Drug repurposing in rare diseases: Myths and reality

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Summary While nearly 8000 rare diseases have been identified, only 5 percent have licensed treatments. As most of these diseases are life threatening, it underscores the urgent need for new drugs. Drug repurposing (also called drug repositioning) consists in identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication. It represents an opportunity for rare diseases and patients with unmet needs. It is an alternative option in drug development and is often presented as being a viable, risk-managed strategy for pharmaceutical companies developing orphan drugs. Drug repurposing is presented as offering various advantages over developing an entirely new drug for a given indication: fewer risks, lower costs and shorter timelines. However, matters are not as simple as this. There are notable successes for drug repurposing. Nevertheless, repurposing does not always succeed. The repurposed drug may fail to demonstrate a benefits-harms balance in clinical trials. Moreover, there are legal and regulatory issues which are specific barriers to drug repurposing and which have to be carefully analyzed before any development of repurposed drugs. The objective of this article is to identify major challenges and opportunities of drug repurposing in rare diseases and to separate fact from fiction.

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Abbreviations

\begin{itemize}
  \item ALS amyotrophic lateral sclerosis
  \item APIs active pharmaceutical ingredients
  \item BCC business communications company
  \item HD Huntington disease
  \item PUMA pediatric-use marketing authorization
  \item R&D research and development
\end{itemize}

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Introduction

The discovery and development of entirely new medicines (known as de novo drug development) is an expensive, time-consuming and risky process. The total average cost ranges from $2 to $3 billion and the total development time takes at least 13—15 years. Further, it suffers from a high attrition rate; of the drugs entering phase 1 clinical trials, only 10% are approved, the rest failing due to adverse drugs reactions or inefficacy [1]. Drug repurposing has been proposed as an alternative strategy to develop new therapies that has fewer risks, lower costs and shorter timelines than developing completely new drugs [2]. It is increasingly becoming an attractive proposition.

According to business communications company (BCC) research, the global market for drug repurposing is estimated to reach $31.3 billion in 2020, growing from $24.4 billion in 2015 at an annual growth rate of 5.1% [3].

Key benefits of drug repurposing

Drug repurposing is also known as repositioning, repurposing, re-tasking, rediscovery, rescue.

All these expressions are relatively synonymous for describing the same process that seeks to discover new applications for an existing drug/compound that was not previously referenced and not currently prescribed or investigated. Some authors distinguish between repurposing and repositioning, drug repurposing refering to the use of existing approved drugs for new indications, while repositioning involves the development of an existing, previously evaluated but unapproved active pharmaceutical ingredient for the treatment of a different disease [4]. Drug repositioning may also be defined as a process when new biological effects for known drugs are identified, leading to recommendations for new therapeutic applications [5]. Finally, drug rescue has also been used to highlight that the drug has failed for its primary indication [6]. A PubMed search focused on titles and keywords of articles published since January 2019 highlights the preponderance of drug repurposing over drug repositioning without any particular distinction. Given the disparity and inconsistency of terminologies and classifications in the literature [7] and for consistency, this article will refer to all terminologies as drug repurposing. Repurposed drugs are generally approved sooner (3—12 years), at reduced (50—60%) cost and at lower risk: approval rates for repurposed drugs are close to 30% [8]. Indeed, the starting point is a compound for which key characteristics in humans — particularly its safety profile and its pharmacokinetic properties — are already well understood. It refers to both approved drugs and compounds shown to be safe in phase 1—2 trials but that never reached the market for reasons unrelated to safety [9]. This means that it may be possible to move straight to clinical trials for a new indication, bypassing the costly and lengthy discovery and early-stage development research that is needed for completely new drugs [2]. The regulatory and phase III costs may remain more or less the same for a repurposed drug as for a new drug in the same indication, but there could still be substantial savings in preclinical and phase I and II costs. The costs of bringing a repurposed drug to market have been estimated to be US$300 million on average, compared with the estimated cost of around $2—3 billion for a new chemical entity [6].

Drug repurposing in rare diseases

Drug repurposing may be particularly attractive for the development of treatments for rare diseases.

