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Review Article

Repurposing Drugs for Orphan Diseases

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Abstract

Drug repurposing, also known as drug repositioning or reprofiling, develops and commercializes new uses for existing or abandoned drugs. In past decades, ~30% of repurposed drugs were approved by the United States Food and Drug Administration (FDA), while less than 10% of de novo drug applications achieved approval.

Repurposing drugs were developed for various diseases, including cancer, infection, inflammatory disorders, and neurodegenerative diseases. Experimental and computational strategies have been applied in drug repurposing. Professional expert guidance is an essential support for developing a successful regulatory and clinical drug repurposing plan. Our knowledge and experience in regulatory, clinical research, and biomarker consulting provide high-value and support our clients' operational and functional needs. The opportunity to support clients' implementing the most appropriate FDA 505(b)(2) and EMA hybrid submissions maximizes the benefit of drug repurposing for orphan indications. It helps patients with rare diseases and the healthcare system.

This review focuses on developing repurposing drugs for orphan indications and rare diseases. Due to the significant complexity of orphan drug development and lack of effective treatment for many of them, we aim to provide options to address the current unmet medical needs for a wide range of patients worldwide.

Keywords: Drug repurposing (DR); Food and Drug Administration (FDA); Drugs

Introduction

Drug repurposing (DR), also known as drug repositioning or reprofiling, develops and commercializes new uses for existing or abandoned drugs [1]. Developing a de novo product is an extremely long process, from a clinical investigation to regulatory agencies' review and approval in the marketplace. Unlike the traditional de novo drug development, DR is an alternative way to obtain approval of existing drugs for new indications after a de novo product has been regulatory approved in the marketplace. In past decades, ~30% of repurposed drugs were approved by the United States Food and Drug Administration (FDA), while less than 10% of de novo drug applications achieved approval [2]. According to recently released data, 12 out of the 28 drugs approved in the first quarter of 2020 by the FDA were DRS [3]. The DR approval process is an effective tool that accelerates the development of drugs for new indications or drug reformulation [4]. Repurposing drugs were developed for various diseases, including cancer, infection, inflammatory disorders, and neurodegenerative diseases. This review will focus on the development of repurposing drugs for orphan indications and rare diseases.

Due to the significant complexity of orphan drug development and lack of effective treatment for many of them, we aim to provide options to address the current unmet medical needs for a wide range of rare diseases worldwide.

Why repurpose existing drugs for orphan diseases?

Repurposing existing drugs for orphan indications offers a valuable trade-off compared to the traditional de novo drug development. Figure 1 summarizes the advantages of DR in comparison to the conventional process.

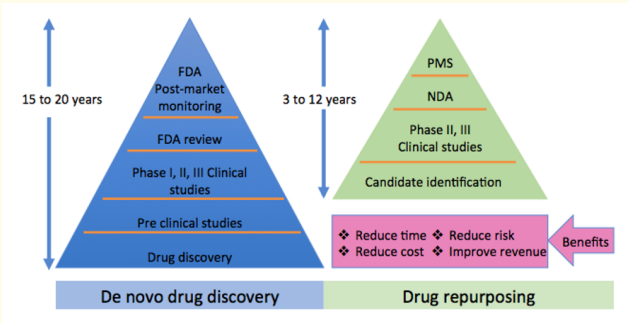

Figure 1: Schematic representation of steps involved in drug development. Explore the advantages of DR with the process comparation between De-novo and Repurposed drugs.

Abbreviation: PMS: Post-Marketing Surveillance; NDA: New Drug Application.

Reduce time of drug development

Drug development is a long-time process requiring significant resources. In general, a successful drug needs to go through 5 stages: discovery and development, preclinical research; clinical research; regulatory review; and post-market drug safety monitoring [5]. The estimated time from initial discovery to the marketplace is between 15 to 20 years. However, DR requires four steps, including identification candidates, clinical trials (mostly phase II and III), new drug application (NDA), and post-marketing surveillance (PMS). The observation and analysis of the approved repurposed drugs show that the development of DR takes 3 to 12 years [6]. The time saving of DR's development occurs at different levels. Those existing drugs have already completed the discovery and validation process and accrued much data on the mechanism of action and more, which generally require at least 2 to 3 years. In addition, the adoption of the approved drug's pharmacokinetics, pharmacodynamic, and safety profile can save about 5 to 6 years in development [7]. Finally, RD would benefit from requiring fewer subjects in clinical trials, which is one of the significant limitations of rare diseases and orphan indications.

