REPOSITIONING's role in drug discovery and development

The large number of drug candidate failures in recent years has been enormously costly for the pharmaceutical industry, but has also created the tremendous opportunity of repositioning these molecules into new disease areas. Companies which can systematically reposition stalled drug candidates could create significant value by bolstering their late-stage pipelines and meeting the needs of patients with innovative medicines.

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The term 'repositioning' of drugs or drug candidates has come to take on several meanings. The focus of this review will be on repositioning as defined by the discovery of new therapeutic utility of a compound that is in addition to, or instead of, the originally intended disease. It is acknowledged that there are different forms of drug repositioning, most notably improved formulation and patient stratification, and several excellent reviews have been written in these areas.

Repositioning of drugs through clinical observation and serendipity has been with us since the beginning of the pharmaceutical industry. However, one might ask what is responsible for the recent interest in systematic repositioning approaches, particularly as applied to mid and late stage efficacy failures. The emerging interest is likely a function of two factors. One is recent advances in technology and a growing understanding of systems biology and the second is business need. Below we first discuss the business need as well as two repositioning approaches that help address these needs. Second, we discuss how the emergence of new technologies and the co-ordination of biotechnology and the large pharma industry can realistically execute on the potential of drug repositioning.

Industry realities

Innovation is the core of pharmaceutical R&D, and thus the major driver of the industry's growth. In looking at the industry's productivity over the last decade, it is clear the relationship between the emergence of new NCEs (New Chemical Entities) and R&D investment has not been favourable (**Figure 1**).

Many factors have contributed to this, notably the high attrition rates in the clinic, owing to a greater focus on complex and late-onset chronic diseases, requiring combination therapies and having to learn by failing in the clinic. Some believe that this low rate of success will not improve and thus represents a significant threat to the pharma and biotech industries. Therefore, senior executives in this industry are not only looking at ways to enhance efficiency of steps in the existing R&D process, but are also looking toward innovation on distinct paths that achieve the ultimate goal of enhanced overall productivity.

A common strategy for filling gaps and/or supplementing development pipelines is to in-license compounds from other biotechnology or pharmaceutical companies. Numerous early stage therapeutic compounds are available to in-license from smaller companies, although intense competition for the best

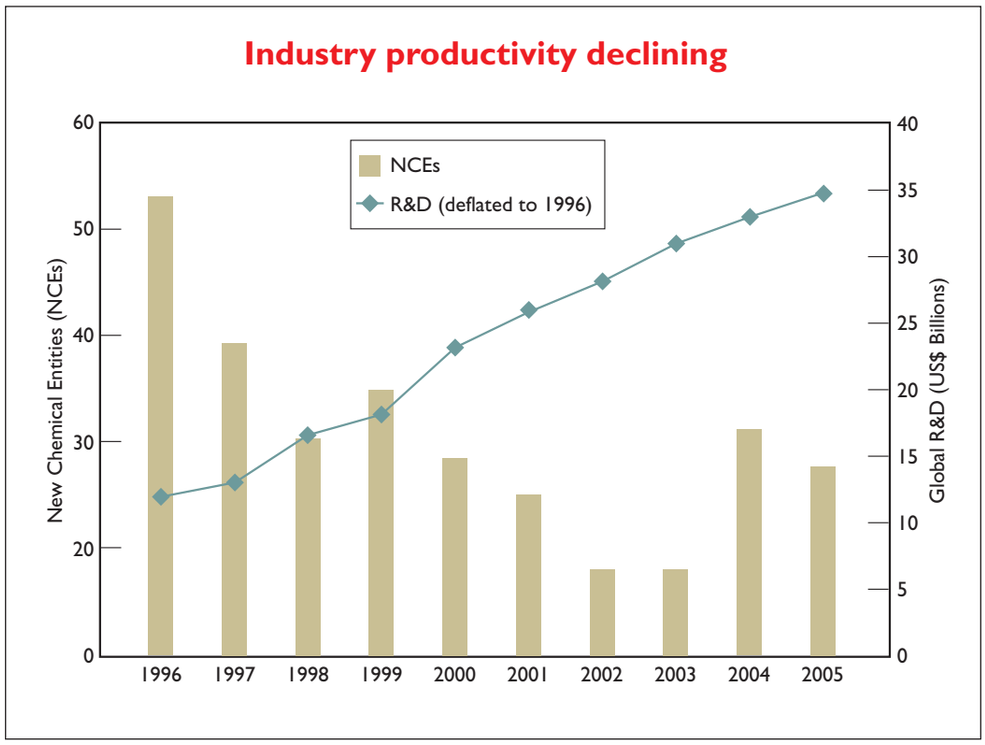

Figure 1
Fewer drugs are being launched, despite increasing R&D investment
Source: Adapted from CDER, PhRMA, US GDP

