

# The repositioning revolution: save me from extinction to find me pastures new

Cost containment and improving ways of treating people are key drivers for healthcare systems. Unfortunately, these do not often go hand in hand. Finding novel therapeutics with enhanced efficacy is both time consuming and costly – and offers low rates of success in relation to effort expended, in terms of time that needs to be invested.

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**R**epositioning drugs provides alternative routes for bringing drugs to market. This includes both repurposing and rescuing drugs. Repurposing drugs is the study of small molecules or biologics already approved for one disease or indication to investigate whether they may be suitable for treating other diseases. Rescuing drugs is studying molecules that have previously been through some clinical trials but for some reason have not been submitted for approval as a drug.

Drug repositioning is supported by a couple of scientific concepts. One is that a single drug interacts with multiple targets; the other is that targets associated with one disease or biological process are often relevant to a number of biological processes. There are, therefore, two main approaches for repositioning. One is having a known compound and new target site of action, the other is a known target and new indication.

In essence, repositioning is not new. Some pharmaceutical companies reposition during the early stages of development, as they recognise that bio-

logical systems overlap and researchers share compounds, and libraries of compounds, that fail in one disease with researchers working on other areas. This recognises the fact that a side effect in one disease could be the disease indication in another.

Additionally, serendipitous clinical effects have, and continue to be, a significant source of repositioned drugs. Indeed, this was true for one of the most famous repositioned drugs – Viagra®. It was originally on trial as the active Sildenafil for angina and hypertension. However, Phase I trials revealed more than the researchers had bargained for, and the drug was eventually approved for erectile dysfunction.

Repositioning drugs has grown in recent years – a trend that is predicted to continue – with notable activities occurring. Dedicated conferences such as the World Drug Repositioning Congress and the Drug Repositioning & Indications Discovery Conference did not exist a few years ago<sup>1</sup>. Significant government changes have also occurred, encouraging researchers and drug companies alike to make more out of existing

therapeutics or molecules that may have hidden beneficial effects.

In 2011, the National Center for Advancing Translational Science (NCATS) became the latest NIH center. Its aim is to transform the translational science process to get new treatments to patients faster. It encourages broad collaborations focused on what is common across diseases and the translational process, rather than targeting particular diseases and fundamental science.

In May 2012, NCATS created the Discovering New Therapeutic Uses for Existing Molecules programme. This is a pilot programme aimed at developing partnerships between pharmaceutical companies and the research community. Its aim is to advance the development of new therapeutics from existing molecules that have already undergone significant research and development by industry, including early clinical trials.

The programme is a direct result of a 2011 NIH-Industry Roundtable Workshop and matches NIH-funded researchers with specific pharmaceutical compounds to explore new treatments for patients. AbbVie, AstraZeneca, Bristol-Myers Squibb Company, Eli Lilly, GlaxoSmithKline, Janssen Research & Development, Pfizer and Sanofi provided 58 compounds for the pilot programme. In June 2013, following the NIH challenging its research community to come up with ideas for new uses for the molecules, nine projects in eight disease areas, including Alzheimer's and schizophrenia, worth close to \$13 million, were awarded by the NIH.

The 505 (b)(2) route for drug approvals from the FDA is another great example of the push towards developing products that have significantly lower development costs but provide new and improved treatments for niche markets. Filing an NDA under the 505 (b)(2) route allows for at least some reliance on earlier findings for the safety and effectiveness of the previously-approved drug, hence simplifying the development pathway and making the development less expensive and potentially faster to approval. Such drugs can be developed in as little as 30 months and, unlike generic drugs that have to follow the 505 (j) route, where exclusivity only lasts for 180 days, approvals through 505 (b)(2) can command three, five and sometimes up to seven years' market exclusivity.