Almost 8000 rare diseases exist worldwide, affecting approximately 350 millions people. Nevertheless, only 5% receive a specific authorized or licensed treatment. Only 112 orphan drugs were available on the European market in July 2017, of which almost half were for rare oncology diseases, whereas more than 450 are under development [4]. As the majority of rare diseases are life threatening, these facts further underscore the need for new drugs. The de novo drug development may be complicated for this huge number of rare diseases with the current research and development (R&D) costs, timelines and risks and there are potentially notable advantages of drug repurposing over the traditional de novo drug discovery process. Using existing active pharmaceutical ingredients (APIs) to validate the biochemical pathways and facilitate the discovery of new compounds can really speed the development of drugs for patients with no current options. Furthermore, there are approximately 2800 drugs and more than 4000 compounds that have been discontinued at Phase II clinical development, providing a rich pool of possible therapies for patients with rare diseases [10]. Development costs may be reduced when starting a clinical trial of a repurposed drug in a new indication. For example, repurposing of the emergency contraceptive, mifepristone, for Cushing’s syndrome required a cohort of less than 30 patients to test its efficacy, whereas a clinical trial for the same indication evaluating the efficacy of a new chemical entity, levoketoconazole, required ∼ 90 individuals [8]. This reduced number of patients in the clinical development process is of paramount importance for rare and especially ultra-rare diseases.

Risks associated with drug repurposing

However, drug repurposing presents several often underestimated risks and may be a really challenging pursuit. While there is compelling evidence supporting its interest in rare diseases, it does not always succeed. Drug repurposing may be in some cases an expensive, time-consuming and risky process as compared to the de novo traditional drug development one. Risk is analogous to that for any new drug, late-stage failures may happen in the development and some specific reformulations may be as expensive and costly as for a de novo drug development.

First, new drugs and repurposed drugs undergo the same approval process with the same quality, efficacy and safety concerns. Like any new drug, a repurposed drug may fail to demonstrate a benefits-harms balance in clinical trials that would support regulatory approval for the new indication. Even if the safety profile is already well understood - as for drugs that have been on the market for some time - differences in the benefits in the new indication may affect the overall benefits-harms balance [2]. Again, like
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for any new drug, market access for the new indication will depend not only on regulatory evidence of quality, efficacy and safety, but also on health technology assessment based on comparative clinical efficacy and cost effectiveness. Pricing and reimbursement assessment may vary across European countries. In a paper published in 2017, authors have noticed that time-to-market for repurposed drugs versus new drugs was longer in some analyzed countries; that is, 979 days versus 462 days in Italy, 502 days versus 350 days in France, and 624 versus 378 days in Spain [4]. In addition, while repurposed drugs have globally a higher success rate from development to approval than novel drugs (30% vs. 11%), there are also examples where drug repurposing failed in late-stage development [6]. Latrepirdine had originally been developed and marketed as a H1-antihistamine for the treatment of skin allergy and allergic rhinitis. It was repurposed as an effective treatment for Huntington disease (HD) following preliminary reports showing its neuroprotective functions and ability to enhance cognition in animal models. However, latrepirdine failed to show efficacy in phase III trials in HD patients following encouraging phase II trials [11]. Similarly, ceftriaxone, an approved beta-lactam antibiotic and a third-generation cephalosporin with good central nervous system penetration had been shown to have neuroprotective properties in a number of neurological disorders, including amyotrophic lateral sclerosis (ALS) by increasing glutamate transporter expression. However, it has failed to show clinical efficacy in ALS phase III study despite promising phases I and II data [2—13].

Repurposed drugs may not only require additional clinical development in other disease areas but also additional pharmaceutical development when new and different formulations are necessary.

New patent protection can be obtained for new formulations that allow new routes of administration for known drugs and drug developers apply such successful strategies to bring repurposed drugs to market. However, depending on the intended route of administration, the nonclinical evaluations needed to assess the safety of the new route can be costly and extensive. Reformulation for respiratory delivery, for example, has strict constraints as regards technical, clinical, legal and regulatory requirements [14]. To begin with, the chemical form of the molecule itself may need to be custom-tailored for delivery to the respiratory tract, which is physiologically and biochemically different from the gastro-intestinal route or other delivery sites. Then, there is a need to conduct studies to demonstrate efficacy and safety. And there is also a need to develop and study the product together with the intended delivery device. In such cases drug repurposing may turn out to be as expensive, time-consuming and risky as the traditional development process.

