



No. 046/2022/MAN/MKT

RARE DISEASES ARE NOT RARE IN CHINA

What can be done more for this Special Category of Patients

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March 2022

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RARE DISEASES ARE NOT RARE IN CHINA
WHAT CAN BE DONE MORE FOR THIS SPECIAL CATEGORY OF PATIENTS

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draft

Abstract: During the 2022 session of “two meetings”, rare diseases have been cited as one of the focus in healthcare in Prime Minister working report². It is an important recognition of the severity of the issue and the need to find practical solutions. This article summarizes the situation of drugs against rare diseases in China and the progress already done. Moving forward, it suggests upgrading their positioning in the healthcare strategy in order to solve an important social issue and bring more steam into innovation in pharmaceutical.

There are more than 7,000 confirmed rare diseases in the world³, accounting for about 10% of human diseases. And in China, there exists more than 1,400 known rare diseases. Rare diseases are not rare in China, as it is estimated that the total number of patients with rare diseases in China have exceeded 20,000,000⁴. A recent updated methodology estimates the number of patients in the range of 300 million in the world⁵.

In 2016, The outline of healthy China 2030 plan⁶ clearly stipulates that China should improve the drug use protection policy for rare diseases. In the following 2~3 years, policies on rare diseases were issued one after another, which brought hope to patients with rare diseases. However, improvements have slowed in last 2 years, which is probably due to Covid 19.

The initial thinking of State Council is that rare diseases should be treated after the general diseases

¹ The author would like to thank Annie Chicoye, Sandrine Hu, Andie Li and Senya Lor for their invaluable comments. The author expresses his personal views.

² We will strengthen research on rare diseases and ensure drug use. See : 2022 Government work report [A/OL] [2022-03-12] [2022-2-22] http://www.gov.cn/premier/2022-03/12/content_5678750.htm

³ MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). National Institutes of Health (NIH). Rare diseases; [updated 2020 Dec 9; reviewed 2017 Jun 5; cited 2022 Feb 22]; [Summary]. Available from: <https://medlineplus.gov/rarediseases.html>

⁴ for 1,400 diseases. <http://health.people.com.cn/n1/2022/0309/c14739-32370431.html>. See also *Research Report on medical security of high value drugs for rare diseases in China*, IQVIA 2020.

⁵ Nguengang Wakap, S., Lambert, D.M., Olry, A. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* 28, 165–173 (2020). <https://doi.org/10.1038/s41431-019-0508-0> . If epidemiology was similar in China vs rest of the world, it would mean that the number of patients would be in the range of 40M in China.

⁶ State Council Healthy China 2030 Plan [A/OL] [2016-10-25] [2022-2-22] http://www.gov.cn/zhengce/2016-10/25/content_5124174.htm

are well covered (保基本)⁷. This is understandable in a poor economy, but it needs to evolve as China is now a middle income-country. China launched universal healthcare coverage in 2011, now one decade later and with a strong economy, it should move toward more specialized diseases⁸. Rare diseases are a severely unfair situation as they are genetically based, while many chronic diseases are often the result of patient behaviours or could be significantly reduced by awareness and screening campaigns. When you have a rare disease, you cannot do anything about it. Neither preventing. Neither reducing its impact.

China is now the second largest pharmaceutical market of the world and is increasing its global leadership in many areas. But in the rare diseases field, China is not playing in its league⁹. This paper proposes to look at this issue from a different point of view. China has the biggest pool of rare diseases and patients in the world, and thus could turn this issue to its advantage and make it a differentiating point in its strategy for innovation.

1. RARE DISEASES GLOBALLY

We will look at the definition of rare diseases and then the two most important steps: registration of suitable drugs against rare diseases and the access to these drugs (social protection).

1.1. Definition

Rare disease refers to diseases with low prevalence but chronic in nature, very serious and often life-threatening¹⁰. These diseases lack reward for innovation and R&D is insufficient and drugs limited¹¹.