To further emphasise the push for new drugs sooner, rather than later, for certain disease areas, the FDA has set out a resource, The Rare Disease Repurposing Database (RDRD). This database contains products that have received orphan status designation and are already approved for the treatment of other diseases. It proposes to offer a useful



tool for finding opportunities to develop niche therapies that are already advanced in their development, ie have preclinical and some clinical safety and efficacy data.

This activity is not just US centric. A recent study investigated the background of the 78 orphan drugs approved in Europe. It highlighted that 38% of these were from drugs repurposed from other indications. Indeed, EMEA has a directive with similarities to the 505 (b)(2); Article 10 of Directive 2001/83/EC, a guideline on 'similar biological medicinal products'.

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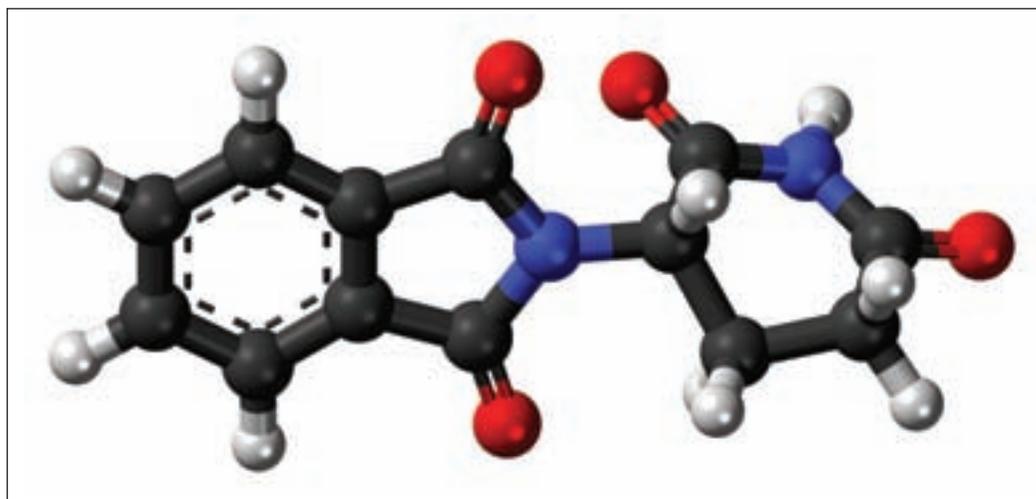
### So why is there such an interest in repositioning?

Depending on what already exists in terms of human trial data, repositioning a drug can reduce the need for certain clinical trials and significantly cut the estimated time of 10-15 years and cost of between \$1 billion and \$2 billion it can take to bring a new drug, based on a new molecular entity, to market. Repositioning is therefore faster and less costly – and also has higher success rates. It is estimated that 10% of new molecular entities get to market from Phase II clinical trials and 50% from Phase III, whereas the rates for repurposed compounds are 25% and 65% respectively.

So the benefits of repositioning are experienced by the pharmaceutical industry, the healthcare systems and patients. For the pharmaceutical industry there are lower development costs and time, potential for patent extension when applicable, longer lifecycle management and lower risk of development. For the patient there is the potential for medical efficacy where none may have previously existed or improved efficacy or therapeutic profile, lower side effects, better scheduling or dosing and the potential for lower costs than existing therapies. Healthcare systems experience some similar benefits in the potential for lower costs, servicing unmet patient needs and a faster safety approval process resulting in more and improved ranges of drugs to treat patients.

With all this positive encouragement for repurposing and rescuing drugs, why isn't every pharmaceutical company chasing these opportunities rather than new chemical entities or generic products?

For some large pharmaceutical and generic companies, the economies of scale are just not there for these programmes as these often result in niche products to treat niche indications – particularly when considering repurposing old drugs for new indications. In addition, the ability to extend IP or gain patent protection does not always provide the runway length of exclusivity large pharmaceutical companies are geared towards. While the price per dose or treatment cycle can be relatively high, a point that also needs to be discussed, the volumes of sales are sometimes just not significant enough for some of the larger companies to manage as they are often set up to market drugs globally, to vast numbers of patients, rather than through tighter networks of key opinion leaders. Historically and culturally, the way some of the large pharmaceutical companies are structured does not support repositioning as they are, in essence, very entrenched in new drug discovery and focus less on cross-disciplinary and translational approaches.