candidates has created a seller's market, with the cost of an early development candidate up more than 50% today compared to 2002 and prior years[1]. This approach is so frequently used that buyers risk getting caught in 'bidding wars' or being shut out of the market for the highest potential candidates.

A reduction in clinical attrition is of paramount importance, and therefore repositioning presents itself as an additional attractive possibility for enhancing productivity. One might even view repositioning as a distinct enough approach that it can be mapped as a separate category of major methods by which productivity can be enhanced to reduce costs and clinical attrition (**Figure 2**). For purposes of clarity, we will discuss separately two applications of repositioning. The first is the repositioning of the large depot of existing failures and the second is the incorporation of repositioning into the standard R&D process.

The value of repositioning efficacy failures 'sitting on the shelf' today

It is estimated that there are currently more than 2,000 compounds that have failed in Phase II or Phase III clinical trials that are sitting on the shelves of big pharma. The majority of these have failed due to concerns over efficacy, safety or in the case of followers, failure to demonstrate clinical differentiation. If we exclude those compounds which failed for safety reasons, there is a substantial subset that could be suitable candidates for repositioning. The current number of drugs that stall in the clinic is estimated at 200 annually[2]. An obvious question to ask is whether there should be a reasonable expectation that many of these could have utility in other disease indications. A *New England Journal of Medicine* article reported that nearly 90% of launched drugs surveyed had important indications for use that were in addition to those for which they were originally approved[3]. These new indications were identified within five years of launch. By extrapolation, it seems logical that a clinical-stage molecule which failed in its initial indication may have one or more additional indications. It is simply that these clinical failures never had the broad population exposure that resulted in the serendipitous repositioning of the launched compounds. There are examples of blockbuster drugs, including Viagra® (sildenafil citrate), that have been serendipitously repositioned after patients in unsuccessful clinical trails reported side-effects that signalled the drug's potential in other indications. However, in these cases the drugs' effects were striking enough to be observed in these smaller patient populations that were otherwise healthy.

Systematic repositioning is uncommon and consequently its financial value has not yet been closely examined by many pharmaceutical companies. However, even if one were to assume modest success rates, we estimate that each individual compound repositioning attempt would result in considerable potential value. For example, even an assumption of successfully repositioning one compound back into Phase II per 10 compound attempts, followed by standard attrition rates after that point, would unlock tens of millions of dollars of net present value (NPV) for every initial repositioning attempt. This is under the assumption of relatively cost-effective repositioning technologies, which will be discussed below. Extrapolating this view to encompass the veritable treasure chest of 'failures' a top pharma company has amassed over time could unlock huge value for the company.

The potential patent advantages of repositioned drug candidates versus in-licensed candidates also offer a compelling economic case for repositioning. A typical drug takes approximately three years from the lead stage, when composition-of-matter patents are typically filed, to go to Phase II. On a repositioned drug, however, a novel method-of-use patent could be filed just prior to entering Phase II trials. In typical drug development timelines, this means that a repositioned drug could have up to a three-year extension of patent protection over its in-licensed counterpart and therefore benefit from longer exclusive sales revenue. In many instances, successful drugs have come to market solely under method-of-use claim protection. In a pessimistic scenario, where a compound can neither benefit from composition-of-matter or new method-of-use patent protection, a repositioned compound can still achieve market exclusivity in the US via Hatch-Waxman regulations and in the EU under data exclusivity protection periods. Specifically, a pharmaceutical company receives five years of market protection after approval of an NDA for the first indication of a newly-launched compound in the US under Hatch-Waxman. In the EU, the new data exclusivity period could provide a pharmaceutical company with 8-11 years of market protection.