Most of the world's major markets define precisely rare diseases by prevalence or absolute number of patients. The definition of rare disease in the United States is that the number of patients is less than 200,000 (the prevalence is about 6.4/10,000). The EU definition of rare disease is a chronic, progressive and life-threatening disease with a prevalence of less than 5/10,000 (the number of patients is less than 256,000). The definition of rare diseases in Japan is diseases with less than 50,000 people (the prevalence is than 4/10,000). The rare disease in Taiwan, China, is defined as the diseases with a prevalence of less than 1/10,000 or the diseases that have been listed¹².

⁷ The Central People's Government of the people's Republic of China Decision of the State Council on establishing the basic medical insurance system for urban workers [A/OL] [1998-12-14] [2022-2-22] http://www.gov.cn/banshi/2005-08/04/content_20256.htm

⁸ For essential universal health coverage package in Low- and Lower-Middle- Income countries see [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(20\)30121-2/fulltext#sec1](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30121-2/fulltext#sec1) and the appendix [https://www.thelancet.com/cms/10.1016/S2214-109X\(20\)30121-2/attachment/91028eb3-efde-4d6c-94c7-c05de67f0bc0/mmc1.pdf](https://www.thelancet.com/cms/10.1016/S2214-109X(20)30121-2/attachment/91028eb3-efde-4d6c-94c7-c05de67f0bc0/mmc1.pdf)

⁹ China is behind most countries, until it started to improve in 2018. See : <https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-017-0618-0.pdf>

¹⁰ Rare Disease Terminology and Definitions—A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. *Value in Health*, 18 (2015) 906 – 914.

¹¹ *Orphan Drug Act* of 1983. Pub L. No. 97–414, 96 Stat. 2049.

¹² 《可及性报告 2019》 (China Rare Disease Drug Accessibility Report, IQVIA&CORD, 2019)

Currently there is no official definition in China in terms of prevalence or absolute number patients¹³. The national rare disease academic group proposed a new definition in the China rare disease definition Research Report 2021¹⁴. It is suggested that the disease with "neonatal morbidity less than 1/ million, incidence rate less than 1/ million and disease number less than 140 thousand" should be included in rare diseases.¹⁵ There are debate, but we do not think this is the point. What is needed is to have one clear definition in order to help patients but also in order enable suitable planning and diseases management. Additional concepts are important: severity of disease (life threatening or source of a serious chronic handicap) and absence of effective treatment.

1.2. Regulatory approval

Drugs are special products that require a specific registration process in order to ensure patient safety and scientific innovation is made in an orderly way. As we all know this process is long and generate high cost of R&D. Logically, the consequence of the economic model is that prices are skyrocketing in order to compensate the very narrow target population. A robust access program is a must for public policy in order to enable research centres and drug manufacturers to play their role.

More recently the situation is accelerating in EU and US, thanks to smart policies, like regulatory pathways with early consultations, priority reviews, grants by associations etc. Some of the development can also be continued after marketing authorization, which is also a way to decrease the initial investment¹⁶. The result is that 55% of new drugs approved by the FDA in 2020 benefited from orphan drug designation. It has become a focus of pharma development¹⁷.

Most of the markets have developed specific processes in order to incentivize companies to invest in the development of drugs to cure rare diseases¹⁸. These schemes are different but include regulatory fast-track and financial subsidies. The USFDA has established a "Rare Disease Cures Accelerator" to incorporate the patient's perspective in clinical outcome assessment measures, and build clinical trial readiness in the pre-competitive space.¹⁹ EU fast-tracked Orphan Medicinal Product (OMP) through the licensing system under-exceptional-circumstances (EC) and grants

¹³ National Health Commission Notice on publishing the catalogue of the first batch of rare diseases [A / OL] [2018-5-11] [2022-2- 22] http://www.gov.cn/zhengce/zhengceku/2018-12/31/content_5435167.htm

¹⁴ The very first rare disease definition in a Chinese context was proposed in 2010 by the Chinese Society of Medical Genetics as "prevalence less than 1/500,000 or neonatal incidence less than 1/10,000", which is considered as the "point 0" in history. "2010 年，中华医学会医学遗传学分会曾经制定了“患病率小于 1/50 万或新生儿发病率小于 1/万”为罕见病的中国定义，这被视为史上“0”的突破并一直沿用。此次报告是自 2010 年来，罕见病定义的首次更新。

