysis is also shown in Table 5. Companies with more than 10,000 employees are more likely to have drugs approved (ORadj=16.75, 95%CI=3.27-85.88). Also, medium-sized and large companies are both more likely to have drugs been approved than small-size companies, yet less likely than top-sized companies.

The other two associations are not considered statistically significant. Drugs that are from the US sponsors (OR=0.46, 95%CI=0.08-2.66) seem numerically less likely to be approved than from EU (OR=0.82, 95%CI=0.14-4.99) or Japan (OR=1.50, 95%CI=0.09-25.39) sponsors. Companies which have developed orphan drugs before are numerically more likely to have drugs been approved (OR=1.67, 95%CI=0.79-3.55).

Determinants for orphan drug reimbursement in China

Among all the 68 approved drugs, 38 of them have already been included in the NDRL. Descriptive statistics of the 38 orphan drugs are displayed in Table 6.

Characteristics related to the orphan drug substance

58.8% (40 of 68) of them are small molecules. 72.1% (49 of 68) of them have not been used before for any other in-label indications.

The outcome of regression analysis is also shown in Table 6. Small molecules are considered more likely to be included to the NDRL (OR=7.5, 95%CI=2.53-22.37). The multivariate analysis confirmed that small molecule is the only factor associated with being included in NDRL statistically significant. Drugs that have been used before for other indications have shown a slightly numerically positive correlation with been included in the NDRL, yet this correlation is not considered statistically significant (OR=1.12, 95%CI=0.38-3.27).

Characteristics related to the prior approval status

52.9% (36 of 68) of them have received marketing authorization from more than one region/country. 76.5% (52 of 68) have received orphan designation before in other regions/countries.

The two associations are not considered statistically significant, as shown in Table 6. Having orphan designation is considered numerically negative correlated with been included in NDRL (OR=0.47, 95%CI=0.18-1.25). Though this correlation is not statistically significant, it has revealed the same trend with factors associated with approval.

Characteristics related to the sponsor

45.6% (31 of 68) of the drugs are from USA sponsors, 44.1% (30 of 68) are from European sponsors, 3 of them have sponsors from Japan, and the rest 4 have sponsors from other regions/countries. 44.1% (30 of 68) of the sponsors are top-sized companies with over 10,000 employees, while only 2 of them were from small-size businesses. 72.1% (49 of 68) of the drugs are from companies that do not have prior experience in orphan drug development. Both sponsor nationality and size have shown quasi-complete separation (3 drugs from Japan have all been included in NDRL, 2 drugs from small-size sponsors are both included in NDRL), so the two variables were not included in the multivariate analysis. The three variables related to sponsor are not considered to be associated with reimbursement statistically significant.

Discussion

The analysis of comparing characteristics of orphan drugs approved elsewhere in the world (in the US/EU/Japan) to approved ones in China has clarified several determinants associated with successful orphan drug approval in China. The analysis of comparing approved and reimbursed ones to approved and not reimbursed ones has suggested characteristics of successful orphan drug reimbursement in China. Comparing current effective orphan drug policies with other countries/regions, mainly in the US, the EU, and Japan will further explain these determinants.

According to the regression analysis, rare diseases with registered patients in the NRDRS have a higher chance of having approved drugs in China. Orphan drugs with bigger sponsors have a higher chance of been approved in China. Small molecules rather than biologics have a higher chance of been reimbursed.

Determinants for orphan drug approval in China

Characteristics related to the indication

Regression analysis indicated that having registration data in NRDRS is associated with available rare disease treatment in China. NRDRS is a national rare disease registry. It is part of the nation's rare disease infrastructure, promoted by the National Health Commission, funded by the government's "13th Five-Year Plan" key Research & Development Projects-Precision Medicine Initiative, and joined by more than 20 top academic institutions in China[61]. The registry began in 2019.11.1, it first retrospectively registered rare disease patients diagnosed from 2015.1.1 to 2019.10.31 in member hospitals, and each new case after 2019 was also required to register[62]. The ultimate goal of the registry system is to "evaluate the diagnosis and treatment standards of rare diseases in China" by conducting standardized case registration, cohort identification, and follow-ups of national-wide studies[54]. Among the 18 diseases that have registered patients in the system, only four do not have available treatments in China yet, including Porphyria, Retinitis Pigmentosa, Langerhans Cell Histiocytosis, and Lymphangioleiomyomatosis (LAM)[40]. Since NRDRS aims to contribute to existing knowledge of rare diseases in China and support healthcare policymaking, it might

be reasonable to expect that these diseases could have approved drugs in China in the near future.

