The benefits of drug repositioning

Drugs in development, on the market, or those that are shelved because of lack of efficacy, are excellent starting points for further development. Finding new indications for such drugs will benefit patients who will see a potential new therapy sooner, will maximise their value and will also protect the original IP owner against competitor adjacency moves. Typically, repositioning is done by accident, or in a limited way. New technologies however, enable the systematic evaluation of any drug or mechanism of action against any disease or adverse event.

By Dr Aris Persidis

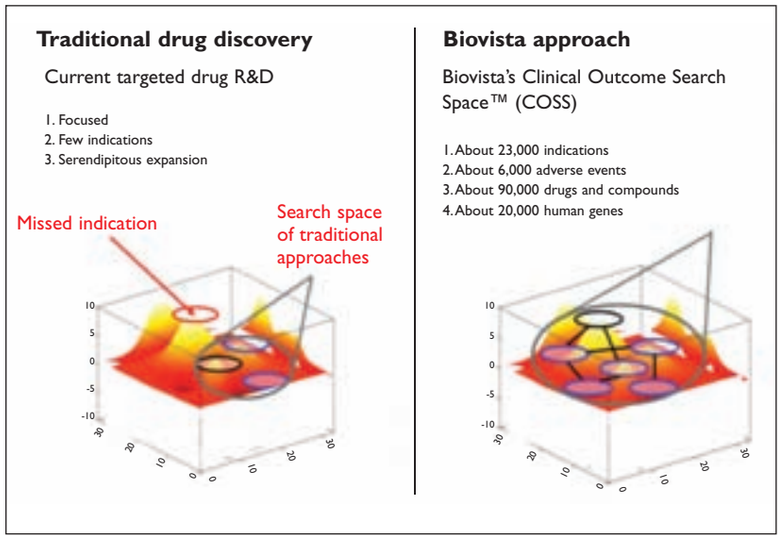
From 2007-09, 30-40% of drugs or biologics that were approved or launched for the first time in the US were either drugs repositioned for new indications, reformulations or new combinations of existing drugs[1]. This is the lifecycle business with repositioning as a major contributor, and it is rarely given much attention outside of its practitioners. Yet, why is it practised, why is it such a big percentage of biopharma approvals and what is its future? How come more than 30% of new market entrants are existing drugs finding commercial success through variations and new uses, and yet this is just recently beginning to be recognised as a high-performance strategy in its own right?

Any business model that relies on product development that takes 10-15 years and costs about $1.3 billion per successful product launch[2] requires constant appraisal and rethinking. How does big pharma make such a model work? To date, the success that this model has enjoyed is the result of multiple shots on goal, meaning multiple drugs entering trials before one makes it all the way to the market: the one that is successful generates enough revenues to fund the attrition of the rest of the portfolio that occurs because of lack of efficacy or because of unexpected safety concerns in clinical trials. The attrition is important to keep in mind, as approximately one in 10 mature preclinical candidates will make it to product launch[3], and hundreds of thousands of molecular library members will need to be screened and developed before the mature preclinical candidates themselves are available for first-in-human studies.

This attrition rate puts tremendous pressure on a drug pipeline since it means that one must assume that failure is the default outcome, given that about nine out of 10 candidates will not be launched. Adding to this pressure is the so-called patent cliff, which vividly describes the more than $100 billion in revenues that are due to be lost in the next few years as patents begin to expire and generic versions of drugs take the place of the original branded forms[4]. The patent cliff and attrition rates are considered to be by-products of a broader R&D productivity and innovation challenge. Multiple authors and commentators discuss specific elements of the R&D process itself, with a view towards improving specific steps that will increase the number of drugs that have a higher chance of success in the clinic, while reducing the overall costs of the effort within a pipeline environment[5].

The specific arguments in favour of drug repositioning as a contributor to pipeline growth and as a defence against generics are simple and potent:

1. The safety advantage. Existing drugs that are either approved or have been shown to be safe in late-stage trials, but have failed to meet end points



of their originally-targeted indications, can leverage their inherently reduced development risk into potentially new indications. They can do so if they can be proven to be effective in the new indications and also sufficiently differentiated against standard of care. When such drugs enter clinical trials, they compete with non-repositioned drugs not in terms of safety, but in terms of efficacy. Since safety accounts for approximately 30% of drug failures in clinical trials, this is a significant development advantage that repositioned drugs enjoy.