¹⁵ Drug Times Research Report on the definition of rare diseases in China released that the number of patients less than 140,000 is a rare disease [EB/OL] [2021-9-13][2022-2-22] <https://www.drugtimes.cn/2021/09/13/zhongguoahanjianbingdingyiyuanjiubaogaofabuhuanbingrenshuxiaoy/>

¹⁶ Patient-Reported Outcome and Observer-Reported Outcome. Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report; *Value in Health* 20 (2017) 838 – 855; <http://dx.doi.org/10.1016/j.jval.2017.05.015> o

¹⁷ <https://www.fda.gov/news-events/fda-voices/rare-disease-day-2021-fda-shows-sustained-support-rare-disease-product-development-during-public>

¹⁸ Orphan Drug Act in US (1983). Orphan Product Development Support Program in Japan (1993). Orphan Medicinal Product in EU (1999)

¹⁹ <https://www.fda.gov/drugs/regulatory-science-research-and-education/rare-disease-cures-accelerator>

conditional-marketing authorization (CA).²⁰ Beyond regulatory, Japan also subsidizes the cost of clinical and non-clinical research during all research periods.²¹

1.3. Social protection

Medical insurance is a key component of healthcare system in order to ensure access to medicine and treatments. It is even more important for rare diseases as the number of patients is limited and there is not enough reward to the companies for the development of suitable drugs.

Globally there are many different models of medical insurance systems, but in essence, it is dominated by the government and supplemented by insurance and co-payment by patients.

Often patients suffering from rare diseases are very vulnerable and benefit from full or almost full reimbursement, like in most of Europe. When there is no full reimbursement policy by the Authorities, there is a cap of individual self-payment, so as to avoid catastrophic expenses to patients.

Examples of "national special fund" model include Japan. In this mode, the payer is Medical Fund for refractory diseases and medical assistance for low-income people. The medical Fund for refractory diseases comes from special appropriations from consumption tax; and the medical assistance funds come from national taxes and social donations. The Medical Fund for refractory diseases pays for 80% and individual pay for 20%.

Taiwan, China adopts the mode of "statutory medical insurance fund". In this mode, the payer is National Health Insurance Fund. The main part of the fund is insurance premium income shared by the insured, employers and the government. The rare disease drugs in health insurance are fully reimbursed, and if health insurance does not pay, the national health administration will pay with another budget, and reimburse up to 80% of the drug cost.²²

2. RECENT PROGRESSES IN CHINA

2.1. Definition

On May 11, 2018, the National Health Commission, the Ministry of Science and Technology, the Ministry of Industry and Information Technology, the National Medical Products Administration and the National Administration of Traditional Chinese Medicine jointly issued *the catalogue of the First National List of Rare Diseases*.²³ It lists 121 rare diseases, it looks very few vs the world total of 7,000 to 8,000, but it was rightly celebrated as a great step forward in order to solve this issue.

²⁰ Uguen, D., Lönngrén, T., Le Cam, Y. et al. Accelerating development, registration and access to medicines for rare diseases in the European Union through adaptive approaches: features and perspectives. *Orphanet J Rare Dis* 9, 20 (2014). <https://doi.org/10.1186/1750-1172-9-20>

²¹ Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. *Intractable Rare Dis Res*. 2012 Feb;1(1):3-9. doi: 10.5582/irdr.2012.v1.1.3. PMID: 25343064; PMCID: PMC4204590.

²² See Report of Deputy director of Central Health Insurance Department, Ministry of health and welfare, Taiwan, China https://www.sohu.com/a/118065503_119250

²³ National Health Commission Notice on publishing the catalogue of the first batch of rare diseases [A / OL] [2018-5-11] [2022-2- 22] http://www.gov.cn/zhengce/zhengceku/2018-12/31/content_5435167.htm

It is reported that the selection of the diseases in this catalogue was based on following factors: 1) There is evidence that the incidence rate or prevalence rate is low; 2) Great harm to patients and families; 3) There are clear diagnostic methods; 4) Treatment or intervention means are available and affordable, or there is no effective treatment or intervention means, but it has been included in the national scientific research project. This list lacks a standard definition.