Higher prevalence of a rare disease is positively associated with orphan drug approval**,** though the result is not considered statistically significant. Despite the fact that different countries/regions have defined rare diseases differently based on their prevalence, this might suggest that prevalence has played an important role in the regulatory strategies. However, measuring the prevalence of rare diseases could be particularly challenging. The data sources of rare diseases could be limited and not standardized, so combining the data could be difficult. Also, some rare diseases lack diagnostic criteria, so the true prevalence could be much underestimated. Besides, it could be challenging from the methodological perspective to measure a small sample size[63]. Even though the prevalence data used in this study might not be actual prevalence data of certain diseases, they may still provide important references for making regulatory decisions. Previous research from the US has shown that higher prevalence is positively associated with approval[1]. Yet another study in Japan found that the number of patients in Japan was negatively associated with approval[3]. The result from Japan might seem counter-intuitive, yet this could be because the number of patients might not be a critical criterion when conducting rare disease clinical trials, even randomized and controlled trials are not a must[3]. However, in this study, higher prevalence is numerically positively associated with approval. As mentioned before, some drugs are not required to redo clinical trials in China, so satisfying medical needs may be prioritized. On the other hand, this variable is not statistically significant in the model, so whether it reveals a true association should be tested further.

Whether having epidemiology studies done in China mainland is another variable that has shown a positive association, yet not statistically significant. Generally speaking, lack of Chinese data might be a barrier to drug approval. This might also explain why NRDRS is critical for decision-making.

Characteristics related to the orphan drug substance

A previous study in the EU[2] showed the lack of an alternative therapy of disease is positively associated with new drug approval. This might suggest that the decision-making of EMA seems to be driven by satisfying medical needs[2]. However, the situation in China was different. Most of the drugs got approved within a very short period starting in 2018, so instead of identifying which diseases have alternative therapies before in China, whether a certain disease has multiple treatment methods was measured instead. This study shows that if a disease has multiple available treatments on the market, the disease is numerically more likely to have approved drugs in China. However, the result is not statistically significant. Having alternative therapy or not might be related to the mechanism of certain indications or the prevalence of the disease[2]. In other words, when the cause for a disease is more straightforward, more drugs could be developed. Or when the treatment method has the potential to treat other diseases with a wider population, pharmaceutical companies would be more incentivized to develop drugs, and more drugs are likely to be approved[64].

Due to the limited sample size of each indication category, no data analysis was done. However, two studies in the US suggested that approval rates would differ based on therapeutic category[65,66], so this study might not mean no such association exists.

Characteristics related to the prior approval status

To receive incentives for orphan drugs described above, sponsors must have received an orphan designation. Nevertheless, not every country has such process, such as Canada, Singapore, and China. In contrast, countries as the US, EU, Japan, and Australia have regulations about orphan status recognition[67]. Different countries have different specific criteria, yet generally, they focus on several aspects, including severity and prevalence of the disease, non-return on investment, the feasibility of research program, and medical needs. Not every drug which has received orphan designation is authorized in the end because it is requested at the early stages of drug development, and not every candidate drug would complete their clinical development process[67,68,69,70,71]. A study showed that 64.3% of orphan designated drugs in Japan had been approved, which is the highest among the four countries. It is only 15.4% in the US and 7% in the EU[67]. In other words, drugs that apply for orphan status in Japan might already have robust drug development evidence[67]. In general, the orphan designation could not be viewed as the guarantee of the safety and efficacy of a drug. It is more of the reflection of medical needs and incentives to sponsors. Pharmaceutical companies would want to obtain an orphan designation to attract new investors and promote research in the future[67]. In this study, orphan designation seems to be negatively correlated with approval, though it is not statistically significant. The result may indicate that at least not every drug that has received orphan designation would be considered in priority when approving a drug in China.

On the other hand, a drug that has received marketing authorization from multiple countries/regions is numerically more likely to be approved. The study in Japan shows that prior approval in the US is positively correlated with approval in the Japanese market[3]. However, studies in the US and EU showed that such associations between approval probability and prior approval status in other countries/regions did not exist because the US and EU are the two leading markets[1,2,3]. Similar in Japan, prior approval status in other countries/regions might increase the likelihood of drugs being approved in China.

Characteristics related to the sponsor

Company size is an essential predictor associated with approval as shown by several previous studies. The study in the US showed that small and medium enterprises (less than 250 employees) are less likely to have orphan drugs approved[1]. Another study from the EU showed that while many university and medical centers or small and medium-sized enterprises initiated the early stages of drug development[2], it is more likely that larger and more experienced companies would eventually sponsor the drugs to the market[72,73]. This study has shown the same result.

A study in Japan showed that the foreign capital of a company would not impact the approval status in Japan[3]. Similar to this study, the associations between the sponsor's nationality with approval are not statistically significant.

