A revolution in R&D – *the managerial challenges*

The genomics revolution is poised to sweep aside the old economics of pharmaceutical R&D. The biotechnology and pharmaceutical industries – and perhaps healthcare delivery in general – are on the brink of transformation, and companies that embrace the revolution in the right way stand to reap enormous benefits. Developing a new drug should become considerably less unpredictable and much less expensive. Companies will record improvements both in efficiency and in success rates all along the value chain, and the average cost and time needed to bring a new drug to market will fall correspondingly. But this benign prospect is clouded by some warnings: great rewards will require comparably great efforts; a new paradigm in R&D economics may necessitate paradigm shifts in R&D management; above all, the great promise is offset by great risks – though, as in any revolution, the risks of standing aside may be greater than those of getting involved.

All biopharmaceutical companies are, or should be, actively deciding how best to engage in the revolution. Making such decisions is no easy matter. The familiar bearings are no longer there, since the competitive and regulatory landscapes have changed so much – and continue to change – in response to the promise that genomics offers. Companies have been rushing to claim intellectual property rights (in the so-called IP land grab), now that the sequencing of the human genome has been completed. Statutes and court decisions regulating those IP rights keep emerging and modifying the picture. And the corporate map is being redrawn: the major mergers of recent years have created industry superpowers, and the pace of acquisitions and alliances is set to quicken, if anything.

With so much change occurring there are bound to be winners and losers. Although the decisions will be unfamiliar and difficult, success will in the end be determined by traditional criteria. The winners will be those who make optimal strategic choices and then implement them in an optimal way. The two components of the winning combination will differ from company to company, according to each company's size, aspirations, financial power, capabilities and so on. In this article, taken from the final chapter of the Boston Consulting Group's 'A Revolution in R&D – How Genomics & Genetics are Transforming the Biopharmaceutical Industry', we identify the strategic and operational issues and examine the various options that different companies might exercise.

Strategy – searching for genomic competitive advantage

Before genomics, biopharmaceutical companies used two basic tools – chemistry and molecular biology – to discover new drugs. Broadly speaking, the drugs that emerged were much indebted to serendipity. Research strategy consisted mainly of choosing which therapeutic areas to investigate, and discovery efforts focused on individual drug targets. Development provided even fewer strategic choices: a promising compound emerging from chemistry would be tested on animals and humans in large and inefficient trials (inefficient because there was no means of identifying in advance likely responders or non-responders). With the rise of genomics, there have come new technologies, new approaches, new

information and new ways of thinking about research and development. These have brought with them a new opportunity, or imperative, to turn research into competitive advantage.

So companies now have weighty strategic issues to address. At the corporate level the question is how much to invest, given the current environment. For R&D leadership, the question tends to be where to focus those investments – in what therapy areas, on what target classes, and so on – as well as which technologies to adopt and how to adopt them (in-house or externally, for example) and how to mitigate the associated risks.

The starting position

Although these same broad questions will apply equally to all companies, there can be no standard answers. The actual options available to any company will depend on its starting position.

Company size

A key restraint on a company's strategic options is size. The largest pharmaceutical companies boast capabilities and finances on a scale that allows full participation in the new technologies, even when the risk is high. Not that this exempts them from having to make choices. In fact, since scale gives them so many options, they arguably carry a greater burden of strategic decision-making. How to select from such an embarrassment of riches? In addition they face the challenge of managing complexity. If they are not selective enough, and embrace too many options, the operational problems could prove overwhelming.

The narrower capabilities and lesser scale of small-to-medium-sized pharmaceutical companies and the larger biotech companies could represent either a severe drawback or a distinct advantage. On the one hand, there are reduced opportunities and even the prospect of being locked out by the big pharmaceutical firms: with disease genetics, for instance, a company with insufficient scale to build an in-house capability would risk forfeiting potentially lucrative intellectual property rights. On the other hand, since lesser scale often means lesser complexity, these modest-sized companies can compete more flexibly, changing their tactics quickly in response to technological advances or competitor moves.

To see how scale can affect a company's options, consider the differing ways in which large and mid-size companies approach the target land grab. The larger companies have been able to take very aggressive approaches – scaling up or pursuing big deals to secure intellectual property rights to targets. The smaller companies, lacking in resources, have been unable to follow suit, but some of them have compensated by choosing very focused strategies, concentrating on their special competencies and imposing higher quality standards.