In 2021, a second list has been prepared and it is said to be announced soon²⁴. According to the working procedure for the formulation of rare disease catalogue issued by NHC, the list should be dynamically updated and the update time should not be less than 2 years in principle. Up to the reply time, NHC has successively received more than 200 applications for increasing diseases and these materials are currently in the stage of review.

2.2. Regulatory approval

The Chinese regulatory agency NMPA (National Medical Products Administration) has now established four special review channels to accelerate registration of drugs against rare diseases, including breakthrough therapeutic drugs, conditional approval, priority review and approval and special approval procedures, so as to improve the review and approval efficiency of innovative drugs at different stages and accelerated the process of drug R & D and listing.

Before 2018, there was no special process in China to register drugs to cure rare diseases. From 2018 to 2020, NMPA has issued three lists of *overseas new drugs in urgent clinical need*, involving a total of 73 drugs and 39 drugs for rare diseases²⁵. It was pointed out that a special channel would be established to review and approve overseas new drugs urgently clinically needed.

Since 2019, taking the first list as the definition basis, NMPA has newly approved 14 rare disease drugs, involving 9 rare disease indications, opening the door to new rare disease drugs.

On February 26, 2021, the NHC further open the door by listing 121 rare diseases. China is the only country in the world that issues a rare disease catalogue. Based on the 121 rare diseases in the First List of Rare Diseases, 86 rare diseases have drugs available worldwide, 77 of them have drugs available in China, and 9 rare diseases face the dilemma of "drugs available outside China but not inside". In China, there are 87 drugs with clear indications for rare diseases, covering 43 rare diseases, of which 58 drugs have been included in the NRDL after the national medical insurance negotiations in 2021, covering 29 rare diseases²⁶.

²⁴ See National Health Commission 's reply to the Fourth Session of the Thirteenth National People's Congress <http://www.nhc.gov.cn/wjw/jiany/202202/6ac97171a1d54f2dad97c6088f2ea080.shtml>

“一是关于扩大医保范围，尽快出台第二批罕见病目录。” (“First, on the expansion of health insurance coverage, as soon as possible to introduce the second batch of rare disease catalog.”)

²⁵ According to Center for Drug Evaluation, NMPA
List1: 19/40. Source: <https://www.cde.org.cn/main/news/viewInfoCommon/21de8acd6c395746b041b2ad93eb5c43>
List2: 17/26. Source: <https://www.cde.org.cn/main/news/viewInfoCommon/82f3bf94dc2c38d1a24d851f0e44914b>
List3: 3/17. Source: <https://www.cde.org.cn/main/news/viewInfoCommon/08818b168ccc85db9a42a0f6623b5688>

²⁶ <https://m.nbd.com.cn/articles/2022-02-27/2141619.html> China Rare Disease Industry Trend Watch Report 2022 《2022 中国罕见病行业趋势观察报告》

2.3. Social protection

In parallel, since 2018, China has issued a number of policies to improve the accessibility of drugs for rare diseases and improve the level of protection for patients with rare diseases. It includes the establishment of national patient registration system for rare diseases²⁷, diagnosis and treatment norms and networks (324 hospital networks) but also some the tax reduction etc. *The notice on the value added tax policy for drugs with rare diseases* issued by the Ministry of Finance in 2019, reduced value-added tax to 3% on the first batch of 21 drugs with rare diseases and 4 APIs with reference to anticancer drugs²⁸.

This administrative activity is improving the situation, but what really matter is the accessibility of drugs. Since 2017, the NRDL process has been gradually normalized, and progressively rare disease drugs have been included in NRDL. As of December 2021, 58 rare disease drugs have been included in the NRDL while the total number of drugs reimbursed is 2,860.