Reduce the cost of drug development

Developing and marketing a new drug has ranged from $314 million to 2.8 billion [8]. The enormous spending has severely affected the development of de novo drugs by reducing the number of new drugs on the market. Due to the bypass of early discovery and development stages, RD could save the cost invested in these stages. Based on recent reports, RD development may cost 50-60% less than a de-novo drug development [3]. Therefore, RD plays a crucial role in drug development as it significantly lowers the investments compared to those needed for a de novo drug development.

Reduce the risk of product failure due to the drug safety profile

Apart from the outstanding reduction in the time and cost in drug development, DR development also benefits from knowing the safety profile of de novo products which is a significant incognito in the de novo drug development and be a cause of the market approval risk. It has been reported that ~45% of de novo drugs failed the regulatory review and market approval due to the drug product's long-term toxicity and safety profile [9]. As the safety of the repositioned drugs has already been established in animal models in preclinical studies and even in humans in clinical trials, DR can significantly increase the approval rate. Indeed, from 2012 to 2017, more than 170 repurposed drugs are entered into different development stages. Among them, ~70% quickly moved forward into phase II clinical trials as these repurposed drugs have been demonstrated to have no safety concern in previous phase I clinical trials [10].

Dictate high investment potential and revenue achievement

Sir James Whyte Black, a 1988 Nobel Prize in Medicine winner, said, "The most fruitful basis for discovering a new drug is to start with an old drug" [11]. More and more successful repurposed drugs have confirmed his opinion. The market for repurposed drugs has been valued at more than $20 billion and is expected to reach $35 billion by 2027. Surprisingly, the market creates ~25% of the annual revenue for pharmaceutical companies [3].

Example of successful drug repurposing for orphan diseases

The FDA and European Medicines Agency (EMA) have approved numerous repurposed drugs. Most repurposed drugs target biological catalysts, signaling mediators, transporters, channels, and

nuclear receptors to treat cancer, inflammatory diseases, infection, skin, and neurodegenerative diseases. Here, we list examples of repurposed drugs that had been successful in orphan drug development in table 1. The typical repurposed drugs, including Tocilizumab, Sildenafil, Infliximab, and Thalidomide, are introduced individually.

Tocilizumab

Tocilizumab is an interleukin-6 (IL-6) receptor antibody manufactured by Actemra. It was initially tested as a rheumatoid arthritis treatment and approved to treat different types of rheumatoid arthritis. Tocilizumab was later approved to treat systemic sclerosis-associated interstitial lung disease, a rare debilitating condition. The reposition of Tocilizumab was based on the common signaling pathway of the same target protein, IL-6, among the diseases [12].

Sildenafil

Sildenafil is an enzyme phosphodiesterase type5 (PDE5) inhibitor. Sildenafil induces smooth muscle relaxation and vasodilation, which releases blood into both penis and pulmonary arterial vessels. In 1998, it was approved as the first oral treatment for erectile dysfunction. Later, it was repurposed for pulmonary arterial hypertension and approved to treat this rare disease in 2005 by the FDA [2,13].

Infliximab

Infliximab acts by blocking the activity of tumor necrosis factor-alpha (TNF-α). TNF-α is a cytokine and plays an important role in the immunity and inflammatory process. The dysregulation of TNF signaling is involved in a variety of diseases. Due to the wide range of potential effects of blocking TNF-α, Infliximab has been evaluated and approved in several diseases such as joint and skin immunity disorders. Infliximab was later repurposed to treat rare diseases, including ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis [14].