Repositioning's impact on productivity as part of ongoing R&D

It is likely that chemical matter inhibiting or activating 2,000-3,000 targets will be realised over the next several years. This is a result of both the successes of genomics as well as advances in screening technologies. These reduced hurdles in lead generation are resulting in the screening of druggable targets with weaker disease hypotheses, which will increase the risk and thus incidence of programmes that fail in the intended therapeutic area due to lack of efficacy. Nevertheless, these activities will result in a set of chemical tools with which to probe target function and thereby link the corresponding compounds to new therapeutic utility. Therefore, the incorporation of repositioning into the standard operations in an attempt to reduce ongoing clinical attrition may have a significant positive impact towards maximising value-creation from the lead generation/optimisation efforts.

The productivity value of repositioning as part of standard practice has been examined[4]. This was done by looking at the impact of repositioning in a steady-state pharmaceutical pipeline. A key assumption was that a company would apply systematic repositioning to each of their Phase II, Phase III or NDA filing efficacy failures on an ongoing basis. It was estimated that this would provide a sustainable 10% boost to portfolio value. It was also noted that the incorporation of systematic repositioning into standard practice might make the process of a 'second try' explicit, leading to fewer 'stealth projects' that can drain resources from the more traditional therapeutic area focused projects. In fact, these calculations may be somewhat conservative, as repositioning can also be applied to compounds that failed for reasons other than efficacy, and the calculation does not capture the additional potential value of out-licensing candidates.

Technology

The second key factor in the recent excitement over repositioning is the emergence of new technologies that make it practical to deploy reverse chemical genetics (ie, Target -> Compound -> Disease -> Drug). What are required are sufficiently high throughput methodologies to make *de novo* links between specific compounds and disease. Advances in technologies such as genomics, imaging, sensitive bioanalytics and robotics have now made it possible to examine a compound for new potential therapeutic utility across a very wide breadth of disease space. In fact, technologies have recently advanced to a point where they can be applied cost-effectively in almost a brute force or disease agnostic manor. Whether applied singularly or in multi-technology platforms, advances in technology have undoubtedly increased the effectiveness of drug repositioning efforts.

For example, technologies such as imaging have developed to a point where they can detect molecular pharmacological events of drug action. Such technologies can be done in real time in live

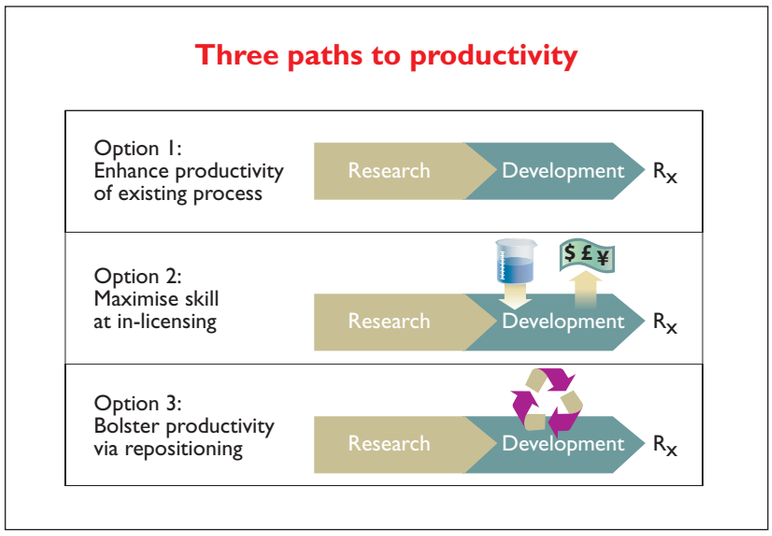

Figure 2
Repositioning allows a company to build on existing compounds and drugs for new indications or improved products

animals so spatial-temporal relationships of drug action can be examined throughout the body. These imaging technologies can be combined with specific transgenic reporter mice that are genetically engineered to show biological pathway activation when the test article hits the appropriate receptor, enzyme or transporter. The rapid analysis of the spatial and temporal pharmacodynamics of a compound across the entire animal body can often reveal effects of a compound in unexpected organs or cell systems. This offers insights into potential pharmacological applications that might otherwise be overlooked.