3. WHY IT IS IMPORTANT TO DO MORE IN CHINA

Looking at the big picture, China has seen a robust improvement since 2018. But the actual coverage is limited (only a few rare diseases are recognized as such) and they are almost not part of the social protection system. In a simplistic way, China is not “playing in its league” here. Second pharmaceutical market in value, and first in volume, China is one of the last markets in middle-income market in the area of rare diseases. It is time now to review this first step and find way to scale -up. There are several reasons to do so. First, the patients with rare diseases should benefit from fair treatments. Second, beyond this moral argument, China could use this opportunity as a leverage of innovation in drug development. Rare diseases are not rare in China.

3.1. Patients with rare diseases should receive fair and accessible treatments

In public circles, we often hear that common diseases are concerning masses and they should be the priority of the medical insurance. Not patients suffering from rare diseases as they are a minority. But if we compare the diseases we can also say that the nature of rare diseases is very special. They are very often genetic based, while more common diseases are sometimes due to lifestyle and lack of public awareness. In other terms, the impact and development of general diseases could be reduced if the society and individuals do something in term of prevention and management. But it is not the case of rare diseases who are very often genetic based. Treatment of rare diseases and access to them are the moral responsibility of the society as a whole. This principle being recognized, implementing universal healthcare coverage requires a pragmatic and step-by-step process starting with the big masses. The issue with rare diseases is that it is sometimes difficult to understand one's drug value thus limiting payers' interest into this category at least at the beginning.

In 2017, the white paper *development of China's health cause and human rights progress* issued by the Information Office of the State Council said that health is the basic condition for human survival and social development. The right to health is an inclusive basic human right and a basic guarantee

²⁷ National Rare Diseases Registry System of China, <https://www.chard.org.cn/#/cooperation>

²⁸ http://www.gov.cn/guowuyuan/2019-04/09/content_5380667.htm

for human beings to live in dignity. Everyone has the right to the highest and equitable standard of health.

At present, China's per capita GDP reaches 11,300 US dollars, which means China have entered the ranks of "middle-income countries" and China has a more matured society. In this condition, from caring for common diseases involving most people to caring for rare diseases with poor prognosis and patients with rare diseases not only represents the fairness and justice of medical treatment, but also reflects the development of society and civilization.

3.2. Rare diseases are not rare in China

China is the country with biggest population, so it has the largest number of patients with rare diseases. It is reported that the total number of patients with rare diseases in China is expected to exceed 20,000,000²⁹. The 121 rare diseases defined in the catalogue is estimated to have more than 3,000,000 patients. It is a huge group of patients actually.

Meanwhile, many patients with rare diseases generally lack therapeutic drugs and timely treatment, which often cause irreversible physical and mental damage to patients. Under the serious burden of disease, it is common for patients to be disabled, poor and return to poverty due to disease.

Hence, on the one hand, we cannot ignore this large social and livelihood issue, it is obliged to assist this group. On the other hand, it also means that improving the situation in China will have a global impact in terms of numbers of patients with rare diseases.

3.3. Treatment of Rare diseases has a potential industrial value

Globally, there is a huge unmet need to treat rare diseases: less than 5% of the more than 7,000 rare diseases known in the world have effective treatment methods. China who has started an innovation strategy for pharmaceuticals is recently slowing down facing lack of differentiation. Authorities could turn rare diseases in an asset and target this area of unmet needs and support the development of new treatments that would help patients and provide opportunities to biotech companies.

If one rare disease does not attract interest from the pharmaceutical industry, to pull them together enable to manage them more comprehensively and create the conditions to attract manufacturer. There is an economic scale to build expert companies on treatment of rare diseases.

Rare diseases are not "isolated islands". The same pathogenesis may span rare and common diseases, which could help to identify treatment opportunities for common diseases. The attrition rate for rare disease is very high. In the US, start-up companies are numerous to disappear (after first clinical trials are started and failed). But they found investors, because one success out of many failures is highly rewarding (thanks to prices). And the big pharmaceutical companies are licensing-in or acquiring these companies for the last ten years, because it is a highly profitable sector. Beyond R&D, there is also the relatively low cost of commercial deployment with small targets populations and highly concentrated clinical centers (who are involved in clinical trials).

²⁹ China Rare Disease Drug Accessibility Report, IQVIA, 2021.