Thalidomide

Thalidomide is another example of DR in the history of orphan drug development. Thalidomide was initially developed to treat motion sickness in pregnant women. It was later withdrawn due to serious side effects on the fetuses. Later, it was repurposed as a first-line treatment for multiple myeloma in 1998. Although thalidomide was generally considered an anti-inflammatory agent, the precise mechanisms of action are unclear [6].

Repurposed drugs	Common disease	Orphan disease
Tocilizumab	Rheumatoid Arthritis	Systemic sclerosis-associated interstitial lung disease
Sildenafil	Erectile dysfunction	Pulmonary arterial hypertension
Infliximab	Rheumatoid Arthritis	Ankylosing spondylitis Crohn's disease Ulcerative colitis Plaque psoriasis
Thalidomide	Morning sickness pregnant woman.	Multiple myeloma
Colchicine	Gout	Mediterranean Fever
Histrelin	Prostate Cancer	Precocious Puberty
Azathioprine	Rheumatoid Arthritis	Renal homotransplantation

Table 1: Examples of repurposed drugs for an orphan indication.

Challenges of drug repurposing

Although DR has gained numerous successes, potential challenges should not be ignored. Unlike the therapeutic target identification for the conventional de-novo drug development pathway, the first important step of DR is to identify the drug that has the potential to be repurposed for other indications and specifically for orphan indications. DR new target identification requires comprehensive knowledge of the drug/compound mechanism of action and impacted signaling pathways to identify and validate potential candidates. Once selecting the drug to be repurposed, acquiring the de-novo product data of preclinical toxicology, pharmacokinetics, and pharmacodynamics, and clinical safety becomes essential. These data are crucial to evaluate the repurposed drug in the clinical trials and the subsequent market approval submission for the target orphan indication. Most of the raw data of the de novo drug development belong to the innovator pharmaceutical company. Lack of access to raw data and material information may slow down the process of DR development [15]. Another challenge for DR development could be collaboration and investment, which may be due to patent conflict. In this case, the DR development process may be discontinued due to the partnership's failure [2].

Drug repurposing strategies

Novel technologies and strategies were established to discover and validate drug candidates for DR. The two primary strategies are experimental techniques and computational methods [10]. There are only a few repurposed drug candidates were found serendipitously. Most repurposed drugs are ultimately identified through hypothesis-driven approaches.

Experimental strategies

Binding assays and phenotypic screening are the two methods to identify binding interactions and discover lead compounds from essential libraries. The binding assays detect the interaction of protein to protein, small molecule, or nucleic acid. In combination with high throughput screening techniques, the binding assay maximizes identifying the protein or molecules associated with previously known drugs. It creates the hypothesis and rationale for the new indication selection [2].

Computational strategies

Computational strategies play an essential role in drug discovery by effectively analyzing bioinformatics systems and network biology. Computational approaches are typically used to analyze massive data involving genetic and proteomic profiling and chemical structure [16]. Multiple computational models and platforms have been developed for drug discovery. The latest computational methods can primarily utilize the preclinical and clinical datasets to explore any drug's pharmacological activity, possible toxicity, and efficacy for new indications. Similarly, machine learning (ML) techniques have been applied to predict the potential therapeutic of drugs for different diseases based on their commonalities [17].

Experimental and computational strategies facilitate the identification of new indications of repurposing drug candidates. However, drug safety and efficacy assessment in clinical trials are required. The clinical study design, including patient population and endpoints selection, remains critical for the RD market approval. We previously showed the surrogate endpoint benefits in drug development, including shortening study time and reducing the study cost [18]. Due to the better understanding of the drug characteristics in RD development, the surrogate endpoints are more likely to be accepted by the regulators in the clinical trials of repurposed drugs than in the de novo drug development.

Regulatory pathways for repurposing drugs

Over the recent years, DR has gained an increasing interest. However, repurposed drugs may fail market approval because of an inaccurate implementation of the regulatory FDA guidelines [19] or the EMA Hybrid guideline [20].

