Research on Incentive Mechanism of Repurposing Drugs for Rare Diseases

Wu Xiaoling, Yuan Hongmei *

(*School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China*)

Abstract

Objective To improve the system of accelerated review and approval, and to speed up the development and marketing of repurposing drugs for rare diseases in China. **Methods** The relevant concepts of rare diseases and the definition of drug repurposing were introduced so as to sort out the advantages and disadvantages of the research and development of drug repurposing for rare diseases. Then, the incentive mechanisms of the research and development of drug repurposing for rare diseases in China and abroad were compared. **Results and Conclusion** Some suggestions on improving the incentive mechanism of repurposing drugs for rare diseases such as policy support for talents introduction, capital investment, and innovation capabilities are proposed. Besides, the government should further improve policies for the research and development of repurposing drugs for rare diseases, which can gradually narrow the gap between the research and innovation of drug repurposing in developed countries, thus benefiting the patients of rare diseases.

Keywords: rare disease; drug repurposing; incentive mechanism; innovation ability

Rare disease is a kind of special disease with a small number of patients, which leads to the high cost of the research and development (R&D). Therefore, most pharmaceutical enterprises do not have enthusiasm for the R&D of drugs for rare diseases. Many countries and regions have issued policies to effectively incentivize sponsors in this area. With the rare disease incentive policies to encourage the development of drugs for rare disease in United States, European Union, Japan and other countries, the innovative drugs for rare diseases in these regions have been greatly developed. At present, almost all major multinational pharmaceutical companies (Sanofi, Pfizer, GlaxoSmithKline) pay more attention to the development of drugs for rare disease than before [1, 2]. Since the formal implementation of the drug management system for rare disease in the United States in 1983, the number of drugs for rare disease on the market has increased rapidly from only 10 to nearly 500 [3].

Although the prevalence of rare diseases is relatively low, the treatment for rare diseases cannot be ignored due to the large population in China. In addition, Chinese government pays much attention to the research and development of drugs for rare diseases. For instance, on May 11, 2018, five governmental departments jointly released the first Rare Disease List, containing 121 rare diseases. This initiative paved the way for the development

* Corresponding author: Yuan Hongmei, professor. Major research area: Pharmaceutical intellectual property rights, pharmaceutical affairs management, etc. Tel: 13604027062, E-mail: yuanhm612@163.com.

of orphan drugs in China [4]. However, compared with developed countries such as United States and European Union, China's incentive policies for the research and development of drugs for rare diseases are still imperfect, which cannot meet the clinical needs of Chinese patients with rare diseases.

Drugs repurposing refers to the process that new therapeutic uses or indications are found after new clinical trials and research for old drugs that have already been marketed [5]. It is possible to develop the indications for rare diseases from approved drugs through the drug repurposing. Therefore, the incentive mechanism for drug repurposing for the treatment of rare diseases is closely related to the vital interests of patients with rare diseases [6]. This article studies the advantages and disadvantages of repurposing drugs for rare diseases, incentive mechanism of repurposing drugs for rare diseases, cases of repurposing drugs to make some suggestions on improving the incentive mechanism, which can provide reference for the incentive mechanism of R&D of repurposing drugs for rare diseases.

1 Advantage and disadvantage of repurposing drugs for rare diseases

1.1 Advantages

It is cost saving. Generally speaking, the early phase development for drug repurposing has been completed, and the later cost for development is less than developing a new drug. With the characteristics of drug development phase and process of drug repurposing, the cost for regulatory and phase I and phase II clinical trials will be greatly saved [7], which brings fewer risks and more rapid return on investment for the R&D of repurposing drugs for rare diseases.

It has high success rate. Since the strategy of drug repurposing is generally based on drug database which includes disease pathogenesis, systematic analysis of gene expression, chemical structure, genotype or proteomic data through computational biological methods, the success rate for repurposed drugs is higher than the development of new drugs. The success rate of applications for new drug for rare diseases is often low, however, about 30% of the research and development projects of drug repurposing have been successful [8].

1.2 Disadvantages

The etiology is complex. There are more than 7 000 rare diseases known in the world, 80% of which are genetically related [6], with the features of complex etiology and difficult diagnosis. Due to the small number of patients, pharmaceutical enterprises and physicians pay less attention to rare diseases. Together with the great heterogeneity of clinical manifestations for rare diseases, the lack of understanding of rare diseases may cause misdiagnosis [9]. All these factors lead to considerable difficulties in repurposing drugs for rare diseases.

The enrollment of patient sample is difficult. As rare diseases are diseases with low prevalence [6], the number of patients is small compared with common diseases. Even though the safety profile of marketed drugs has been verified after phase I and phase II clinical trials, the efficacy for the new proposed indications (rare diseases) still needs to be verified via clinical trials for the repurposed drugs. As a result, it is difficult to enroll large sample size for clinical trials to obtain the data that can support the new indication approval for repurposing drugs.