For business value, the field of global rare diseases has spawned a number of blockbuster drugs, which are popular for investment thanks to supportive policies and thus have a high market value. For example, in December 2020, AstraZeneca acquired Alexion for \$39 billion. In April 2018, Takeda pharmaceutical acquired Shire with \$65 billion, becoming the largest M&A in the pharmaceutical field in that year. The US pharmaceutical industry association has recently issued a report celebrating “a decade of innovation” that enable to create 600 orphan drugs³⁰. BCG predicts that by 2024, the global sales of drugs for rare diseases such as cystic fibrosis, hemophilia A and myasthenia gravis will reach US \$6 billion, US \$4 billion and US \$3 billion respectively³¹. Chinese enterprises can take this opportunity to catch up quickly in the field of emerging technologies.

4. WHAT COULD BE DONE MORE?

Concretely, every phase of drug development could benefit from more support to fight rare diseases. It could be policy support, financial support by the State but also additional resources that could be provided by the society at large (charity).

4.1. Accelerate diagnosis

Systematic epidemiology research is not fruitful, because often it cost a lot of resources and does not help to deliver solution. The “reverse” seems to be more effective. When some therapeutic solution emerges then patients with same pathways for diagnosis and treatment organized themselves. Patients are the best advocate and will find way. Thus what is needed is to foster clinical specialised centers, coupled with research facilities and clinical coverage. Concretely a few physicians find interest in one group of diseases and “plant the seed” of “centers of excellence” dedicated to one disease and create a R&D cluster around it³².

One of the major complaints of patients in China is that most of doctors do not understand rare diseases and spend years, sometime decades to get an accurate diagnostic. Sometime the diagnostic is wrong and there are waste of resources (in wrong treatments) and suffering of patients.

The recent establishment of patient data platform is a great step in this direction³³. But when the initiative is only coming “from the top”, the platform or centers may not be the best to ensure concrete results, eg publication of data. But the Chinese medical experts and scientists are and they will ensure the new knowledge will be made available to the scientific and medical community at large. Also, China has a competitive advantage in digital technologies and could use them in order to

³⁰ A Decade of Innovation in Rare Diseases, PhRMA, Washington, 2022.

³¹ <https://www.163.com/dy/article/GBFVD7IH0519DDQ2.html>

³² The mission and development of [Orphanet](https://www.orpha.net/consor/cgi-bin/index.php) could be a great source of inspiration: <https://www.orpha.net/consor/cgi-bin/index.php>

³³ GUO Jian, LIU Peng, JING Zhicheng, LIU Jianmin, CHENG Jingqiu, DING Jie, GU Weihong, CHEN Limeng, ZHU Yicheng, ZHANG Shuyang. Construction and Application of National Rare Diseases Registry System of China[J]. Journal of Rare Diseases, 2022, 1(1): 7-12. doi: 10.12376/j.issn.2097-0501.2022.01.002

accelerate diagnosis³⁴. The focus on “acceleration of diagnostic” supported by digital tools would have the additional benefit to increase awareness on rare diseases.

4.2. Accelerate & facilitate more registration

We saw that accelerated registration is critical for the development of drugs against rare diseases.

With its first list of rare disease, NMPA has started the fight but is far away to have a significant impact. Looking at the current pipeline of clinical trials of rare diseases registered in China, there is not much hope to come in the coming years. In the first list of 121 rare disease, there are only 14 kinds of rare diseases with clinical drugs under research in China, accounting for a small proportion, and the number of clinical drugs under research is 23.³⁵ These clinical trials of therapeutic drugs for rare diseases mostly focus on hemophilia, homozygous familial hypercholesterolemia, idiopathic pulmonary fibrosis and multiple sclerosis in China.

In comparison, according to the statistics of drug research and development center of Tufts University, there were 766 clinical trials of rare diseases in 2015, and reaches 942 by 2018, with 84% of the new clinical trials of drugs for rare diseases in phase I and phase II stages. China is currently not playing in its league, and the situation is not going to improve in coming years as the biotech industry is losing steam. The registration of rare diseases clinical trials or marketing should be facilitated.

