WHITE PAPER

KNOWLEDGE-BASED DRUG REPOSITIONING TO DRIVE R&D PRODUCTIVITY

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INTRODUCTION

Drug repositioning or repurposing is a strategy by which new or additional value is generated from a drug by targeting diseases other than those for which it was originally intended.

Repositioning of launched or failed drugs has opened up a new source of revenue to large, medium and small Pharma companies as well as attracting venture capital funding, and is expected to generate up to $20 billion in annual sales in 2012\(^1\). Drug repositioning is not a new strategy and there are a number of examples of drugs that have been successfully repositioned such as gemcitabine and sildenafil (Table 1). These and many other examples have addressed an unmet medical need in selected patient groups as well as creating substantial value for the company that repositioned the drug.

One of the most interesting and extreme examples of repositioning is thalidomide, which was launched in 1957 as a sedative but was later found to be responsible for severe birth defects in children when used by pregnant women to alleviate morning sickness. After additional scientific inquiry the drug has since been shown to be safe in selected patient groups and to be very effective in pain relief in leprosy and Kaposi’s sarcoma, generating $528M in revenue per year\(^2\).

**TABLE 1: DRUGS THAT HAVE BEEN SUCCESSFULLY REPOSITIONED**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ORIGINAL INDICATION</th>
<th>NEW INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Fungal infections</td>
<td>Leishmaniasis</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Inflammation, pain</td>
<td>Antiplatelet</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Parkinson’s disease</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Prostate hyperplasia</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Viral infections</td>
<td>Cancer</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Cancer</td>
<td>Psoriasis, rheumatoid arthritis</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Hypertension</td>
<td>Hair loss</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Cancer</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Morning sickness</td>
<td>Leprosy, multiple myeloma</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Angina</td>
<td>Erectile dysfunction, pulmonary hypertension</td>
</tr>
</tbody>
</table>

Apart from the opportunity to create value, drug repositioning has a number of R&D advantages\(^3\) including a reduction of R&D timelines by up to 3-5 years, reduced development cost (due to sunk research costs and, in many cases, the availability of clinical safety, toleration and efficacy data) and the improved probability of success (Figure 1). Despite these advantages only relatively recently have major pharmaceutical companies adopted drug repositioning as a core R&D strategy. Historically, it was not widely pursued through fear that it could jeopardize the lead indication by uncovering safety or other issues. Clearly when considering the repositioning of a drug it is important to not put the primary indication at risk by using doses, dose frequency, patient types and formulations that could create unnecessary concerns. So long as a repositioning team reassures the organization that it will work within the limits defined by safety studies, then repositioning is an excellent way of addressing unmet medical needs and maximizing the value of a drug asset\(^4\).
CMR International data - Repositioned drugs are defined as NCEs seeking new indications once the lead indication has successfully transitioned into Phase III. It excludes new formulations, doses, routes of administration for an existing indication(5).

In addition to repositioning actively developed or marketed drugs, it is estimated that there are 2000 failed drugs sitting in drug libraries that have the potential to be exploited through a repositioning strategy by the innovator company or could be the target for licensing/partnering deals with a third party. It is also estimated that the list of failed drugs is increasing at the rate of 150-200 compounds per year(6).

Protecting market exclusivity is very important when considering drug repositioning; there are a number of options that need to be evaluated on a case by case basis. Patents are the normal means of gaining marketing exclusivity either through protecting the structure of the drug (composition of matter patent) or its use and/or formulation. Drugs can also obtain regulatory exclusivity which may afford protection to drugs that have lost patent protection. Finally the Orphan Drug Act in the USA (and similar acts in other regions) provides R&D incentives and marketing exclusivity to drugs, including repositioned drugs, with an approved orphan drug status.
The trigger for the increase in drug repositioning activity is the improved access to high quality data plus world class analytical capabilities being applied to that data. This has transformed the business of drug repositioning from the opportunistic approach of exploiting a clinical side effect, animal pharmacology or scientific “hunch” to a scientifically robust and logical approach for finding new uses for drugs in well defined and selected patient populations. By using pathway analysis and other computational methods to connect the data on drugs, disease pathways and proteins, drug repositioning can be approached using any of three routes:

1. **DRUG FOCUS**

   Structural features of molecules already approved for particular indications can help to identify active compounds that were originally developed for different indications. Thomson Reuters can perform similarity searches and produce advanced QSAR models based on one of the largest collections of bioactive compounds in the world, including compounds from patents and articles registered in Thomson Reuters databases, and other sources.

2. **TARGET FOCUS**

   Systems biology solutions available from Thomson Reuters provide great opportunities to find new indications when primary and/or secondary targets of compounds are known. The methods include powerful pathway analysis techniques that evaluate:
   - how drug targets are positioned compared to successful targets
   - how your targets are connected to disease biomarkers or if they carry any alterations themselves
   - what signaling cascades and biological processes are regulated via drug targets
   - how drug targets are involved in disease related signaling cascades

   All pathway analysis based drug repositioning techniques utilize the knowledge content of MetaBase™, the most comprehensive systems biology database including about 1,500 pathway maps and more than 1,200,000 protein interactions. Our portfolio of pathway maps includes nearly 600 disease specific pathway maps that are a great tool for drug repositioning.
3. DISEASE FOCUS

Experimental data related to disease (e.g. omics data collected from patients) or knowledge on how drugs modulate phenotypes related to disease (e.g. known from their side effects) are utilized in disease focused approaches.