The access to data is limited. After the new indication approval of repurposing drugs for rare diseases, the access may be restricted due to commercial confidentiality to the two important big data sources, the previous monitoring data and clinical trial data [10].

In summary, repurposing drugs for treatment of rare diseases has advantages such as cost saving and higher success rate. However, due to the characteristics of rare diseases, there are also disadvantages such as difficulties in exploring the etiology and obtaining relevant data. Therefore, it is of great significance to set up an incentive mechanism for repurposing drugs for treatment of rare diseases from the institutional perspective.

2 Incentive mechanism of repurposing drugs for rare diseases

2.1 Incentive mechanism of repurposing drugs for rare diseases in the USA

The method of "orphan drug designation plus marketing approval" was introduced in the registration and authorization system of drugs for rare disease in United States that paved the way for repurposing drugs for rare diseases to share the same preferential policies with the innovative drugs, which will get new indication approval by supplementing new drug application.

2.1.1 Related regulations and organizations for orphan drugs

In 1983, the US Food and Drug Administration (FDA) officially passed the "Orphan Drug Act", which stimulated the enthusiasm of pharmaceutical companies for the R&D of rare disease drugs. Therefore, the United States is the first country in the world to implement the drug management system for rare disease [11]. In 1993, the National Institutes of Health (NIH) established the Office of Rare Diseases Research (QRDR) to support research on rare diseases [12]. The "Rare Diseases Act" of 2002 provides clear legal protection for the development of new drugs for rare diseases. Due to the unique nature of new drug research and development for rare diseases, the FDA provides a variety of preferential policies for the marketing of orphan drugs, even if the drug has been marketed, as long as the new indication of the supplemental application (drug repurposing) meets the specific criteria. It means once the disease affecting less than 200 000 people in the US, and has been designated as an orphan drug, the sponsor will be eligible to enjoy the corresponding incentive mechanism, including but is not limited to, tax credits for qualified clinical testing, waiver of the prescription drug user fee, more guidance and communication opportunities, and accelerated review pathways such as fast-track, priority review, and accelerated approval [13].

The FDA's Center for medical products, including the Center for Drug Research and Evaluation (CDER) and the Center for Biologics Evaluation and Research (CBER), support rare disease product development to address specific considerations in developing and approving medical products for rare disease. It conducts specialized training for FDA staff on rare disease topics, issuing guidance for industry to encourage medical product development in rare diseases, and administering the expanded access or compassionate use program for investigational medical products in rare diseases [14].

2.1.2 Government financial support

One of the barriers to develop drug repurposing for rare diseases is the cost of supporting R&D institutions or manufacturing enterprises, especially through state-run funds. Thanks to the persistence and efforts of the R&D staff, the NIH provides special research funds for the R&D staff. The FDA's Office of Orphan Products Development (OOPD), established in 1983, is also responsible for the rare disease drug funding program, and its core programs target new and repurposed drugs for rare diseases, including but not limited to: the 15 million dollars "Orphan Drug Product Clinical Trial Grant Program" funding and monitoring 85 rare disease clinical trials; the 2 million dollars "Orphan Drug Products Natural History Grant Program" with the National Institutes of Health providing an additional 3.5 million dollars to fund a total of 6 studies [15]. In addition, FDA's CDER and CBER also award research grants, cooperative agreements and contracts for conducting pilot programs and special data analyses to advance the regulatory science for rare diseases [14]. These measures have increased the enthusiasm of pharmaceutical companies to develop repurposing drugs for rare diseases and reduced the financial burden of pharmaceutical enterprises that develop drugs for rare diseases.

2.1.3 Market exclusivity and independent pricing

According to the "Orphan Drug Act",

pharmaceutical companies have a great deal of autonomy in pricing drugs for rare diseases [16]. New drugs for rare diseases have a seven-year market exclusivity after approval. When applying for the same indication for another new drug, if it cannot be proved to have a better efficacy profile than the approved rare disease drug, it cannot be recognized as an orphan drug. For the development of repurposing drugs for rare diseases, after the new indication of a marketed product is granted orphan drug designation and obtained marketing approval, the indication will also enjoy a seven-year market exclusivity period. These measures have become an effective means to encourage pharmaceutical companies to develop new drugs and repurposing drugs for rare diseases.

2.2 Incentive mechanism of repurposing drugs for rare diseases in China

At present, the incentive policy for the R&D of new drugs for rare diseases in China is manifested in three aspects.

The first one is to expedite the review of new drugs for rare diseases. For example, the China State Council issued "Opinions on the Reform of Review and Approval Process for Drugs and Medical Devices" in 2015, which could accelerate the review and approval of innovative drugs for the prevention and treatment of rare diseases.

