Assessing the impact of current trends in genomics on the future of pharmaceutical R&D

'Although the post-genomics revolution promises a brighter future, it also has the potential to engulf the industry'

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The arrival of the 21st century heralded two significant events for biomedical research: (1) the publishing of the first draft of the complete human genome sequence, and (2) the high-density mapping of the genetic variations within it. These two remarkable achievements offer the potential to transform the world of medicine as we know it, altering the ways we target and treat human disease.

Coupled with advances from the genomics revolution in the understanding of cellular processes, these breakthroughs impact every aspect of R&D in the pharmaceutical industry. The genomics era has driven a much greater understanding of physiology and pathology at the molecular level and is enabling scientists to begin to unravel cellular processes as the result of the interplay of networks of genes. The publication of the human genome sequence and the use of expression databases and sophisticated bioinformatics software to find and characterize new genes and gene families has identified a huge number of potential and actual targets in a wide range of disease. Further, the understanding of genome variation and the impact this has on health and disease will significantly improve the development and delivery of new medicines.

As data expands in these areas and downstream processes, such as HTS, come into play, the information mountain grows exponentially. Finally, the post-genomics era is driving change in the environment in which the industry operates, by using outcomes-based medicine and a much greater focus on the cost effectiveness of healthcare delivery. Although this revolution promises a brighter future based on a ready supply of innovative new products, it also has the potential to engulf the industry unless significant changes occur in the processes, organization and systems of pharmaceutical companies.

Process: serendipity to engineering

The industry remains under intense pressure to maintain shareholder value at its historical levels, which means that productivity in R&D will have to increase significantly. One impact of this is a shift to a much greater degree of processes based on genomics and high-throughput activities. The process will be driven by rational approaches to target identification and a much more stringent requirement for early validation of the role of the target in pathology. HTS will increase in scale and efficiency, as well as scope, to include automated and high-throughput preclinical screens. Consequently, parts of the process such as HTS will become almost completely industrialized. Industrialization in this context means the use of screening 'factories' designed by screening, automation and supply chain specialists and run by technical staff and operations managers. The factories will have to use scheduling, planning, manufacturing execution and inventory management systems coupled with robust industrial-scale automation to ensure any chance of delivering the number of leads demanded of them.

Downstream, the impact of pharmacogenetics will be seen in the clinical trials arena where companies will initially stratify data based on a pragmatic set of genotypes, but will ultimately (within five years) recruit patients into Phase II trials based on genotype. Results from these studies will be correlated to a subset of genotypes identified from genome-wide scanning for efficacy and side-effect profile of new drugs in multi-factorial diseases such as diabetes, obesity and Alzheimer's. Phase III trials are likely to be much smaller and based around patient populations with defined genotype subsets.

These changes will require much closer integration of the functions in the traditional silos in research, development and, crucially, marketing. This will ensure the exact targets

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are screened for the right leads in the appropriate formulations for specific patients, and that this process is carried out as quickly as possible. A much greater commercial input is needed, even into early phase research and, as healthcare systems move to value-based prescribing, the use of economic criteria in portfolio decisions will become commonplace. A necessary outcome of these drivers will be changes in organizational models.

Organization: lingua franca or Tower of Babel?

The complexity concomitant with genomics and proteomics has had two key organizational impacts for large pharmaceutical companies. First, it has created a situation wherein the industry no longer has the resources to cover every technology, disease and therapeutic area as world leaders. It now has to start to ask what are its core skills, where does it add value and where are its weaknesses? A honest assessment of this might lead to some uncomfortable answers; how many large pharmaceutical companies know, for example, the number of genuinely innovative targets in previously intractable diseases they have discovered in-house in the past three years? The second impact of the genomics revolution is to lower the entry barriers to new competitors who might be much more nimble in finding and validating targets and leads using virtual networks.

Consequently, aside from the internal changes driven by process integration, we are going to see increased outsourcing of non-core competencies and a much greater and more strategic approach to partnering and in-licensing. The industry must improve its partnering skills to broaden the portfolio and reduce risk. We are also likely to see increased numbers of consortia being established to address the big questions that genomics can answer but are too big and too risky for companies to tackle on an individual competitive basis.

Finally, the pharmaceutical industry needs to recognize that succeeding through the huge burden of change and complexity will fall on its key asset: its staff. The industry will have to address its lack of attractiveness to staff by changing rewards for individuals, how it recruits new skills that are not conventionally associated with the industry and how it maintains high levels of performance. A good starting point to address these issues is the question 'why should the best graduates come to work in the pharmaceutical industry'?

Systems: exploiting the data mountain

As data from different projects in different sites in different countries grows exponentially, managing this is simply not enough. Pharmaceutical companies will have to start to address how they will exploit the massive wealth of information within their own organizations, as well as from a network of sources from outside the firewall, to increase their competitive advantage. The heterogeneity of R&D IT systems does not help in this aim and many organizations will have to address how portal technology coupled to data-warehousing strategies can deliver user-friendly desktop services to the scientist and clinician end-users. The challenge is twofold: first, to provide an information-push service coupled with data mining and manipulation tools across projects, geography and time, drawing from information sources on both sides of the firewall. Second, to make the non-intuitive links across disease and therapeutic areas that, given the sheer volume of data, would not otherwise be made. In other words, provide the innovation without the perspiration. Many companies might feel that the challenge is too expensive and uncertain, and will go to an ASP model, whereby data management is outsourced.

If this is not challenge enough, companies will need to manage the continuous move towards *in silico* predictive discovery and development in the 'learn and confirm' model wherein every new piece of experimental data generated is fed back into and improves the *in silico* modelling technologies. Finally, if the opportunity of these challenges is to be realized, the industry will have to address data standards and data governance issues not least to optimize its usefulness but particularly as more and more early data will be integrated into online dossiers for regulatory approval.

The challenge of choice

The post-genomics era is often described as a revolution. We believe that although the impact of the revolution will be particularly profound on the pharmaceutical industry, it will also impact on the process of the discovery, development and provision of healthcare. The genomics era has produced choice and complexity on a huge scale and pushed the need for effective decision-making earlier in the drug discovery process.

To survive and thrive, pharmaceutical companies need to develop a portfolio approach that starts in discovery, which is balanced for risk and return, and includes in-house initiated projects as well as a wide range of partnerships and in-licensed projects. Importantly, the portfolio should include quantitative, dynamic assessments for targets, leads and technology that are based on value in the new operating environment of outcomes-based healthcare. Therefore, in order to thrive, the industry must embrace the genomics revolution and alter processes and attitudes throughout the discovery, development and marketing functional silos.

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