S-Thalidomide 3D balls

This does not mean that large pharmaceutical companies are not engaged in this activity. As previously mentioned, they can be involved in repositioning during the early stages of drug development. The recent interactions by a number of large pharmaceutical companies through the NCATS programme is also proof of their growing interest in this activity. Large pharmaceutical companies seem to lean more towards drug rescue than repurpose, with a strong focus on their own pipeline, to see what they may be able to recoup from efforts already expended.

Medium-sized specialty pharmaceutical companies are more likely to focus on repurposing drugs and there are an increasing number of these focusing activities on just this. It is also possible, however, that – depending on the indications that result – they may team up with large pharmaceutical companies for marketing activities or specialist orphan drug companies.

The price point obtained by some of these repurposed drugs is a thorn in the side of this otherwise obviously progressive and efficient use of drugs in an ever-dwindling pool of novel molecular entities. This is often a point of discussion concerning rare indications. Debate is centred round the fact that the use of repurposing utilises significantly lower costs of development, however many of the drugs that hit the market as a result often have astronomical price tags that, it is argued, significantly outweigh the cost of investment. In many cases the pharmaceutical form of the drug is the same, original data concerning effectiveness of the drug for that rare indication has been published prior to gaining orphan designation. There are cases where the price difference can be anything between 23 and 56 times the price of the original drug<sup>2</sup>.

Arguments obviously go both ways, and some of the indications can be so rare, with such few numbers of individuals, that the high prices per dose are needed by the pharmaceutical company providing the medication. This is not so much in terms of covering the cost of development but due to the lack of economies of scale afforded by high-volume drugs for more common indications.

### What are some of the notable success stories?

#### Thalidomide: scourge to cancer therapy

Perhaps the best known example of repurposing is for thalidomide; the notorious drug that was launched in the late 1950s, turned out to be a teratogen and was taken by pregnant mothers to ease morning sickness. The drug caused foetal deformities, many fatal. The consequences of the thalidomide scandal resulted in changes to the processes by which drugs are approved and prescribed.

For a period of time thalidomide surfaced as a treatment for erythema nodosum leprosum – a complication of leprosy. However, because of the need to carefully monitor its usage and the requirement for women who were prescribed the drug to take two forms of contraceptive measures, its use is not recommended by the WHO. More recently, Celgene has found new uses for thalidomide in the treatment of newly diagnosed multiple myeloma.

#### Foscavir®: new procedures enable new uses

AstraZeneca obtained approval in 1991 for the antiviral treatment Foscavir® (foscarnet sodium) for use against cytomegalovirus (CMV) retinitis and acyclovir-resistant mucocutaneous herpes simplex virus in patients with immune deficiencies. However, as the usage of the highly successful

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HAART therapy in AIDS patients was widely adopted, there has been an 80% reduction in CMV infections which resulted in a low usage of the drug.

Interestingly, medical advances have given FoscaVir® a new opportunity; it has been used off label for the treatment of CMV in human stem cell therapy patients in the US, Europe and Japan. This is not a blockbuster opportunity but a small significant need. AstraZeneca transferred ownership to Clinigen, which has not only breathed new life into this drug but has gained approval in Japan for an indication for the treatment of CMV in haematopoietic stem cell therapy (HSCT) patients.

### Campath® (alemtuzumab) to Lemtrada: a difficult road

The repurposing of biologics is also an area that is being explored. However, changing the indicated usage of a drug does not always come easily or without collateral damage.