Methods enabled by disease related omics data include:

- Network analysis of high throughput data\(^{7-16}\), which consists of reconstruction of disease-specific networks followed by identification of key drivers and hubs in the network as potential drug targets. For example, one of these methods, causal reasoning\(^{15, 16}\), is based on an assumption that drug targets often play the role of upstream regulators of differentially expressed genes, and drug treatment reverses differential gene expression in pathology to a normal level. The algorithms utilized by Thomson Reuters calculate the ratio of disease-specific genes affected by the treatment via downstream pathways and considers it as a quantitative measure of the efficacy of target inhibition or activation for the disease.

- Expression pattern techniques, developed by the Broad Institute as the Connectivity Map Concept, are utilized by Thomson Reuters among other omics data analysis methods\(^{17}\).

- Pathway pattern techniques based on smart prioritizations and clustering of pathways disregulated in diseases constitute another group of methods in disease focused approaches\(^{18}\).

All omics data analysis methods utilize experimental data owned by customers or taken from public repositories. *MetaBase*, described above, is used as a source of protein interactions and pathway information enabling the analyses.

Drug repositioning based on a drug’s side effects, off label use, epidemiological data, etc. is another group of methods in disease focused approaches\(^{19}\). Thomson Reuters has access to a number of databases that catalogue all of this data, primarily *Thomson Reuters Cortellis*™ and the *World Drug Index* database.
Working on drug repositioning projects, Thomson Reuters has the ability to perform analyses for libraries of compounds, hundreds of targets, and multiple data samples. This wealth of data is processed via all methods in parallel allowing prioritization of indications for each target based on contributions of drug focused, target focused, and disease focused approaches in the same time. Final conclusions on discovered drug – indication and target – indication pairs are made by our best disease molecular biologists and medicinal chemists to ensure the highest likelihood of success.

As a final phase of a drug repositioning project, thorough fact based due-diligence is conducted on potential repositioning opportunities. Steps may involve in-depth analysis of the intellectual property associated with the drug, and evaluation of clinical trial and animal model data that has been obtained to date, in order to determine if there is real-world supportive evidence for a role in a new disease. The existence of databases, such as those owned by Thomson Reuters, makes this evaluation step a simple and highly cost effective basis for any repositioning exercise.
The following case study demonstrates the process by which drug repositioning information can be leveraged and successfully converted into product opportunities.

A pharmaceutical company identified two disease areas of high unmet medical need that were commercially attractive. It wished to select drugs from across the pharmaceutical industry that would target these two disease opportunities with a view to licensing or buying the suitable drugs. Thomson Reuters worked with the client to identify drugs that were discontinued or currently in clinical trials that may be effective in the two diseases. Thomson Reuters approached this task from all three directions: 1) through the drug structures (comparing them to existing active therapeutics), 2) through drug targets (evaluating their relevance to the diseases), 3) through disease knowledge (analysing related omics data and disease-specific pathways). The multi-attribute scoring system helped select drugs with the highest likelihood of success. On the next step the intellectual property (IP) positions of the drugs and their safety were evaluated. The company was provided with a risk-adjusted list of investment opportunities which greatly accelerated their entry into new areas for licensing and development within 8 weeks of starting the project.

THE CHALLENGE

• A pharmaceutical company wished to look for potential investment opportunities in two indications via a repositioning strategy.
• A drug opportunity database of all Phase II, Phase III and marketed drugs in the industry needed to be constructed.
• The opportunities needed to be scored and ranked based on the probability they would work in the new dermatology indications. A shortlist would need to be produced.
• Shortlisted drugs were to be profiled and analyzed.

OUR APPROACH

Drug opportunity database generated (N=15,000)

Drugs scored and ranked to produce a shortlist of high-scoring opportunities (N=100 per disease)

Shortlisted opportunities profiled for IP, clinical and animal model data

BENEFITS

• Identified top scoring targets with scientific evidence for repositioning.
• Produced a list of high scoring drug investment opportunities.
• The client received a list of potential repositioning assets, with supportive clinical trial and animal data.
CONCLUSION

This paper does not discuss in detail the area of protection of intellectual property (IP) associated with drug repositioning. The IP position is much stronger if the innovator patent has not expired, regulatory exclusivity is obtained or if a new patent can be assigned to a repositioned drug based on a new indication which has a different formulation, dosing regimen, route of delivery etc. that is clearly different from the parent drug.

Now is a very good time to be involved in drug repositioning because:
- there are a large number of drugs available for drug repositioning
- there is a ready access to high quality curated scientific data
- there is no need for any large infra-structure
- the lead time to proof-of-concept is short
- it is attractive to many different types of funding models and collaborations

Drug repositioning offers a significant advantage over traditional drug development since the repositioned drug will have passed a significant number of toxicology and safety assessments and so the chances of failure are greatly reduced. Compared to the traditional R&D process, the overall time and cost of bringing a repositioned drug to market is greatly reduced because of the lower failure rate and the avoidance of significant research activities. The process of drug repositioning is greatly enhanced by using computational methods to connect all the scientific data from such sources as Thomson Reuters Cortellis and MetaCore™ on drugs, proteins, pathways, polypharmacology and clinical trials.
REFERENCES


2. Thomson Reuters Forecast.


5. Data from the Centre for Medicines Research (CMR) International, a Thomson Reuters business http://thomsonreuters.com/products_services/science/science_products/a-z/cmr_factbook/


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