The 505(b)(2) pathway allows for an accelerated path to market approval for DRs, which the Hatch-Waxman Amendments established in 1984. The 505(b)(2) pathway supports avoiding unnecessary duplication of data generation at many steps of drug development. The 505(b)(2) path allows for the adoption of the existing data and relevant information generated by external resources (i.e., the de novo drug sponsor). Therefore, the 505(b)(2) pathway allows cost and time saving and accelerates product development. Furthermore, the 505(b)(2) pathway also benefits patient care [19].

The number of approved drugs through the 505(b)(2) pathway had dramatically increased from 19 in 2003 to 68 in 2020. In addition, the proportion of 505(b)(2) approval reached 56% among all the FDA approval in 2019, indicating the critical role of DR in the drug development panorama (US FDA. NDA and BLA calendar year approvals [21].

In preparing a 505(b)(2) submission, there are highly recommended scientific considerations of differences between the proposed drug and the previously approved drug. Additional preclinical and clinical studies may be required if the repurposed drug differs from the approved de novo drug in its dosage form, route of administration, strength, or active ingredient [22]. Finally, excellent knowledge, usually obtained from the de novo marketed drug package insert, is required.

A dedicated European regulatory guideline for drug repurposing is unavailable. The equivalent of the 505(b)(2) application is the hybrid application consistent with a combination of old and new drug developing data. Indeed, the hybrid application relies on the original data source for many aspects of the new application. In addition, it requires clinical studies to evaluate the new formulation and therapeutic indication [20].

Examples of Europeans-approved repurposed drugs are 1. Baclofen initially approved for muscle spasticity, later showed effi-

cacy in treating alcohol-related disorders. In 2018, it was approved by the National Agency for the Safety of Medicines and Healthcare Products (ANSM) in France [23]; 2. Thioguanine was initially developed and approved for the treatment of leukemia in the 1950s. It was further investigated for the treatment of inflammatory disorders due to its immunosuppressive effects. Recently, thioguanine was successfully repositioned as rescue therapy for inflammatory bowel disease (IBD) in the Netherlands [24].

Benefits of hiring an expert consultant

DR offers a shortened timeline and cost-effective drug development, from identifying repurposing drugs to selecting the orphan indication and the clinical trials. Thus, it drives interest from pharmaceutical companies and investors. Despite the barriers and challenges, DR is still a significantly important option of drug development, especially for help with the orphan diseases' unmet medical needs [25]. On the other hand, although the rapid growth of new techniques could overcome the defects and promote the process of marketing approval, professional guidance and fruitful collaborations are critical for the success of the drug repositioning approach (Figure 2).

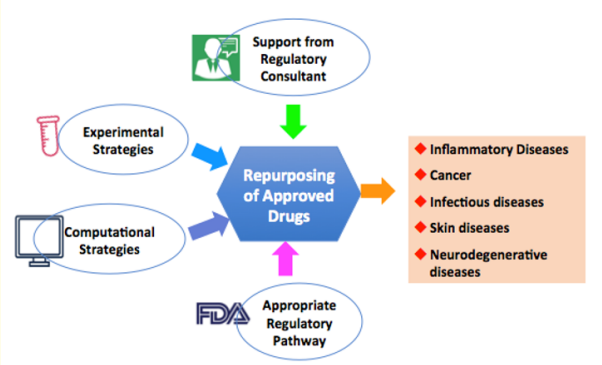

Figure 2: Summary of strategies for target diseases and repurpose drug candidates. Experimental and computational strategies have been applied in drug repurposing. Professional expert guidance of consultants is an essential support for a successful regulatory and clinical DR development plan.

Conclusion

BBCR Consulting has significant scientific and regulatory experience in DR development. We adopt the proprietary Strategic Clinical Innovation Organization (SCIO) method which is an integrative, multidisciplinary approach that allows for time and cost efficiencies, and risk mitigation.

BBCR Consulting offers world-class regulatory, clinical research, and biomarker consulting services that provide high-value and support our clients' operational and functional needs. With the deep knowledge and experience in DR, we believe that the FDA 505(b)(2) and EMA hybrid submission maximizes the benefit for DR development for orphan indications helping patients with rare diseases and healthcare systems.

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