Productivity and attrition: key challenges for biotech and pharma

'The challenges confronting companies today are a direct result of the technology-led discovery approach and the consequent need to reengineer the discovery process.'

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Pharmaceutical companies have seen the writing on the wall in terms of the level of product innovation required for them to sustain earnings growth. Unfortunately, R&D productivity today does not promise the windfall of new molecules that is essential to stoke the engine of earnings growth. The decline in R&D productivity is represented most starkly by the statistic that the US Food and Drug Administration (USFDA) approved only 17 new drugs in 2002, as compared to 24 in 2001.

Is this the end of a golden era for pharmaceutical companies as some observers would have us believe [1]? If so, pharmaceutical companies no longer have the means to sustain R&D productivity and must, instead, focus on improving operational efficiencies in other areas. Taken to an extreme, it can be argued that big pharma should shut down internal research and focus on the marketing of products that are in-licensed from biotech companies. However, this change only shifts the problem of R&D productivity to biotech companies, which have not performed any better than big pharma in this regard [2].

Over the past decade, several new technologies have been implemented with the intention of accelerating the discovery process. Post-genomic technologies, such as microarrays [3], haplotype maps [4] and chemical genetics [5], offer hope for companies wishing to lift themselves out of the R&D productivity trough. However, the promise of these technologies is yet to be realized. Indeed, the challenges confronting companies today are a direct result of the technology-led discovery approach and the consequent need to reengineer the discovery process.

The challenges of technology-led discovery

Three challenges that result from the technology-led discovery approach are (1) bias from the application of selection filters in different stages of the discovery process; (2) the application of emerging technologies before their validation; and (3) the appropriation of resources that favor new technologies over established ones.

Selection filters are often applied in the discovery process as a means of coping with the large volume of information and materials generated by high-throughput technologies. The unevenness in the scale of activities at different points in the discovery pipeline means that selection filters have been applied to winnow the output from higher-throughput upstream processes to make that output manageable downstream. For example, early in the discovery process, a company may set arbitrarily stringent potency criteria for selecting compounds on the basis of the results of a high-throughput screen. Although potency is a desirable feature for a lead compound, there is a point at which a further increase in potency yields diminishing returns and may blindside one to important issues such as toxicity and selectivity. Similar distortions can result from the strict application of Lipinski criteria to reject molecules [6]. Arbitrary selection filters prevent us from finding the best solution within the class of available solutions by introducing bias. The distortion is compounded when selection filters are applied sequentially during the discovery process.

The decision by pharmaceutical companies to adopt new technologies is often based on theoretical assumptions as the decision is taken at a stage when the practical utility of these technologies in increasing R&D productivity remains hypothetical. *In silico* techniques are a case in point. They may be useful as a guide in the selection of drug candidates but relying on them for crucial decisions, such as compound selection, could be more problematic than productive. As reported in a recent analysis, compounds known to be ligands for a particular target would not have

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been selected as ligands for that target on the basis of their ranking on scores from an *in silico* docking procedure [7]. A similar criticism can be leveled against *in silico* tools for the prediction of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties. It would therefore be prudent to implement such technologies on an experimental or pilot basis before replacing better-established approaches.

While technology hubris has its intrinsic downside, there are other more insidious negative effects, including the appropriation of space and budgetary resources for these 'exciting' new approaches. This weakens traditional strengths in areas such as systems biology and *in vivo* pharmacology by starving them of resources and leadership. Today, many companies face critical shortages of staff and resources in these areas. This problem has been self-inflicted because of the piecemeal approach to the drug-discovery process that focuses on enhancing productivity one step at a time at the cost of downstream activities.

Reengineering the discovery process

The current productivity crisis also demands a reappraisal of the discovery process as it exists today. The R&D process needs to (1) accommodate the need for more exploratory work, even in later stages; (2) shift from a focus on being 'fast to market' towards a diverse portfolio of products in various stages of development; and (3) outsource with a more global scope.

The potential revenue loss of US$ 3 million per day of delay in the launch of a potential blockbuster (more than US$ 1 billion in annual sales) can force a linear and sequential approach to drug discovery that leaves little room for exploratory research. There are several examples from the recent past of drugs that have revealed commercially attractive applications, quite unrelated to the approved indication, after reaching the market. The discovery of the potential use of statins for multiple sclerosis [8] and celecoxib for cancer [9] are examples that illustrate the importance of exploratory research. In such cases, thorough exploration of serendipitous pharmacological observations made during late pre-clinical and early clinical development may reveal novel properties that could form the basis of new and expanded marketing approvals. In fact, early clinical development can be viewed as an extension of the discovery research process. This is especially so if unexpected data from early human pharmacology studies are used to initiate a thorough exploration of the pharmacology of the drug to uncover the potential for novel therapeutic applications. Leveraging data obtained serendipitously would require pharmaceutical companies to improve the way in which they manage the data flow and knowledge creation processes within their discovery and development teams [10].

The 'fast-to-market' philosophy of drug development is relevant in a situation in which most molecules beyond a certain stage are very likely to succeed. However, recent experience shows that this situation will not continue. Many molecules now fail or are withdrawn in the very last stages, some after they reach the market. In such a situation, R&D strategy should focus on building a diverse portfolio of products in various stages of development.

Finally, many of the new technological and strategic approaches in drug discovery call for scarce resources that could be accessed by global outsourcing. The outsourcing model helps to alleviate potential shortages by transferring key activities to a service provider. Unlike the situation during drug development, outsourcing in the discovery stage is still relatively modest and largely restricted to the US and Europe. Thus, endemic skill shortages in areas such as chemistry and *in vivo* biology remain as bottlenecks because the pool of talent available in these disciplines is relatively limited in these regions of the world [11]. Although there may be a shortage of chemists in the US, there is a surplus of chemistry talent in other regions of the world, such as Eastern Europe, Russia, Israel and India. In fact, there are many established companies in these regions that offer chemistry resources to US and European companies. The solution to the productivity crisis must involve a global mindset that makes cost-effective use of skill resources in other parts of the world.

In conclusion, there are important lessons to be learned from the R&D productivity problems facing the pharma industry. Technology-led discovery is certainly a part of the solution to declining R&D productivity. However, the adoption of new technologies without an evidenced-based evaluation of their proper role may create new problems, related to the quality of information and decision making, that can undermine the ability of these technologies to enhance productivity. Discovery companies also need to take a holistic approach and reengineer the discovery process to include opportunities for exploratory research, to diversify the product pipeline and to outsource globally.

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