Building the fact base

Apart from company size, the two most important facets of a company's starting point are the beliefs and hypotheses held by its leadership team (roughly, its corporate culture) and its current R&D capabilities. Companies need to scrutinise both.

It is crucial to understand and shape the beliefs and hypotheses of leaders throughout the organisation, especially since, with genomics and genetics, the contributions and effects are cross-functional – that is, the managers or sections that contribute most are not necessarily those that benefit most. All those affected need to articulate their perceptions of the value and applicability of genomics and genetics to the company. Once tested, these perceptions should be given considerable weight when it comes to defining company strategy.

An equally thorough assessment needs to be made of the company's relevant R&D capabilities – its technologies, skills, specific knowledge of diseases and disease mechanisms, and so on. Ideally, this will include an audit of current R&D productivity at every step in the value chain, identifying bottlenecks and other constraints. The more accurate and detailed the assessment, the more effectively the company can address the strategic questions as they pertain to its specific situation.

Corporate decisions

How much to invest and where

As suggested above, even the largest pharmaceutical companies will have to make choices. Consider some of the huge deals of recent times: the $500 million deal between Bayer and Millennium for targets, the $800 million deal between Novartis and Vertex for *in silico* chemistry, the $500 million deal between Roche and deCODE for disease genes. Note that these deals concern discrete steps of the value chain: in each case it appears likely that the companies concerned were acting on an explicit preference – an established strategic preference. After all, given the magnitude of these deals, it seems unlikely that any one company would have placed all three bets. More to the point, such large deals, although essentially R&D ventures, are not R&D decisions alone. Almost certainly, the decisions were thrashed out at the corporate level.

For more modest-sized companies, strategic choices often go beyond matters of preference or emphasis. The question might be whether to concentrate all their efforts on some value chain steps

and forgo others altogether. Certainly it no longer makes sense for even mid-sized pharmaceutical companies to compete in target identification. And at the smaller end of the scale, companies with less than $400 million in R&D, say, may find themselves asking even more radical questions: Can we afford research at all? Should we not focus exclusively on licensing instead? Again, it is at the corporate level, rather than within R&D alone, that such questions will eventually be settled.

It is not just through major partnerships and investment decisions, however, that the corporate level is impinging on R&D strategy. More and more, specific R&D activities are having ramifications beyond R&D itself and invoking corporate-level participation. Pharmacogenetics, for instance, often touches on corporate strategy as much as on R&D strategy. Should the company continue to pursue a promising compound, say, when the risk of market fragmentation might outweigh the positive market effects? Should the company attempt to resurrect candidate drugs previously killed because of rare side effects? And so on.

R&D leadership decisions

Where and how to compete

With genomics and genetics now part of the landscape, R&D decision-making has become more complex. The options are far more numerous: there are more ways of gaining access to capabilities, more technologies to choose among and even new dimensions in which to compete. R&D executives must select a combination of options that not only dovetail with the company's starting position and aspirations but can also be integrated smoothly with one another.

Choosing a research focus

The dimensions of competition include:

Disease states. Some disease states have become more tractable thanks to genomics approaches, and any company continuing to investigate them will have to deploy genomics if it is to remain competitive. Just which therapeutic areas or disease states are most amenable to genomics is determined by several factors: the degree to which the disease is genetic in nature, the current understanding of disease processes at a molecular or genetic level, and so on.

Target class. Some genomics approaches are at odds with traditional therapeutic-area borders, and favour a broader deployment – around target class – rather than the old focus on disease state. (The targets within a class are usually similar in structure and biochemical function.)

Therapeutic modalities. Small-molecule drugs still dominate the market, but they no longer monopolise it. Some new therapeutic modalities have already established a foothold – injectible protein therapeutics, for instance, based on secreted factors and antibodies. Others remain very much in the experimental stage – gene therapy and anti-sense technology, for example – though adventurous companies are pursuing them undaunted (as exemplified by Lilly's recent $200 million deal with Isis to gain access to anti-sense capabilities).

