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The Benefits and Pitfalls of Repurposing Drugs

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INTRODUCTION

It has been estimated that it costs approximately US$1 billion to bring a drug from the laboratory to market and takes about 10 years on average[1]. However, when the costs of failed projects are taken into account, the real cost rises to about US$2.6 Billion[2].

Taking the stagnant productivity in major pharmaceutical companies, lengthening timelines to get to market and pressure on revenues from generics as patents begin to expire, the interest in drug repurposing has grown significantly. Drug repurposing, also referred to as repositioning, allows biopharmaceutical companies to reduce the time, risk and cost[3] .

For a marketed drug, the major appeal is a faster, less risky and less costly (less resources) clinical development as the approved product has already met pharmacovigilance and regulatory requirements, and undergone post-market surveillance[4].

The various organizations focusing on drug repurposing range from biopharmaceutical companies to non-profit organizations, government divisions, and academic institutions (Bloom, 2017). Indeed, patient support groups are also engaging to an unprecedented level in repositioning to find and develop new therapies for rare diseases[5]. In addition, there is a great interest in repurposing inexpensive, generic drugs that bring the promise to extend the lives of cancer patients[6].

Drug repurposing of existing Active Pharmaceutical Ingredients (APIs) refers to the process of identifying novel uses or therapeutic properties for the original product[4]. These APIs in their original formulations may have failed to show sufficient efficacy in clinical trials or been halted in development for commercial or safety reasons[7].

Despite the fact that drug repurposing has been taking place since the early 1990's[3], there is still no clear definition for a repurposed drug from the regulatory point of view[8].

APPROACHES TO DRUG REPURPOSING

Some repurposed drugs have been found by accident[9] while for others, a more recent understanding of basic biological processes has enabled the discovery of new mechanisms of action for existing molecules or identifying relevant existing targets in a new disease.

There are clear regulatory procedures for developing repurposed drugs. The FDA's 505(b)(2)[10] new drug application pathway allows the approval of a new drug when a product contains similar active ingredients to a previously approved drug. In 2016 the number of 505(b)(2) drug approvals reached a 13-year high of 48[11]. The EU has a similar regulatory approval route (Article 10, Directive 2001/83/EC). In practice, the late-stage trials, the most expensive part of clinical development, apply to a repurposed indication[12].

Drugs have generally been shown to not possess an absolute selectivity of drug action and, as a result, many drugs have the potential to work against more than one disease[13].

The development of a drug for repurposing can be considered to run through two core approaches: 'on-target' and 'off-target', where the target can be defined as a gene, a protein, an enzyme, or a chemical in the body[4, 14]:

1. On-target → new use based on the same mechanism of action of the molecule
2. Off-target → new use based on a different mechanism of action of the molecule