Some patients suffering from rare diseases are well aware about the limitations of the economic model that prevent the development of needed treatments. Limited market potential prevents the eco-system (from scientists to the pharma companies) to invest in this area. Some policy support like higher price could help. The best policy support for orphan drugs in China is to allow the registration without clinical trials. When the compound and the indication have been launched years ago abroad. But one direction that cannot be followed is the lowering of clinical standard for economic reasons. Clinical trials on rare diseases are already facing a lot of medical challenges (limited number of patients, non-ethical placebos etc). It is also the request of patient associations like EURORDIS³⁶ to get quality and conclusive clinical trials. Also, from insurance point of view, reimbursement can only happen when proof of efficacy and tolerance are well established.

Another area of policy support could be after the Marketing Authorization by reducing cost of and reaching patients. Increasing awareness and acceleration of diagnosis work would enable a quicker and cheaper deployment of drugs in a limited number of specialized centers.

4.3. Increase financing efforts of R&D

There is no doubt that increase development of drugs against rare diseases will cost more on the short term to the economy and society. But before looking on how to increase the amount of investment, let us see the way to improve the accuracy of investment.

³⁴ An example of efficient use of digital technologies: https://www.sanofi.fr/fr/-/media/Project/One-Sanofi-Web/Websites/Europe/Sanofi-FR/nous-connaître/domaines-therapeutiques/maladies-rares/LIVRE_BLANC_UNIR-39BIS-ENG-HD.pdf

³⁵ 《第一批罕见病》国内药物治疗现状调研, see https://med.sina.com/article_detail_103_2_56909.html

³⁶ <https://www.eurordis.org/>

The core issue is the cost of the development of a drug. From international experience point view, we know it costs in the range of 200 to 500 million USD per orphan drug³⁷. One way to improve investment in R&D is not linked to rare diseases, but to the behavior of the market. Lack of awareness and accurate policy from the regulator have long generated an “herd-innovation” where companies are copying each other and try only to bring incremental improvement to the markets. Innovation is not well protected and thus at the end all actors are copying each other. We get situation where some so-called me-better innovations are mushrooming with no value in China or on international market because they developed without proper IPR protection. In July 2021, NMPA has finally announced that it would only approve real innovation to the world.³⁸ It had a dramatic impact on some companies, but it was the right thing to improve differentiation on the market. This has been announced only for oncology products. More needs to be done. And IPR has to follow-up. By this way, economic actors will stop to waste resources in doing same investment than their competitors and thus it will free resources for new therapeutic areas. Rare disease will benefit greatly from this.

There is another interesting way to reduce cost of R&D in drugs is to authorize investment in new indications of drugs. Many rare diseases could be cured with existing chemical compounds but would require the development of new indications. NMPA and CNIPA (China National Intellectual Property Administration) could unleash a lot of innovation by recognizing the patent for indications. The new indications would be far less costly than new chemical compound. These developments can only happen if the regulatory authorities lead the way.

4.4. increase investment by State

Increase of investment by the State will be necessary in order to improve the access to drugs against rare diseases. But there are some ways to keep it under control due to the nature itself of rare diseases.

Now it is well understood that we need to collectively increase investment in health, medical science and health education. Spending in health care in China accounted for just over 7% of GDP in 2019, and the figure increased slightly to 7.2% in 2020 due to Covid-19 epidemic.³⁹ Most of developed markets are in the range of 10 to 12% of GDP while the world average is 9.8%⁴⁰. China is not playing in this league. For a middle-income country, China is spending relatively too much on highways, buildings and not enough in services especially healthcare.

Amount of investment per patient with Rare Diseases maybe higher than average patient (the net cost of rare diseases requires to deduct the cost of non-treatment and lack of social output for these patients). Reimbursement for common diseases are sometimes difficult as prescription can be

³⁷ Jayasundara, K., Hollis, A., Krahn, M. *et al.* Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet J Rare Dis* **14**, 12 (2019). <https://doi.org/10.1186/s13023-018-0990-4>.