2. The money savings advantage. According to a recent report based on a survey of 30 pharmaceutical and biotechnology forms, the cost to relaunch a repositioned drug averages $8.4 million, whereas to relaunch a new formulation of an existing drug in its original indication costs an average $41.3 million[6]. In both cases, the drug has reached the market. The difference between the costs of market attainment for a repositioned drug versus a new drug, however, is simply staggering. Given that the latter averages more than $1.3 billion, successfully bringing a repositioned drug to market seems to cost approximately 160 million times less than the current standard of NCE/NME development. Even if this differential is off by a hundred million or more, from the purely financial perspective, repositioning is in a completely different league of investment needed to create a new drug product in the market.

3. The market potential advantage. Not all drugs are blockbusters, but some that are achieved this status as repositioned drugs. Two excellent examples are Celgene's Thalomid®, which is repositioned thalidomide, and its derivative Revlimid® (lenalidomide). These two repositioned drugs represent a combined global revenue stream of more than $2.8 billion for Celgene[7]. Although one should not assume that such success for a particular repositioned drug will automatically mean the same success for all repositioned drugs, it becomes very hard to argue against the financial potential of repositioning as a strategy. Potential for market success depends on numerous factors, including market need, competition, differentiation, an excellent product, IP barriers, payer acceptance, compliance and a successful market strategy. These factors apply for repositioned drugs in the same way as they do for NCE/NME drugs as well, and it is thus important to remember that there is no inherent property of repositioned drugs that would limit their market potential.

4. The return on investment potential. If it takes an average $8.4 million to launch a successful repositioned drug, and there is no limit to market returns as the Celgene case shows, then all things being equal, the disparity in upfront investment means that repositioned drugs will always represent a better return on investment than NCE/NME drugs. However, exactly like with NCE/NME drugs, it is very important to keep in mind that this should also be a portfolio strategy: it is prudent to have a reasonable stable of repositioned drugs under development as a portfolio, to allow for attrition due to potential lack of efficacy (but not safety), when any drug is tested in clinical trials.

5. The out-licensing potential. Pharmaceutical companies are said to be exploring new models to out-license some of their clinical drug candidates that may have been shelved for whatever reason, even though they have met their end points and have proven themselves to be safe. If such drugs were to be repositioned, then the pharmaceutical company increases the attraction these drugs have, and gives itself more options to find interested buyers. For example, the pharmaceutical company may retain the original use rights to the drug, and out-license the rights to the new indication only. Or, the company may retain the rights to the new indication and out-license the original use if the latter has become a non-strategic one, whereas now the new use falls within the company's areas of interest. With either scenario, repositioning grants a pharmaceutical company specific and novel business development possibilities for out-licensing that it otherwise would not have.

The combination of specific financial advantages, coupled with the realignment of the risk profile of a pipeline that includes repositioned drugs, are the key reasons why pharmaceutical companies look to this strategy with vigorous interest. This is further supported by the existence of business centres within certain pharmaceutical companies whose remit is to explore repositioning opportunities for drugs in their respective portfolios. Examples include Pfizer's Indication Discovery Unit, Bayer Healthcare's Common Mechanisms Research group, Novartis' New Indications Discovery Unit and others that are not perhaps as formally organised as these specific cases. Interestingly, a repurposing angle has the potential to integrate well with the efforts of pharmaceutical companies to virtualise the development of selected groups of drugs in their pipeline, such as GSK's virtual proof of concept (vPoC) unit, or with the efforts of these companies to out-license some of their assets as discussed previously.

Beyond financial sense, drug repositioning is often analysed in terms of its patent protection scenarios and possible inherent limitation because of off-label use of such drugs in their new indications. The recent example of Cephalon acquiring Bioassets Development Corporation (BDC) for the new-use rights to Enbrel, which BDC repositioned in sciatica via epidural delivery, addresses both of these points[8]. First, one can obtain very strong patent protection for a new use of an existing drug whose composition of matter patents are still running, if that new use is not covered and proven in the original patents. Second, by administering Enbrel epidurally, which is a different route of administration to the original use of Enbrel, off-label use of Enbrel is lessened significantly and becomes solely the risk and responsibility of the physician. Payers do not support off-label use and more importantly, off-label use is a practice that applies to all drugs, including ones that are not repositioned. Repositioning does not increase the risk of off-label use. Also, when a drug is repositioned, it is always a good idea to include, if medically appropriate, a different dose, formulation or route of administration as additional barriers.

Having established that drug repositioning makes significant commercial sense, it is important to turn our attention to the concept of novelty and innovation. The decreasing amount of novelty and innovation in pharmaceutical R&D is a major issue, and one that is discussed and analysed with intensity[5]. If drug repositioning is to be considered a valid strategy for maintaining and growing the effectiveness of a drug development pipeline as an investment vehicle, independently of the pipeline belonging to a large pharmaceutical company and the stakeholders being the millions of public shareholders, or the pipeline being that of a smaller private biotech and the stakeholders being its private investors and VCs, then it has to survive and flourish because it also makes a legitimate contribution to the generation of novel or unexpected ideas and product opportunities.