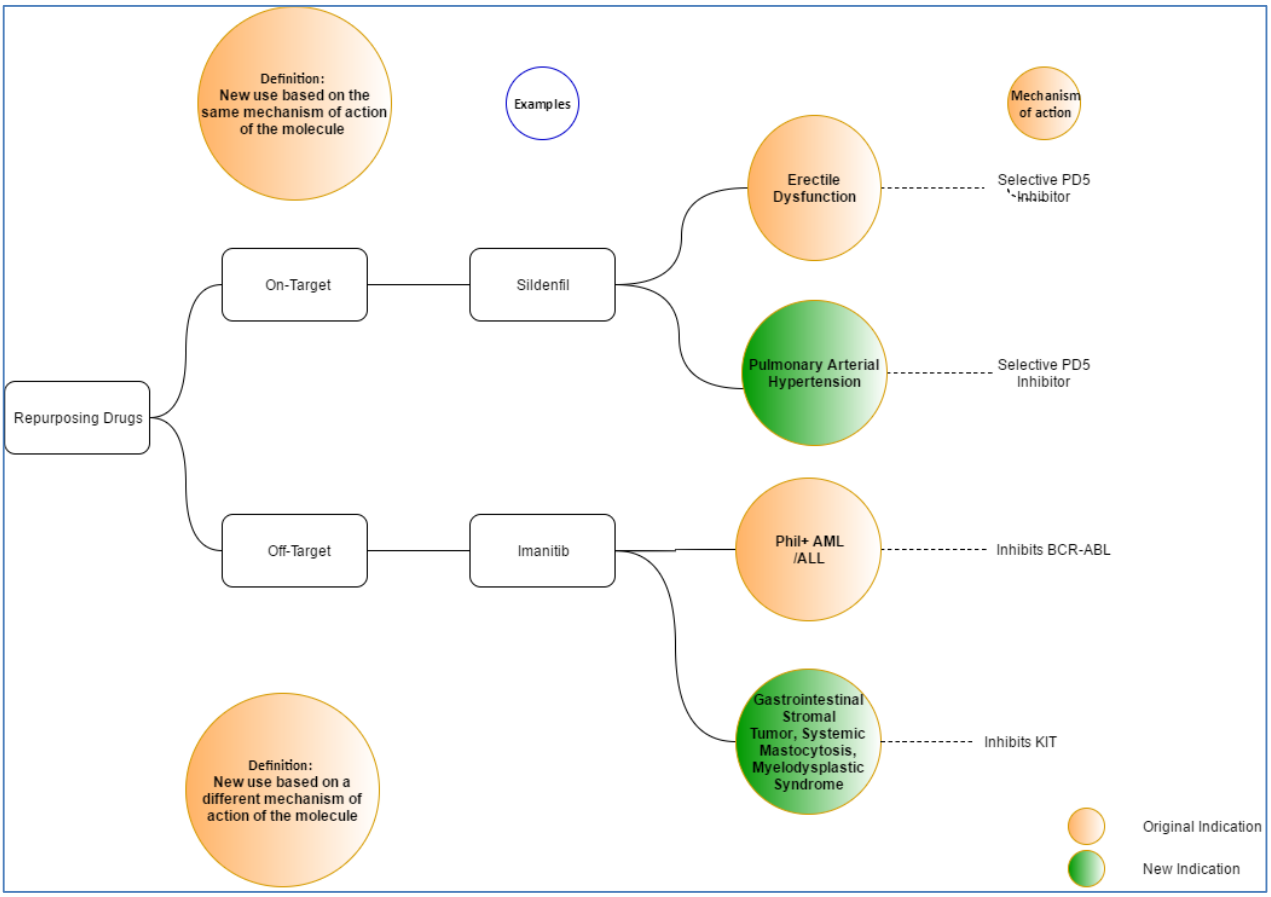

Figure 1: Examples of On-target/Off-target repurposed drugs

As a proportion, approximately 80% of drug repositioning efforts have, to date, used the on-target approach[3, 15]. However, the Human Genome Project has increased the number of known drug targets to close to 6000 potential targets, thus increasing the opportunities to create drugs for diseases[16].

The first challenge of drug repurposing is to identify off-patent molecules including those that have failed to reach the market. According to statistics from DrugBank[17], globally the total number of approved drugs is 2254 out of over 7800 drugs recorded.

These molecules are obviously particularly attractive for repositioning when their toxicology packages, pharmacokinetic and safety data, formulations and manufacturing methods are in place and up to date[18].
New technologies enable the *systematic evaluation* of any drug or mechanism of action against any disease or adverse event[19]. There are now several new strategies that can be used to identify drug candidates for repurposing[4]:

- Screening of published libraries of pharmacological, biological, and chemical data to identify new links between a drug bioactivity, target, and disease through text mining and bioinformatics
- Re-screening known drugs against an array of disease-relevant targets that were previously unknown at the time of the original indication
- Combining a known interaction between an existing drug and a specific target with new knowledge about the target's role in a new indication
- Taking an agnostic approach by screening existing drugs to discover new uses for both on- and off-target effects

These strategies can help to identify potential candidates for further laboratory testing but the efficacy and safety in the new indications have still to be studied in the clinical setting.

With the advancement of these strategies, aided by computational tools and phenotypic screening, the development of repurposed drugs is set to progress faster, more efficiently and less costly than with traditional screening.