The second one is to loosen data requirements from clinical trials on the development of drugs for some rare diseases. For example, the guidelines on "Encouraging Drug and Medical Device Innovation to Accelerate the Approval of New Drug Therapeutic Devices (Draft for Comment)" were released in 2017.

The third one is to shorten the gap with drugs for rare disease by releasing the list of clinically urgent overseas new drugs. Among the 73 drugs listed in the three batches of overseas new drugs, 37 were drugs for rare diseases, accounting for 50.68%. Among the 46 drugs approved, 21 were drugs for rare diseases, accounting for 45.65% [17].

However, the introduction of these policies only applies to new drugs for rare diseases. There are no incentive policies issued yet for the R&D of repurposing drugs for rare diseases, so relevant regulations are needed. Besides, it also needs the support and supervision of professional institutions.

3 Cases on incentive mechanism of repurposing drugs for rare diseases

3.1 Incentive case on myeloid/lymphoid neoplasms (MLNs)

The first indication of Incyte's pemigatinib was for cholangiocarcinoma, and its second indication was granted orphan drug designation by the FDA for the treatment of relapsed or refractory MLNs with fibroblast growth factor receptor 1 (FGFR1) rearrangement on August 21, 2019 [18].

MLN-Eo FGFR1 is generally regarded as an rare disease, and its incidence has been difficult to quantify. The complex diversity in its presentation characteristics may lead to inadequate diagnosis and, unless definitive cytogenetic or molecular analysis is performed, it cannot be diagnosed correctly. In a study from the Mayo Clinic with more than 24 000 patients of leukemia analyzed cytogenetically, only 4 patients (0.000 164%) showed an FGFR1 rearrangement. This is under the background of leukemias that take place of only 10% of all cancers. which also proves the rare nature of this disease in the population. Therefore, our understanding of its pathobiology is limited, and it is challenging to conduct clinical trials for drugs for this disease [19].

Given the rarity of the disease and the challenging nature of clinical trials, it is hard to obtain an adequate sample size of clinical data. The approval of the rare disease indication for pemigatinib is not based on the clinical data from traditional large controlled clinical trials. Its efficacy was evaluated in a small sized single-arm trial that included 28 patients, and this application was granted priority review and breakthrough designation [20]. All the measures accelerated the rapid development and marketing of this indication to the maximum extent.

3.2 Incentive case on polycythemia vera (PV)

The first indication of Incyte's ruxolitinib was for myelofibrosis, and its second indication for the treatment of PV was granted orphan drug designation by the FDA on March 26, 2010 [18].

PV is a rare disease. For all races and ethnicities, the incidence (newly diagnosed cases) of PV is approximately 2.8 per 100 000 population of men and approximately 1.3 per 100 000 population of women. The prevalence (estimated number of people in a population with a diagnosis of a disease) of PV is approximately 22 cases per 100 000 people [21].

At that time, there was no specific drugs approved for PV. Ruxolitinib is the first drug approved by the FDA for the treatment of this rare disease, the clinical results demonstrated the potential to provide significant improvement in safety or efficacy over the other available therapy for PV at the time of its application. This application was granted priority review for its accelerated approval [22].

3.3 Incentive case on chronic graft-versus-host disease

Incyte's ruxolitinib was first agent approved for myelofibrosis, and its fourth indication for the treatment of chronic graft-versus-host disease was granted orphan drug designation by the FDA on November 3, 2016 [18].

Graft-versus-host disease is a rare disease, which can only develop after a stem cell transplant with a small number of patients. The incidence of graft-versus-host disease is estimated at 9.5×10^{-7} per 100 000 cases. There are approximately 5 500 cases per year [23].

As the orphan drug for rare disease, this application was granted priority review, and its review was conducted under "Project Orbis", a concurrent submission and review plan, which was a collaboration mechanism and framework initiated and led by the FDA, allowing international health agencies for concurrent review of the application, aiming to accelerate the marketing process in different countries for oncology products [24]. For this review, FDA collaborated with the Australian Therapeutic Goods Administration (TGA), the Brazilian Health Regulatory Agency (ANVISA), Health Canada, Switzerland's Swissmedic and the United Kingdom's Medicines & Healthcare products Regulatory Agency (MHRA) [25], giving the repurposing drugs lots of guidance.

4 Suggestions to improve the incentive mechanism on repurposing drugs for rare diseases

4.1 Providing the legal basis for the identification of repurposing drugs for rare diseases

The World Health Organization defines rare diseases as diseases that affect 0.65‰ to 1‰ of the total population. In EU, US, and Japan the definition for rare disease slightly varies according to different epidemiological data in each country. At present, there is no official definition of rare diseases in China. In May 2018, the National Health Commission and other five departments jointly released the "First Rare Disease List" for 121 diseases [26]. In order to encourage the development of drugs for rare diseases, including the development of repurposing drugs for rare diseases, it is suggested to clarify the definition of rare diseases in China, issue a follow-up rare disease list, improve the dynamic release mechanism of the rare disease list [27], providing legislative basis for the recognition and management of rare disease indications so that sponsors can develop repurposing drugs for rare diseases.