These dimensions are interconnected, of course, and even interdependent. Take Novartis's interest in oncology, for example – a broad disease state. Given that interest, it made sense for the company to focus on kinases, a key target class in oncology. Kinases constitute one of the few target classes that are amenable to a particular genomics approach, *in silico* drug design. Novartis has duly set about augmenting its expertise with the appropriate genomics technology, forming an alliance with Vertex to that end.

Selecting technologies

According to the research focus adopted by the company, certain technologies will press their claims immediately. An oncology programme, for instance, would certainly argue for the incorporation of a transcription profiling approach, as more and more cancers are being redefined at the level of RNA expression. But each claim would have to be assessed by reference to the company's aspirations and current capabilities. How comfortably would a candidate technology fit in with the company's risk profile or existing skills mix, for example?

In addition, companies will need to consider the current stage of development of genomics technologies. When is the best time to buy into the favoured technology? As noted throughout this report, although some genomics approaches are practicable today – in the early steps of the value chain, notably – others remain speculative: genome-wide association studies, for instance. A company's risk profile will determine whether it wishes to be on the 'bleeding edge' or to be a technology follower. Either way, the company will want to chart the evolution of genomics technologies and approaches and adjust its own strategy accordingly. A technology scouting function is indispensable, now more than ever.

Whether the technology is proven or unproven, companies will need to decide not just whether and when to invest, but also how – how to keep a sharp focus and mitigate the risks involved. The options vary from company to company, again according to company size. With disease genetics, say, a large pharmaceutical company that chooses to pursue the

technology in-house would face the question of how to apply it – to which therapeutic areas, for example. A smaller company, by contrast, unable to build a programme in-house and obliged to take a different approach, would face such questions as what kind of joint ventures to pursue and what focus to apply.

Deciding how to acquire or gain access to capabilities

In general, there are several ways to attain a desired capability, but in some cases the options are limited. When the item is a proprietary database or tool, for instance, the company will have to license it in (or pay a provider for service) rather than buy it outright; or when a company views its own information as too confidential to outsource, it will be forced to implement the related technology in-house. In many cases, though, a company will face the choice between building in-house capabilities and out-sourcing. The in-house option, to justify itself, would have to confer some significant strategic or cost advantage. A company could have a cost advantage if it had developed a proprietary method, for example, or if it could boast greater scale or experience in a given approach.

Some, though not all, of the new technologies show clear scale benefits, thanks to industrialised processes and informatics. (Among the most obliging technologies in this regard are expression profiling, traditional HTS and uHTS, and exploitation of informatics-based analysis. The least obliging are medicinal chemistry and animal models, and somewhere in between are compound synthesis and management, proteomic expression analysis, structural biology, and *in silico* chemistry). Unfortunately, building scale in-house could be disproportionately costly for small-to-mid-sized pharmaceutical companies, even for the most scale-friendly technologies. These companies are unlikely to realise cost advantages; they risk spreading their technology dollars too thin. The wiser option would be partnering or licensing.

If a company decides to develop a given technology in-house, it should review that decision regularly. What is today a strategically advantageous capability may be commoditised tomorrow. The perception of sequencing, for instance, seems to be shifting, from a need-to-have technology to something that can readily be outsourced.

If a company decides to outsource a given technology, it will have to decide further on a prospective partner or partners. It might even opt to join forces with competitors. A model partnership of this kind has been the SNP Consortium. A group of pharmaceutical companies, helped by various academic institutions, banded together to identify 300,000 SNPs (in the end, the total was about one million) and put them into the public domain. This joint effort had two very beneficial effects for its participants. First, it enabled the companies to concentrate more on their core interest, finding drugs; second, it forestalled the efforts of genomics companies, which would have sought to patent and extract rents from these SNPs. Other candidates for 'coopetition' of this kind include protein structure modelling and broad-scale sample collection for disease association studies.

Putting the strategy into operation

Defining a genomics strategy is a good start, but even the most brilliant strategy is futile if it remains defined on paper only. The point is to put it into operation. Putting a strategy into operation consists essentially of making changes and managing them effectively. In the case of genomics and genetics, the changes that need to be made are profound, affecting all aspects of the R&D organisation and, by extension, the corporation as a whole-core process, organisational structure, job descriptions, interfaces and so on. The necessary work can be divided into three broad areas:

- Rebalancing the value chain.
- Establishing the new organisation and its governance.
- Managing organisational change.