KEY BENEFITS OF DRUG REPURPOSING

Saving in Cost : It costs approximately US$300 Million to bring a repurposed drug to market representing a saving of about 85% compared to the US$2.6 Billion for a new drug if the cost of failed projects is taken into account[1, 3].

Saving in Time: While appropriate studies are still required to obtain regulatory approval, the duration of the discovery phase for a repurposed drug is shorter as safety and toxicology studies have already been assessed in the original indication.

Other Benefits: A significant number of drugs are being repurposed for rare diseases or conditions which leads to many developers being attracted by the incentives associated with obtaining orphan drug designation. Both the FDA and EMA provide incentives to encourage research into these conditions as, without these incentives, the small numbers of potential patients would mean that they would be less commercially viable.

Orphan Designation Status Related Incentives

Incentive	EMA	FDA
Protocol Assistance	Yes	No
Financial Incentives		
Fee Reduction in product development	100% fee waiver for SMEs, 40% for non-SMEs	No
Tax credits	No	Equal to 50% of clinical trials
Marketing Application User Fee Waiver	No	Yes
Marketing Exclusivity if first approved	10 years (+2 years with endorsed PIP*) following market approval	7 years following market approval
Rare Pediatric Disease Priority Review Voucher	No	Yes

Source: Worldwide Orphan Medicinal Designation Workshop, 10 March 2014[20]. PIP: *Paediatric Investigational Plan

However, even if the drug does work, there is no guarantee of reimbursement. It is therefore essential that biopharmaceutical companies establish a clear strategy for pricing and market access from inception of drug development.

In addition to a lower cost of clinical trials and a shorter development time, drug repurposing is associated with a higher success rate from Phase II to launch[3, 18, 21].

LEGAL IMPLICATIONS ASSOCIATED WITH REPURPOSED DRUGS

❖ Patents and Intellectual Property Rights

The requirements set out in patent law strongly recommend filing a patent application covering a new drug or treatment process as early as possible[22]. Many different approaches have been used to protect the Intellectual Property Rights (IPR) for the discovery of new indications for existing drugs[3] but all the approaches aim to increase the original patent protection period for the drug.

However, most of the work done in repurposing drugs has been to find new uses for generic drugs, that is, in those whose original patents have expired. There may also be occasions where new mechanisms of action are identified for drugs that are still under patent by the originator company. This leads to two possibilities:

1. Originator company has an existing patent: If a company wants to develop a new indication for a patented drug, it must get permission and/or a licence from the person or company holding the patent.

2. API is no longer under patent: There is no need to obtain permission or license from the originator company, nor do they have any beneficial rights to further development.

❖ Protection of Intellectual Property

As has been said previously, obtaining marketing authorization for an orphan condition is entitled to a period of market exclusivity but how can this be protected? Realistically, the best that can be done is to try and raise barriers to entry through:

- New formulations or modes of delivery
- New dosing schemes
- Having a monopoly on the production of the drug

This may not necessarily be an issue for not-for-profit organizations, but for a company set up to exploit the new indication, it is difficult to see how they can ask for premium prices and also secure their exclusivity, particularly if the product is prescribed generically as against by brand name.

❖ Product Liability

Clearly, when a drug still under patent is marketed and used in accordance with its marketing authorization, any untoward effects not identified in the product's Summary of Product Characteristics (SmPC) in the EU or Package Insert in the United States, or the equivalent elsewhere, would be the responsibility of the originating company. Physicians have always been able to prescribe drugs for 'off-licence' use but it is essential that they obtain prior patient consent as they take on the responsibility for use.

In the case of a company undertaking clinical studies with a view to obtaining marketing authorization, various EU Directives insist that there must be valid and sufficient indemnity insurance (European Directives (2001/20/EC and 2005/28 EC)).

In the case of drugs that are no longer under patent and are being manufactured by a number of generic companies, provided that the drugs are used correctly, these companies have no liability vis-à-vis the patients. However, recently in the US, GlaxoSmithKline were held liable in a case where a patient committed suicide while taking a generic version of paroxetine. The label indicated that suicide risks stop at age 24 and the court ruled that GSK continued to hold a responsibility to inform of the risks beyond this age. Since the original label is maintained with the generic drug version, GSK was held liable for a faulty information in the package insert[23].