Previous studies showed that having experience in orphan drug development is an important predictor for subsequent approval in the EU and the US[1,74]. Orphan drug development could be more complex than usual drug development. Experienced companies might be more

familiar with designing and conducting clinical trials, getting access to patients, and reaching out to regulatory departments[74]. This study also shows that drugs from more experienced companies are numerically more likely to be approved, though this result is not statistically significant.

Determinants for orphan drug reimbursement in China

The latest update of NRDL was conducted in 2017. Evidence of Health Technology Assessment (HTA) or pharmacoeconomic evaluation were included as essential criteria of decision-making[76]. Also, a pilot project was implemented that the central government would negotiate with pharmaceutical companies about the prices for innovative and expensive drugs that were still not included in the National Formulary[75,76]. In other words, drugs that are considered clinically valuable but expensive would be put into the price negotiation process before officially becoming part of NDRL[76]. Most of the orphan drugs are considered in this category. However, there are uncertainties in the effectiveness, safety and economic evaluation process of orphan drugs. Such uncertainties would hinder the access of orphan drugs to the medical insurance list[37,75]. The national government has proposed to set up a special procurement project for orphan drugs this year, details yet not been published[37]. This study has not studied the economic side of orphan drugs because their prices would be undergoing the negotiation process. However, this is an essential factor determining whether a drug could be included in NDRL. Instead, this study focused on characteristics of the drugs related to drug type, prior approval status, and the sponsors.

This study suggested that among all the characteristics, the type of the drug (i.e., small molecule drug or biologics) is of vital importance associated with successful reimbursement. Small molecules are produced by chemical synthesis processes with well-defined and stable structures. Yet, a biologic is usually a large and complex biomolecule derived from living cells or through biological processes with heterogeneous structures. Unlike small molecules, biologics are very sensitive to process changes[77]. Due to the structural complexity of biologics, their clinical effects are usually hard to predict[77]. A previous study in the EU showed that small molecule drugs are more likely to get marketing approved than biotechnology products[2]. This could be explained because more knowledge was available for small molecules[2]. While this study does not show that small molecule is associated with a higher rate of approval, small molecules are more likely to be included in the NDRL. The decision-making criteria of drug reimbursement in China focus on safety, efficacy, clinical needs, price and pharmacoeconomic evaluation in other countries, and budget impact[62]. Small molecules may satisfy the requirement for safety than for biologics. Also, from 2015-2019 in China, more small molecule drugs have been approved than biotech drugs every year[78].

Limitations

There are some limitations of this study that should be addressed. Clearly, the confidence intervals of the association estimations are wide. This could be due to the limited sample size. Indication category interaction could not be tested due to the small number of each set. Also, some of the explanatory variables are correlated with each other. For example, whether been able to receive an orphan designation is associated with the prevalence of the disease.

Mechanisms of specific indications may be related to the type of molecules, availability of alternative treatments, and applications to other indications. Third, some other possible variables are not tested in this study, such as clinical trial characteristics. For example, previous studies have shown that positive outcomes of the primary endpoints could be related to success approval[1]. Some orphan drugs could directly use overseas clinical trial data to apply for approval, yet some still need new clinical trials been done again in China. Since the source of clinical trials are different, and it would be inappropriate to include them in one study, so the characteristics of clinical trials are not studied here. However, such variables could be further tested and adjusted in the model. Also, some other factors may impact whether a drug could be included in NDRL, such as the budget impact on the national insurance system[79]. Future studies could further examine such factors. Fourth, data such as the prevalence of rare diseases may not be accurate and complete, as discussed above. Also, prior marketing status has only be collected among the US/EU/Japan, and results could be different if involving other countries/regions into the analysis.

Summary

In general, this study has pinpointed two critical characteristics related to orphan drug approval in China, and one crucial factor related to orphan drug successful reimbursement in China. First, rare diseases that have been registered in the NRDRS have a higher chance of having approved drugs in China. Particularly, prevalence and incidence data of most rare diseases are still lacking in China and face many challenges of getting the true estimate, so having exact registration information in the system is especially critical for policymaking.

Drugs from larger-sized companies have higher chances of being approved because the orphan drug development process is often more complex and requires more resources. Second, small molecule drugs have a higher chance of been included in NDRL than biologics because they are more stable in structure and clinical effects. These findings may provide information for drug developers and sponsors when submitting applications for orphan drugs approval in the near future. The review and approval of orphan drugs have been accelerated significantly in China in recent years. Last year, it has been proposed at the National People's Congress and the Chinese People's Political Consultative Conference that all drugs targeting the 121 kinds of rare diseases should be approved and be included in NDRL step by step in the future[37]. However, this process needs continued reform of the healthcare payment system, social welfare support, and administrative process. Medical care for rare disease patients now has a good start yet still has a long way to go in China[80].

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