Rebalancing the value chain

The old ways of conducting R&D are often unsuited to the new area. As the first chapter showed, the traditional R&D value chain no longer works. For one thing, its smooth flow quickly becomes disrupted by a series of bottlenecks, induced by the different productivity gains at different phases. For another, its sequence is unsustainable, since the new technologies dance to a different schedule: much of the chemistry phase might now take place simultaneously with target validation, for example. To reinstate a smooth flow (while enjoying the new, much accelerated rate of throughput), R&D needs to ease the bottlenecks and adjust to a reconfigured value chain. And that means redistributing resources and, more importantly, redesigning processes, as well as keeping the new value chain in balance.

Restoring balance: reallocation versus redesign

At first sight, the bottleneck problem would seem fairly simple to resolve: scale-up downstream steps to meet the increased demand. But how feasible would that be? The number of targets identified could increase six-fold or more. To scale up to meet that increase, a company accustomed to spending

$1 billion on all of R&D would now have to spend more than $1.5 billion on target validation alone.

Another simple approach suggests itself: adjust resources along the value chain in order to bring the uneven phases back into balance, shifting funds from more efficient phases (notably target discovery) to less efficient downstream phases (such as preclinical). But such reallocation of resources is, on its own, an overcautious measure, and will not have a really dramatic impact on R&D economics. It neglects, or even distracts from, the central opportunity that genomics offers: the opportunity to 'raise the game' by changing fundamentally the way R&D is conducted.

This transformation of R&D will derive above all from the bold reconfiguring of processes, for the sake of both physical process flow and information flow. For the former, new technology platforms need to be integrated and optimised, both within value chain steps and across the value chain. (In some cases, this may require a discipline and a rearrangement comparable to the moving assembly line introduced by Henry Ford in 1913.) As for information flow, the tremendous amount of information generated by the new technologies remains worthless unless translated into functional information and supplied punctually – that is, in time to influence the decisions being made.

The extent of the redesign, and the particular shape the new flows take, depend very much on the company's strategy choices. Processes that are newly industrialised, but that still follow a traditional R&D sequence, need to be systematised. In some cases, however, the traditional R&D value chain will need to be disrupted. To integrate chemical genomics and genetics, for instance, would necessitate a major restructuring of the value chain. Chemical genomics introduces a new parallelism, as target validation and chemical activities are conducted simultaneously; the two processes now interact rather that just interface. And genetics introduces feedback loops, where late-phase findings (such as genetic information from the clinic) feed back into earlier steps of the value chain (such as disease-genetics-based target discovery).

In anticipation of any process redesign, individual function heads should be pondering the contingencies: how and when genomics might affect them, and what actions to take when it does. As one bottleneck is relieved, another is created: When will the bottleneck reach their step in the chain and what will its impact be? What new technologies and approaches will be available and how effectively will they relieve the bottleneck? The head of development, for example, should already be contemplating the inevitable increase in demand for clinical trial capacity and weighing the various options, such as pharmacogenetics, for meeting it.

Retaining balance: Capacity Planning and Management (CPM)

After the initial jolt of genomics, supply and demand should get back into alignment, thanks to the combined forces of resource reallocation and process redesign. But this restored balance is a precarious one, and needs careful and regular maintenance. That is where capacity planning and management, or CPM, can play an invaluable role. By enabling an organisation to keep supply and demand aligned, CPM also enables it to make rational plans, linked to capacities and resources, and thereby to manage projects with optimal efficiency.

Though well established in high-profile corporations such as General Electric, Hewlett-Packard and Cisco, CPM is conspicuously rare in biotech and pharmaceutical companies. For the genomics revolution to realise anything like its full productivity potential, efficient CPM will be immensely beneficial if not imperative.

Establishing the new organisation and its governance

Implementing the process changes just mentioned will entail a thorough review of a company's existing hierarchies and procedures. For the process changes to yield optimal value, changes also need to be made in traditional decision-making methods and in organisational structures.