PRICING AND REIMBURSEMENT

The issue of pricing of drugs has recently raised a great deal of controversy and none more so than that for repurposed drugs.

Emflaza (deflazacort) from PTC Therapeutics (previously Marathon Pharmaceuticals) gained marketing authorization in the US for the treatment of Duchenne muscular dystrophy (DMD) subjects over five years old regardless of their genetic mutation[24]. While deflazacort has been used off-label to treat DMD for over 21 years, the developers presented decades-old efficacy data to secure approval and promptly raised the price from $1000-2,000/year to $89,000/year when they obtained marketing authorization[25].

Daraprim (pyrimethamine) which was originally developed for malaria was found to be effective in toxoplasmosis and pneumocystis pneumonia when used in conjunction with other drugs. Pyrimethamine which is on the World Health Organization's List of Essential Medicines, was not available as a generic medication in the United States but in 2015 when Turing Pharmaceuticals obtained marketing authorization, the price was increased from $13.50 to $750 a tablet ($75,000 for a course of treatment).

The pricing of repurposed drugs therefore comes down to two options:

- Not-for-profit: In these cases, the need for profit has been removed and the aim is to simply develop the clinical data to support the use of a generic drug for the new indication and if successful, eventual use off-label with no attempt to manipulate the price.

- Commercial: In the ideal world, the value of a medicine will depend on the unmet patient need, the existing standard of care, and the individual healthcare system. In reality, other, more commercial, factors come into play such as return on investment and shareholder value.

A fair price should be a price that assures that new medicines are affordable to all patients and health systems, allows for a reasonable profit margin, and assures a stable supply. However, in the case of repurposed drugs, where the additional clinical work required to establish a new indication is less than that required for a novel drug, a different approach is needed to understand what constitutes a fair price and how a framework could be developed to define that price.

For patented medicines, the WHO Advisory Group recognizes that medicine prices must be sufficient to cover R&D investment, including the costs of medicines that fail to secure final approval. In the case of repurposed drugs, because of their well-known safety characteristics, the risk of failure has largely been reduced.

The application for orphan drug designation and ultimately marketing authorization provides one potential business model. Apart from the benefits derived from protocol assistance, reduced fees or tax credits, depending on the locality, the market exclusivity provides a period to recover the investment. However, the current system may encourage companies to redefine and artificially create orphan designations, contributing to the proliferation of orphan drugs[20].

For example:

- an existing medicine already in widespread use for one indication may be repurposed and receive orphan drug approval to treat a rare disease
- manufacturers may secure a series of orphan drug approvals for indications that are for a sub-group of a larger patient population
- manufacturers may encourage the off-label use of orphan drugs

Orphan and anticancer drugs generally command higher prices than those in the primary care sector making these areas of particular interest.

CONCLUSIONS

Drug repurposing is largely no longer dictated by serendipity but by science and the undertaking of a strategy for drug repositioning can be complex and requires expertise across many disciplines involved in drug development[3]. In addition, access to potential compounds and the availability of accurate scientific and clinical data are essential.

Having determined the disease area of focus, developers must prepare a clear strategy which includes disciplines from intellectual property rights to commercialization, as appropriate.

Ideally, study designs of clinical trials and patient selection should be innovative and be able to capture patient outcomes and therapeutic effectiveness. Clinicaltrials.gov. and the EU Register of Clinical Trials, as well as patient advocacy groups, may be useful to identify the latest developments in these fields.

The possibilities associated with seeking and obtaining orphan drug designation can confer a range of benefits including protocol assistance and reduced fees and/or tax credits, but perhaps most importantly, varying durations of market exclusivity the length of which depending on geography.

In summary, drug repurposing has several potential benefits including shorter development time, reduced costs, regulatory support and possible market exclusivity in the case of drugs obtaining marketing authorization for orphan conditions. However, it is essential that the pricing and reimbursement strategy is considered early in the process, particularly where the price is likely to be high in rare conditions and cancer.

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