4.2 Providing data support for the R&D of repurposing drugs for rare diseases

In view of the complex etiology and difficult diagnosis of rare diseases, it is suggested to establish a database of rare diseases to provide reference and query of information. Besides, pharmaceutical enterprises should cooperate with domestic hospitals to collect clinical cases of rare diseases, which can provide a platform for the diagnosis and treatment of rare diseases. At the same time, the knowledge

popularization and training of rare diseases should be strengthened. The diagnosis and treatment guidelines for rare diseases should be optimized and updated on time. Improving the diagnosis and treatment mechanism of multi-disciplinary consultation and multi-detection means can effectively help physicians to identify and treat rare diseases, better guide the R&D of drugs for rare disease [27], and provide the natural history research of repurposing drugs for rare diseases.

In recent years, advances in technology and bioinformatics have enabled machine learning-based models to use data to predict new associations among diseases. As to the drug repurposing rare diseases, relevant computer methods can be used to match the mechanism of approved drugs and the treatment of rare diseases, including genetic association, pathway mapping, retrospective clinical analysis, novel data sources, phenotypic screening, binding assays to identify relevant target interactions, signature matching, molecular docking, etc. [28]. It is suggested to establish a foundation to increase the funding for the calculation method of early R&D of drug repurposing, as well as the monitoring of clinical trials to achieve a high degree of confidence in the identification of suitable drugs for the treatment of rare diseases.

4.3 Improving the review and approval policies for the R&D of drug repurposing for rare diseases

Learning from the FDA, a delegated agency of rare diseases should be set up to deal with the rare disease products including the new drugs and repurposing drugs equally [29]. It means that the preferential policy for new drugs for rare diseases is also applicable to the review and approval of repurposing drugs. Only if the registration and approval of repurposing drugs for rare diseases are concerned, the relevant regulatory system should be greatly improved, and the sponsors engaged in the R&D of repurposing drugs for rare diseases can be encouraged to develop new indications with high clinical value. It is also suggested to further simplify the registration and designation process, appropriately referring to the relevant designation mechanism of the FDA. Besides, a direct application and approval mechanism for the repurposing drugs for rare diseases should be set up according to China's national conditions, which can gradually enhance the efficiency of review and approval [30]. The patent protection period of the repurposing drug shall be extended appropriately after the rare disease indication is approved. A special fund to be set aside to support the Marketing Authorization Holders on the R&D of repurposing drugs for rare diseases, and financial support should be provided for clinical trials. In addition, international cooperation among different regulatory agencies should be strengthened to share information about the repurposing drugs for rare disease. Some incentive policies should be made to accelerate the review and approval process for repurposing drugs for rare diseases in China.

4.4 Improving the medical insurance system for drug repurposing for rare diseases

The government should improve the accessibility of rare disease drugs, coordinate and optimize medical insurance access, enhance independent pricing by pharmaceutical industry, extend market exclusivity period, reform medical insurance payment methods, supervise medical institutions to apply centralized drug procurement projects [27].

The pricing mechanism of drug repurposing for rare diseases in China is relatively imperfect, and the cooperation among relevant regulatory agencies needs to be further strengthened. In addition, the standard for the alternative pricing of repurposing drugs is not clear, so it is suggested to develop a clear pricing mechanism for repurposing drugs with significant incentive effect when considering the accessibility of drugs for rare disease [31]. Pricing protection mechanism should be implemented for repurposing drugs for rare diseases, and price protection period should be given after entering the medical insurance catalogue. Lastly, the repurposing drugs for rare diseases should not be included in the assessment of drug proportion.

5 Conclusions

The establishment and improvement of the incentive mechanism of drug repurposing for rare diseases can allow more pharmaceutical companies and social forces to participate in the development of drugs for rare diseases. Promoting legislation for rare disease is an important prerequisite for establishing a positive incentive mechanism, it is conducive to achieve a virtuous cycle to direct the stakeholders in the R&D of drugs repurposing for rare diseases by transforming the fragmented rare disease policy into a multi-sectoral regulatory system.

The incentive mechanism of drugs repurposing for rare diseases in China still need improvement, which should increase its efforts in terms of talent, capital investment and innovation policy investment, so as to gradually narrow the gap between with developed countries on the R&D and innovation of drugs repurposing. Besides, the above investment needs to be based on China's national conditions and gradually expanded. The implementation of the incentive measures is conducive to promote the continuous investment of pharmaceutical companies in drugs innovation and talents introduction, which in turn can enhance the patients' accessibility to repurposing drugs for rare diseases.

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