New linkages and interfaces

To begin with organisational changes. With the value chain so much altered in appearance, and processes now so different from before, many disparities and stresses will inevitably develop in an unaltered managerial system. The old structures will creak and strain under the unfamiliar new pressures. To restore congruence, a company may need to undertake some bold organisational reshaping – shifting or moving divisional borders, reassigning personnel, redistributing areas of responsibility, and so on – not just within R&D, but also within the company as a whole and even beyond, in the alliances the company might enter into.

The R&D Department. Incorporating the requisite new capabilities, it goes without saying, represents a formidable organisational challenge: not only do they have to mesh with existing capabilities, they need to co-ordinate with one another as well. To implement *in silico* drug design, for example, it would be almost essential to provide an informatics interface between structural biology and chemistry data. Meanwhile, a comparable reorganisa-

tion of personnel has to be undertaken. Biologists and chemists, for example, can no longer proceed in isolation, but must now work alongside each other – often literally – on collaborative projects or in formal discovery partnerships. And genetics requires far closer collaboration between basic research and development than ever before.

One excellent example of rethinking traditional organisational structure and boundaries is GlaxoSmithKline. Alert to the impact of scale, the company has on one hand consolidated functions where scale and co-ordination provide a clear advantage, and on the other hand engaged in decentralising where size and complexity could prove a drawback. Specifically, prompted by the scale benefits, the company decided to organise centrally both the front end and the back end of R&D (that is target discovery and full development). For the steps in between, conversely, where the company's enormous scale would risk encumbering innovation, it has established smaller, more autonomous centres of excellence (based on different therapeutic areas), which attempt to simulate the feel of smaller biotech companies.

The Entire Corporation. So, enhanced control of data and increased cross-functionality of personnel are set to change the structure and tone of the R&D department. But their sphere of operation is broader than that. As with the strategic issues discussed earlier, the company as a whole is implicated. New lines of communication, and possibly new chains of command, will need to be extended between R&D and other units. In particular, the relationship between R&D and marketing will be fundamentally transformed: with R&D facing greater choice and placing bigger bets earlier than ever, commercial input will be crucial. And pharmacogenetics will require new ways of thinking about markets, competitors and customers. (Pharmacogenetics may also inspire new linkages between pharmaceutical and diagnostic units for corporations that have both.)

Co-ordinating the commercialisation process between R&D and marketing has always been a delicate balancing act. Most biopharmaceutical companies have established product development project teams to drive the process. These cross-functional teams are charged with developing product strategy and co-ordinating the various functions as products progress from R&D into the market. The job has now become even more complex and tricky, owing to larger global efforts, greater information flow, more specialised functions and increased liaison with global strategic marketing (especially when companies consider the options for applying pharmacogenetics to molecules in development).

Beyond the Corporation. Finally, new partnership models need to be considered. Although traditionally organised partnerships are still appropriate in many cases, new and more flexible forms of alliance will sometime be required, notably when it comes to collaborating with academic or not-for-profit institutions and to joining horizontal networks or consortia.

R&D governance

One potential source of gain in R&D is improved decision making. Consider again the example at the start of the value chain – the glut of identified targets and the need to decide which ones should proceed to the next phase. Genomics technologies have created this quandary, but they have also provided the means for solving it. Using new genomic methods of 'aptitude testing', decision makers can confidently pre-select the most promising targets and forward them downstream.

Even decisions unrelated to genomics technologies stand to improve, since the new genomics regimen fosters a culture of rigorous selection criteria. In fact, one of the most important, though perhaps least noted, benefits of genomics is the way it encourages a thorough rethinking of decision-making processes. New kinds of data now present themselves for interpretation, and they enter the calculations earlier and in greater abundance than the old kinds did. And R&D decision makers have to take into account a new set of factors too, beyond the confines of R&D, in order to maximise value – factors such as marketing and IP implications, for example.

Managing organisational change

With the advent of genomics, R&D personnel suddenly find themselves in alien territory. As the scientific methods change, the old instinctive approaches and behaviours need to change as well. Among the greatest challenges facing R&D executives is managing the human side of change.

