Accelerating drug discovery: creating the right environment

Steve Arlington

Technology can help with throughput; new drug discovery, information capture and screening techniques can produce thousands of compounds and speed potential products into preclinical trials. However, quantity and speed do not guarantee quality, uniqueness and therapeutic or commercial potential. Even with state-of-the-art automated systems, innovative and creative scientists are required to evaluate new compounds and to take research in new directions. The author discusses how companies can improve efficiency in new drug discovery without sacrificing creativity and quality of output in today's high-pressure process-driven environment.

Pharmaceutical companies are under heavy pressure (Figure 1). The cost of bringing a single drug to market using traditional R&D techniques can be as high as $600 million[1–3], and this figure is likely to rise. The old producer-driven market, where new drugs were launched on an unsuspecting and (hopefully) grateful population is long gone. Companies are now faced with a customer-driven market in which governments, healthcare organizations and patients demand cost-effective innovative products for specific needs[4]. Institutional investors want a good return on capital, but achieving this is increasingly difficult in the face of escalating drug development costs[5], heavy competition and government-imposed price ceilings[6]. The predicted growth of the traditionally well populated 'me-too' market is only 7% per annum[7] – too low to justify further investment. There is no longer room for anything but excellence; all products leaving research to enter the development phase must have a sound scientific and technological basis, fulfil an unmet medical need and represent a significant commercial opportunity.

It is unlikely that the pharmaceutical industry will be able to escape further consolidation in the next few years. Drews and Ryser[8] have calculated that 'Industry will not be able to generate a number of novel drugs which would allow it to grow at 5–10% or even to maintain itself at the present strength'. To be successful, the industry must concentrate on producing a steady stream of blockbuster drugs at reduced cost and with ever-shortening development times. Though a tall order, many of the smaller biotechnology companies are

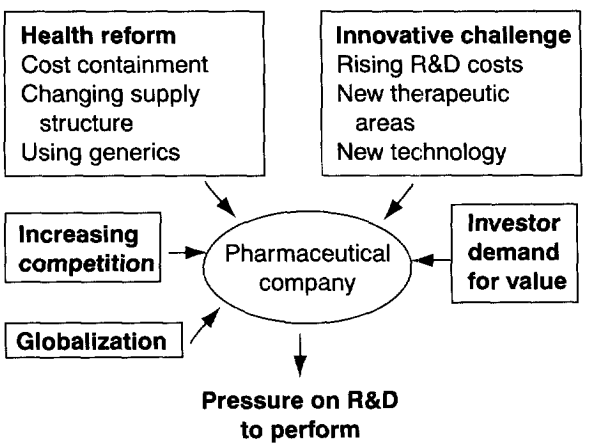

Figure 1. *External pressures on pharmaceutical companies leading to pressure on R&D performance.*

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already some way towards this goal. Typically, biotechnology companies spend only $230 million on bringing a new drug to market – under half the cost of traditional development routes[2].

The race is on

In 1995, Glaxo Wellcome announced its intention to launch three new products per year from the year 2000. Whether or not the company succeeds with this ambitious goal, there is now pressure on the rest of the industry to follow suit. Only those companies capable of improving the productivity of their research and development departments will remain important players in the future healthcare environment[9].

Accelerating the development process

It is critical that the development process is fast, to ensure that the novelty of a potential blockbuster product is maximized and the company achieves a prolonged competitive advantage post launch. Drug development times have already been cut from about 12 years to 6–7 years, but in spite of this, a shortage of potential blockbuster compounds in development remains[8]. To cut time to market further, or perhaps more importantly, to cut time to peak sales, companies must be 'fast in and fast out'[10] throughout R&D and into the marketplace – maximally efficient, with money being spent on the right compounds in appropriate ways. All processes must be carefully targeted and streamlined to obtain maximum efficiency and no-go projects abandoned early[4].

Some companies are particularly effective at fast product development, and these generally have the profile shown in Box 1. Fast developers are successful in three main areas: procedures, people/culture and effective management.

Most companies are now using business process re-engineering techniques to automate and streamline their development processes to be as fast as possible. Clear business objectives combined with a thorough analysis of existing processes and benchmarking against industry best performance standards will provide substantial rewards. Companies will experience faster throughput of potential lead molecules and greater cost-efficiency in the development process. The application of business process re-engineering to clinical trial procedures, for example, has produced time savings of up to 70% in the critical pathway through realignment of work practices alone.

Such approaches can also be successfully applied to elements of the drug discovery process, where realignment of work practices coupled with the effective use of advanced automation technology has the potential to produce significant improvements in efficiency.

Box 1. Qualities exhibited by fast pharmaceutical product developers

Basics
Excellence and speed in basic product development activities

- Effective partnering (internally and externally)
- Automation

Management
Excellence and speed in management of drug development activities

- Invest in knowledge management (decision-making tools and processes)
- Efficient time-based management of processes
- Key performance indicators

Culture
Environment promoting staff behaviour supportive of fast development

- Install and promote a climate of innovation
- Motivational, mould-breaking recognition and reward policies

Increasing the rate of new drug discovery is vital

Although research and development are often bracketed together, they are actually very different functions. In fact, within many companies there is a major divide between research and development[11]; the passage of a lead compound from research to development has been described as being akin to 'throwing it over the wall' rather than a 'hand-over'[4]. The gearing up that is required when a product arrives in development is a rate-limiting step, so a smooth transition process including knowledge management and information systems is vital to speed the passage of a product through research and into development. The whole company must be encouraged to treat R&D as a continuous process rather than as a series of separate functions. Successful early research relies upon a combination of innovative science, advanced automation techniques and the informed decision-making of the research scientist. To increase the number of successful lead molecules reaching the development phase requires the optimization of:

- spread of capabilities and knowledge across emerging fields of investigation;
- efficiency in the application of drug discovery, synthesis and screening technology;
- culture – aligned for speed;
- informed and effective decision making.