Legal and regulatory challenges

Although there are drug repurposing success stories and good rationale for that, drug repurposing is not as widespread as expected. Companies do not always see a worthwhile return from investing in the research and development work to gain regulatory approvals for repurposed drugs [2]. There are both legal and regulatory barriers to drug repurposing that may explain it [6]. On one hand there is a lack of regulatory incentives, formal approach or guidance and on the other hand patent considerations are a real issue for drug repurposing. Indeed, repurposing may refer either to an old drug for which patent protection has expired and for which cheap generics exist or to an approved drug (or investigational drug) that has a limited remaining patent life and/or for which there is no interest of further development in a rare disease from the IP owner. In all cases, such issues need to be considered and addressed as early as possible. Composition of matter claims are considered to be among the most powerful patent claims and refer to newly synthesized chemical compounds or molecules. Repurposed drugs are, by definition, known to the scientific and medical communities. Consequently, there is theoretically no opportunity for gaining intellectual property for composition of matter. Another patent protection would be to focus on new methods or uses of existing compounds, but such claims may be often viewed as insufficient to offset the financial risks [15]. In any case, they are not so easy to support. Drug repurposing can be protected from a legal point of view through "new use patent", also called "second medical use patent". In order to obtain such a patent claim, specific conditions should be met: the new use must be supported by evidence; novelty and inventiveness over the previous use have to be established [16]. It is often complicated for the manufacturer to enforce such new use patent and protect the new market for drugs with known off-label use. If a generic is already marketed for the first indication, it is very difficult to prevent prescription/delivery of the generic for the new indication [2]. In fact, off-label prescribing of medications is legal [17] and physicians prescribe drugs for an unapproved indication up to 20% of the time [18]. The pharmacist dispensing the prescription cannot differentiate effectively between patented and unpatented uses. Moreover, the systems of many countries provide a financial incentive to the pharmacist who is encouraged to (or must) dispense a cheaper generic drug when available [2]. Fortunately, such legal and regulatory barriers are not totally insurmountable for repurposed drugs. They need to be considered and addressed at the earliest development planning stages in order to be better solved. Ways of maximizing chances of patentability do exist: by developing new formulations, new dosage forms, new routes of administration, newer derivatives or combinations. Although a robust patent protects against competitors, regulatory exclusivities may also provide ample protection to repurposed drugs especially in case of new indications in a pediatric population or for an orphan disease.

Repurposed drugs may obtain market exclusivity in case of orphan drugs. The introduction of the US and the EU Orphan Regulations in 1983 and 2000 respectively has been successful in making drugs for rare diseases commercially viable, giving incentives associated to orphan drug status, principally the 10-year market exclusivity (plus 2 years for pediatric indications) in the EU and 7 years under the Orphan Drug Act in the US. In the EU, incentives associated with orphan drug status have facilitated the development of 127 orphan drugs to date. About 1 in 5 orphan drugs are repurposed [19].

Repurposed drugs may also obtain market exclusivity resulting from the use of a special marketing
authorization called pediatric-use marketing authorization (PUMA) introduced by the European Pediatric Regulation. The PUMA process was implemented in 2007 to encourage research into pediatric medicines [20] in the face of widespread off-label use of drugs in children with little supporting clinical evidence. A PUMA may be requested for a medicine which is already authorized, but no longer covered by intellectual property rights (patent or supplementary protection certificate) and which will be exclusively developed for use in children. If a PUMA is granted, the drug product will be granted 10 years of market protection [21]. The first PUMA was granted in September 2011 to Buccolam® (midazolam) which received a marketing authorization for the treatment of prolonged, acute, convulsive seizures in pediatric patients from the age of 3 months to 18 years [22].

Buccolam® was formulated as a pre-filled solution delivered through the lining of the mouth so that dosing could be tailored effectively to pediatric use to avoid confusion with formulations designed for adults.

**Conclusion**

Repurposing drugs represents a good opportunity to find treatments in the field of rare diseases. Its use however is not so widespread as expected despite the obvious benefits. There are remarkable success stories but there are also bitter failures. It is essential to separate myths from facts.

Although presented as offering notable advantages such as cost effectiveness and shortened timelines, drug repurposing may also be expensive, time-consuming and risky. Furthermore — and most importantly — there are legal and regulatory barriers which have to be taken into account. As all these limitations are for some of them not insurmountable, drug repurposing remains a promising field but it needs better incentives, structured guidelines and support.

**Disclosure of interest**

The authors declare that they have no competing interest.

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