How the scientist's job is changing

R&D science is shifting from an arena of experimentation to one increasingly concerned with theoretical biology. The challenge is now less how to get the data than what to do with the data collected. Scientists who formally could do their jobs virtually on their own – conduct their own experiments, and generate and analyse the data themselves – now find they need to collaborate with others who have more specialised technological skills, in areas such as informatics, robotics, or microfabrication. Indeed, the scientists of the pre-genomic era are destined to evolve into two kinds of successors: those

who interpret the data and devise plans to exploit it, and those who continue to develop and optimise the technologies required for generating the data. (Companies should be sure to recognise and reward the latter group for its contributions, and not relegate it to second-class status.)

All scientists will need to become comfortable with new ways of working together – more sharing or collectivist now, less conducive to solitary initiative. The scientists of the future will still take responsibility for their own work, but perhaps will no longer take the credit for it: that will be ascribed to team effort.

Managing the transition

Changing from bench-based to information-based work in this way, and from favouring fairly independent endeavours to promoting a more collaborative ethos, is bound to be awkward or even painful for most of those involved, scientists and managers alike.

The formidable operational and organisational changes will entail cultural changes too: in fact, the new processes and structures may prove far less difficult to establish than new habits and attitudes.

Consider informatics. It is not enough simply to introduce powerful new IT tools within traditional silos – within chemistry, for example, where *in silico* approaches would boost the efficiency of screening and optimisation. To achieve their full impact, these IT tools need to be deployed across functions: to bring biologists and chemists together, to incorporate data from the clinic into discovery, and so on. And that will require not just new software, or even new managerial positions, but new ways of thinking and of relating to colleagues.

Some idea of what lies in store can be gleaned from the history of another transformational technology – CAD/CAM for airplane design. Like genomics, it promised to transform a costly and labour intensive R&D process into a highly automated and efficient one. After languishing in niche applications in the 1970s and '80s, it finally proved its worth in the 1990s when Boeing used it in designing the first 'paperless' airplane, the Boeing 777. To exploit the technology fully, the company had to break down departmental barriers and encourage collaboration across the full range of functions. Jobs and job responsibilities had to change. Cherished traditions were called into question. The company held quarterly meetings at which employees could ask questions and voice their concerns. The transformation was a struggle, but ultimately a great success: Boeing continues to push the envelope in *in silico* design.

When pharmaceutical companies convert to genomics, they will have to temper the discomforts of transition in their turn. And that means engaging the emotional and behavioural issues – the human issues – as deeply as the operational ones. Attentive management of the human issues, which has played such a prominent role in so many industries in the throes of reform, is going to be particularly crucial when it comes to the massive institutional changes demanded by the genomics revolution.

A final word

To stake a claim in the changing biopharmaceutical landscape, let alone feature prominently within it, a company will have to make itself radically amenable to change. Defining a strategy is certainly a step in that direction, and initiating that strategy is certainly a gesture of commitment. But wholehearted commitment is evidenced not by initiating the strategy but rather by maintaining it – that is, monitoring the new structures and procedures constantly, responding to shifts in external and internal circumstances, and introducing further changes repeatedly, aggressive or defensive, as new opportunities or new challenges arise, though always in line with the controlling wisdom of the strategy itself.

If the unfamiliar outer landscape provokes feelings of unease, so too will a company's inner landscape, once all the requisite operational and organisational changes are in place. In particular, the increase in cross-functional activity may be disorientating for some executives of the old school. Many of the ancient landmarks, tidy borders, and familiar categories will no longer be there to give them their bearings. Short of attempting a counter-revolution or withdrawing into obscurity, they will need to familiarise themselves with new terrain fairly promptly – and accept it affirmatively not grudgingly. Changes in attitude will perhaps prove the most difficult changes of all to bring about, and a company's prosperity could be in jeopardy if they fail to take effect. DDW

This article has been extracted from The Boston Consulting Group's major report entitled 'A Revolution in R&D, How Genomics and Genetics Are Transforming the Biopharmaceutical Industry'. Report authors are: Peter Tollman, Vice-President, Boston; Philippe Guy, Senior Vice-President, Paris; Jill Altshuler, Manager, Boston; Alastair Flanagan, Vice-President, London; Michael Steiner, Senior Vice-President, Munich.

For more information or to obtain the full report contact one of the authors or Michael Tutty, e-mail: tutty.michael@bcg.com, or visit www.bcg.com