Multiplex bioanalytics can now be deployed across hundreds of disease relevant biomarkers in a cost-effective manor. These technologies have advanced to a point where very small fluid volumes are required, including CSF and bile from individual rodents. By observing changes in the levels of specific bioanalytes in biological fluids, affected biochemical pathways and processes can point to a wide-range of organ systems that may be involved in potential disease pathologies.

In vitro disease assay technologies have benefited from advances in high-throughput screening and miniaturisation so that a large collection of high-content sentinel assays can be performed efficiently over a wide breadth of diseases states. Examples of these assays might include platelet aggregation, osteoblast activation, glucose responsiveness, and adipose cell differentiation. The individual assays are not necessarily new, but performing them on an aggregated high-throughput basis with multiplex tools and liquid handling robots is where the innovation has occurred. Traditionally, each department of a pharmaceutical company has its own set of assays that correspond to a specific disease space. However, the process of systematic repositioning would seem to require the aggregation of hundreds of such assays to be run in parallel.

Similarly, these high-throughput screening advances have enabled the potential to establish high-content *in vitro* assays to discern pathway regulation. By monitoring the transcriptional modulation of well-defined genetic elements, insight can be gained regarding the capacity of a compound to alter defined signal transduction events. New effects of the compound on known cellular pathways and potential new links between previously unidentified pathways are now discoverable.

The field of pharmaceutical informatics has also grown exponentially over the last several years. These advances have taken place on both the bioinformatics and chemoinformatics side. Informatics databases now exist that contain transcriptional profiling information from thousands of human disease versus normal tissues. This *in silico* information can be used to expand the knowledge of where a target is expressed and what disease states modulate the target. Elucidating pathway regulation is facilitated by pathway analysis tools that integrate genomic data with literature-based findings and other bioinformatics data. In addition, chemoinformatics databases now exist that alert investigators to all known activities of drugs with closely related structures.

The concept of systematic repositioning by applying multiple *in vivo* disease models is yet another emerging approach for repositioning. The idea is simply to take a drug candidate of unknown disease utility and screen it against dozens of disease specific models. In one sense, this is similar to what was done decades ago in the pharmaceutical industry prior to target-based screening. However, advances in the analytical technologies that can be applied to these models as well as the potential of linking molecular mechanism to disease model hits has reinvigorated this approach.

The role of biotech in repositioning

The biotechnology industry will likely take advantage and hence productively contribute to repositioning in several ways. These approaches will differ both in terms of the specific type and breadth of technologies deployed, as well the business model of the biotechnology company. One way for biotechnology companies to contribute is to continue to develop technologies that can screen quality chemical matter against a wide breadth of different disease indications, hence optimising the

probability of a new disease hypothesis being found. In this way pharmaceutical and biotechnology companies can work together (the pharmaceutical companies supplying the quality chemical matter and the biotechnology companies supplying the disease screening technologies) to enhance overall productivity.

Conclusions

Enhancing R&D productivity is a growing focus in the pharmaceutical industry. Intense competition for attractive drug candidates has made in-licensing an expensive and sometimes a difficult option for bolstering a pharmaceutical company's compound portfolio. Repositioning failed drug candidates for alternative disease indications offers a near-term, value opportunity to alleviate pipeline gaps and improve development successes.

Drug repositioning is benefiting from new technologies that provide a highly systematic, multifaceted approach to discover new development paths for failed drug candidates that extend beyond the initial therapeutic area of interest. These technologies can be used to explore a compound's effect on disease-relevant biological indicators, providing a broad assessment of its potential therapeutic utility. Compelling new disease hypotheses can then be validated in disease-specific *in vivo* model systems.

The economics of repositioning are impressive. One compound repositioned into Phase II can add hundreds of millions to the NPV of a development programme. This could be even more advantageous than a comparable in-licensing opportunity, due to the potential extended period of patent protection. If used systematically to investigate a company's repository of accumulated failures, repositioning can add a one-time NPV windfall worthy of serious consideration. In addition, if incorporated into ongoing R&D, repositioning could add as much as a 10% sustainable increase to portfolio value. DDW

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