³⁸ CDE, NMPA Notice on public solicitation of opinions on 《relevant technical requirements for pharmaceutical common problems at the pre marketing application meeting of chemical innovative drugs (Exposure Draft) 》 <https://www.cde.org.cn/main/news/viewInfoCommon/edb93676c34f3478090f7809944b642f>

³⁹ Statistical bulletin of China's health development in 2020

⁴⁰ Global spending on health more than doubled in real terms over the past two decades, reaching US\$ 8.5 trillion in 2019, or 9.8% of global GDP <https://apps.who.int/iris/bitstream/handle/10665/350560/9789240041219-eng.pdf>

enlarged by prescribers and patients. In the case of rare diseases, prescription are backed by specific and scientific diagnostic. Over prescription is limited. Thus the situation is manageable due to the limited number of patients who need these specific drugs. The individual financial risk is limited. The cumulative risk, or collective cost of orphan drugs, is significant⁴¹ but it is a matter of priority (currently China is not investing enough in healthcare) and part of the incremental spending could be allocated to rare disease.

Number of patients with rare disease is limited and, because they are acutely aware of healthcare cost, they may be ready to try innovative approach for funding. Historically some provinces with better financial resources have created interesting local schemes, it proves that innovation can also be useful in funding. More could be done for patients with rare diseases. Partnership with some insurance companies⁴², payment by instalment etc are all interesting ways to improve the efficiency of the medical insurance for patients with rare Diseases. They are very responsible patients ready to test new approaches.

4.5. Power of elites and charity should be mobilized

Chinese society has profoundly changed in last decade. People are more caring about the society at large. Elites have generated sizeable financial resources. Each catastrophe hitting the country trigger massive donation and charity. They could become a supplemental force to help patients with rare diseases, while the State is taking care of the masses.

A survey of 38,634 Chinese medical workers conducted by China rare diseases Alliance showed that 1,770 had never heard about rare diseases, accounting for 4.6%; 23,514 have heard about but do not deeply understand rare diseases, accounting for 60.9%. At the same time, 87.6% of medical workers thought they did not understand the national policy on rare diseases. It means that the protection of patients with rare diseases has a long way to go.⁴³

But, on the other hand, in 2016, the global "ice bucket challenge" publicized the concept of caring for patients with rare diseases. At the same time, many influential people from all walks of life participated, which made rare diseases come into the public view. At that time, the domestic donor "porcelain doll" rare disease care center received millions of donations.⁴⁴ In a similar way, Genethon is a remarkable success story of a charity coupled to a patient associations that has now become a key player in emerging R&D for rare diseases⁴⁵.

Therefore, in order to better solve the health problems of patients with rare diseases, we should raise the public awareness about rare diseases. It would enable general population to better understand the situation and be gentler to these patients and their families who have difficult lives.

⁴¹ <https://www.healthaffairs.org/doi/10.1377/forefront.20220128.987667/> or <https://www.ahip.org/news/press-releases/drug-prices-for-rare-diseases-skyrocket-while-big-pharma-makes-record-profits> --> CHECK REFERENCE

⁴² Knowing that most private insurers are attracted by the masses and therefore they usually show limited interested in providing better coverage for rare disease drugs as it would not attract many patients

⁴³ <https://zhuanlan.zhihu.com/p/355826137>

⁴⁴ https://www.sohu.com/a/220705214_465192

⁴⁵ <https://www.genethon.fr/>

It would also enable to get more interest and support from charity organizations to donate and support patient associations and organisations fighting rare diseases. Raising the attention of the public and medical workers to rare diseases would unleash the financial power of elites and give full play to the power of charity.

In summary, China has made a lot of progress in terms of treating rare diseases. Before 2018, there was no specific Government policies in terms of definition, registration and drug access. The Last 5 years have seen the creation and improvement of many needed policies and tools. This paper proposes to move to the next level by:

- clarifying the Chinese definition of rare diseases*
- continuing to accelerate registration of drugs and indications vs rare diseases and improving their accessibility of drugs through public schemes, addressing the specific situation of these drugs,*
- making rare diseases an asset and thus improving attractiveness of related treatments to the industry in order to make it an engine to develop innovation,*
- all these will require additional financial resources that could be invested by the State but also the society through charity and foundations.*