Biomedical research moves forward based on different kinds of innovation. To date, the most frequently discussed ones fall in four major categories:

1. New tools to do things (these would be reagents to explore biological phenomena or new types of drugs, such as aptamers, chimeric proteins, peptidomimetics, multi-valent antibodies and others).
2. New ways to measure things (these would be techniques of scientific observation and measurement, including new visualisation methods, multiplexed assays, real-time biological kinetics measurements and others),
3. New 'things' themselves (devices, including the use of new materials with novel properties).
4. New ways to handle and extract insights from experimental observations (including advances in bioinformatics, data integration, knowledge management, artificial intelligence and others).

One can consider the development of gene cloning, the PCR reaction, PAGE electrophoresis, monoclonal antibodies and mass spectrometry as the all-time singular advances that have defined modern biomedical research now and in perpetuity, and that no further true innovation that has generated the same quantum leap in our understanding of biology or the development of drugs has occurred since. And although this would be a fascinating debate, the key point is that without fundamental new biological knowledge, all of these wonderful advances are solutions in search of a problem to solve and would not have been possible in the first place.

The key question is whether drug repositioning can usefully advance our knowledge of basic biological mechanisms, helping us discover new biology that we can use to develop novel drugs, even though these drugs may have been used in other indications. Every other kind of innovation, including the specific examples listed above, is not only indispensable in this effort, but can only realise its full potential if it can produce new biological insights that teach us something we did not know and with which we can use to do good.

Drug repositioning by its very nature is probably one of the single most powerful tools we have in our research arsenal today to accelerate our discovery

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and understanding of new biology. What supports such a grand statement? Simply put, if we think of drugs not as drugs, but as reagents or probes of biological function, then drugs used for repositioning have the ability to uncover new pathways and mechanisms that would otherwise be invisible to us and to do so much faster than other tools. They can do so because of their ability to bind to targets that are not always the ones they were originally designed for. This is often called the 'off-target' effect, but in reality, the drugs are completely 'on target', binding exactly to what they are capable of binding. It is just that we may not always be fully aware of what they bind to or may not have known enough to look in the right direction and thus when an effect is later attributed to the binding of our drug to an unexpected target, this is called 'off target'. The important point is that a drug binds to multiple biological targets no matter how much effort has been exerted to render it as selective as it can be.

One of the most celebrated examples of this would be Imatinib, or Glevec, originally generated by rational drug design as a small molecule inhibitor that is selective for the cancer target bcr-abl, and is approved for the treatments of chronic myeloid leukaemia and gastrointestinal stromal tumours[9]. It is also known to inhibit c-kit, PDGF-R and NQO2, and this set of 'off targets' is now studied in concerted efforts to reposition Glevec in new indications including ischaemic stroke, rheumatoid arthritis, psoriasis, Crohn's disease, type I diabetes and spondyloarthritis[10]. Observation of this drug binding to targets beyond that which it had originally been selected led to multiple hypotheses about its potential usefulness in other diseases, and encouraging early data have created multiple new research opportunities.

Another recent example of repositioning is ibuprofen in Parkinson's disease[11]. This study showed that the effect was specific to ibuprofen but not to other NSAIDs or acetaminophen, and this specificity was unexpected. The consequence here is that this unexpected observation is opening research possibilities into novel biology for Parkinson's disease that would not have existed without repositioning.

A third compelling example is the unexpected observation that certain anti-depressant drugs are able to inhibit the growth of glioma cancer stem cells[12]. Since anti-depressants are believed to operate mostly through neurotransmitter modulation, this observation is leading to research of potential new biology in cancer that may involve other unexpected targets previously unidentified.

The common theme in the three examples of Glevec, ibuprofen and anti-depressants – and there are many others – is that the repositioning of these drugs led to unexpected observations in new diseases, thus contributing in a major way to current innovation in our biological understanding that we would not otherwise have.

In addition to the internal efforts of biopharmaceutical companies, there are increasing numbers of vendors and CROs offering a variety of repositioning services, including widescale *in vitro* binding, cell line screening, protein-protein interaction studies, phenotypic screening of animal model sets and classic pathway and data mining approaches.

Finding new uses for existing drugs makes commercial and research sense. It accelerates the development of novel products with less risk, provides further protection to embattled pipelines, has the potential for significant returns and efficiently generates true innovation in our understanding of the basic biology of disease. As such, its future is assured and bright. DDW

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