Sanofi generated much negative publicity when, in 2012, it started to withdraw Campath®, a treatment for leukaemia. Why? Not because the drug was ineffective but because it had found a new indication in multiple sclerosis. The challenge was that the dosage in multiple sclerosis was a fraction of that used in treating leukaemia. Hence with Campath® on the market Sanofi would only get a small fraction of potential revenue. Since September 2012, Campath® has no longer been available commercially but provided free of charge to patients who respond to treatment through the Campath Distribution Program.

The European Union approved alemtuzumab as an MS treatment in September 2013. However, in November 2013, although the FDA advisory committee voted overwhelmingly that alemtuzumab (Lemtrada) has been shown to be adequately effective for the treatment of relapsing/remitting multiple sclerosis, the committee considered that Sanofi (Genzyme) had not provided substantial evidence of improvement in disability and raised concerns about the safety profile. The FDA has still to decide on whether to licence the drug but, with a crowded market for treating multiple sclerosis, and with the approval of oral therapies, repurposing Campath® may not be the safe bet it originally appeared to be.

### Glycopyrronium bromide: takes a deep breath

Repurposing may result in other different delivery routes, especially to minimise dosing and reduce side effects – and therefore require drug delivery devices. In 2012, Novartis received European

approval for Seebri® Breezhaler®, a once-daily maintenance treatment for chronic obstructive pulmonary disease (COPD). The active is a glycopyrronium bromide, which originally had a use in pre-med to minimise salivary secretions.

More recently, Glycopyrronium bromide was shown to be a high affinity muscarinic receptor antagonist with a higher selectivity for the human M3 receptors, which are found in a number of locations, including the lungs. Thus if the drug could be delivered locally using a device there would be less potential for side effects. A collaboration between two early-stage companies, Arakis and Vectura, resulted in a successful Phase IIa trial and licensing by Novartis.

### How do companies uncover these potential golden opportunities?

While many companies employ specific activities relating to the mechanism of action of the drug and its targets, understanding the market opportunity for such resultant products is a key driver in deciding to continue with the development of such drugs, not really that different from any other drug development. Thus, ensuring there are clear unmet market needs and a clear commercial proposition are crucial. The competitive environment and the patent landscape are both critical aspects to have clear sight of, as are the potential price points, volumes and growth rates that may be expected.

A further aspect that can sometimes be overlooked is not just how well accepted the drug will be in the market and the potential returns but how well this product will fit with the company that needs to take the drug to market. This could cover aspects including whether the company is able to engage with the physician, or even patient group that needs to be convinced of its appeal, as many of these drugs will be for rare indications. It also covers more practical aspects such as manufacturing-related issues and how well the product ‘sits’ in relation to other products the company is marketing. This indication area could be too far outside the company’s therapeutic franchises to make it a sensible choice from a company point of view, even if the returns look exceptional.

Cambridge Consultants has worked with a variety of companies with regard to locating drugs for acquisition and licensing, aspects of which include repositioning. It uses a number of approaches that help focus decision making concerning which potential drugs to acquire or license to grow a company’s pipeline strategically, in terms of repurposed drugs. It has conducted these projects on significant numbers of potential drug products,

building databases of drugs to search out and select those that will be the most relevant to a particular company's needs. Examples include drugs to be repurposed for delivery through the lung via an inhaled route through a drug delivery company's proprietary inhaler; in addition a broader search for another company involved the need to find drugs that had the potential to be used in different indications in critically essential areas.

### Conclusion

While the leading news in the pharmaceutical industry often concerns the impending patent cliff for blockbuster drugs and the rise of generic competition, there is significant potential available in the world of repositioning. It not only may make sense from a commercial perspective, but also has the ability to open up a wealth of new therapeutics that could service very critical unmet needs in otherwise poorly or untreated areas. Increasing assistance and encouragement from the regulators and governments with regard to this activity is welcome. The more that can be done to find therapeutic benefits of otherwise forgotten or unloved drugs the better.

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