Increasing the rate of lead compound identification

Researchers looking for potential lead candidates can make use of a range of drug design technologies and a variety of molecular libraries. Over the past five years perhaps the greatest impact on new drug discovery has been the widespread use of combinatorial chemistry, high-throughput screening, informatics, genomics and automation of standard laboratory procedures. However, this alone will not be enough to bring about the increases in efficiency that the industry seeks.

Even the largest pharmaceutical companies cannot afford to bring in-house all expertise in every emerging field of investigation, so increasingly they are developing strategic alliances with external organizations offering relevant skills. For most pharmaceutical companies, a close look at key activities and expertise will reveal which research requirements should be handled in-house and which can be contracted out or handled as part of a strategic alliance.

Companies can obtain possible lead molecules from a number of sources (Box 2), including strategic alliances with combinatorial chemistry, biotechnology, chiral chemical companies and universities. These organizations offer different drug design methodology and have different molecular libraries – with various advantages and disadvantages. Some combinatorial chemistry companies aim to produce vast chemical libraries for sale to pharmaceutical companies, and others specialize in producing specific types of library, such as small peptides or oligopeptides. Most major companies have now formed a number of such strategic alliances – between 1988 and February 1997, 750 alliances were initiated between the top 20 pharmaceutical companies and the biotechnology industry (Box 3)[12–15]. Some companies are making use of the new virtual drug development corporations (VDDCs). These are temporary, flexible networks of expert resources (usually discrete companies) that work together to streamline the drug discovery process[16]. In future, it is likely that an increasing number of companies will manage their research entirely as a VDDC[17].

Possibilities for business process re-engineering

Business process re-engineering can be effectively applied to elements of the research process. However, many companies mistakenly believe that automation of synthesis and screening *is* effective re-engineering. Few consider the 'rubbish in, rubbish out' principle – fast throughput of inappropriate molecules yields many inappropriate molecules in a shorter time. The key to really increasing efficiency and

Box 2. Advantages and disadvantages of different lead compound sources for drug discovery

	Advantages	Disadvantages
Company's internal R&D facility	• Exclusive • Rights to all compounds • Control of area of research to fit with corporate global strategy	• Expensive • Constant overhead • No defined return on investment • Management of research staff
External R&D (e.g. biotech company)	• Ready-made product • Known up-front investment • Purchase of molecule allowing all budget to be diverted to development and marketing	• Dealing with separate corporate entity with own objectives • Unlikely to have exclusive relationship with the external company unless wholly-owned • 'Not invented here' issues in-house • May not be products available to suit portfolio
External R&D (academic)	• Unlikely to be fully developed • Known up-front investment	• Unpredictable number of products per year • Not exclusive rights

Box 3. Some notable examples of relationships between large pharmaceutical companies and drug discovery firms

Strategic alliances
Schering Plough & Pharmacopeia
Berlex Laboratories & Pharmacopeia
Pfizer & Oxford Asymmetry
Pfizer & Myco Pharmaceuticals
Pharmacia Biotech & ArQule
Abbott Laboratories & ArQule
Bayer AG & Arris Pharmaceuticals
Boehringer Mannheim Therapeutics & PharmaGenics
Novo Nordisk & Houghten Pharmaceuticals

Acquisitions
Eli Lilly & Sphinx Pharmaceuticals
Marion Merrell Dow (now Hoechst Marion Roussell) & Selectide
Glaxo Welcome & Affymax

quality is maximizing the interplay between improvements in automation and the creativity of research scientists. Therefore, it is as important to address the need to recruit and retain innovative and creative scientists as it is to streamline scientific processes and to adopt new working practices aligned with the new technologies available.

Creating the right environment

Synthesis and screening processes have already been extensively streamlined, but few companies have investigated the increased efficiency to be gained from creating the correct working environment for creative scientists. Some companies treat their research departments as unmanageable – almost mystical – environments that are peopled by strange, highly intelligent beings involved in impenetrable tasks. Perhaps this explains why the efficient use of skills, techniques and processes involved in research is only now being investigated.

Culture clashes

Historically, research departments and corporate management have had an uneasy relationship. Like any other specialist field, science has its own language and jargon, and this can make non-scientists feel excluded. Managers can feel challenged or threatened when faced with a seemingly impenetrable discipline. Management can also feel that scientists do not understand the need to control expenditure or respect corporate goals or policy. Scientists, on the other hand, can feel that corporate management does not understand experimental methodology, the necessity for rigorous procedures or the need to publish for personal academic credibility. This divide has often resulted in management attempting to direct the course of research and keep a tight control on budgets, with a corresponding rise in resentment from scientists and a stifling of innovation. The key is to involve the scientists in the overall corporate strategy by giving them the corporate objectives and working with them to reach a solution for changing processes and incorporating performance measures.

In spite of the technological advances now available to those involved in modern drug discovery, it is essential that data are analysed and systems refined and applied by innovative and creative scientists. Scientists involved in manipulation of combinatorial chemistry data, for example, must first define the acceptable standards in terms of technology and methodology, and then identify the software solution that best approaches those standards. Creative thought processes are important, therefore, at all stages in the R&D process (Figure 2). Once an efficient mechanical process has been established, the temptation is to abandon the expensive creative element and to employ scientists simply as operators of a sophisticated system. Ultimately this approach will not be cost-effective. Creative and innovative personalities will quickly become bored, creativity will cease and good staff will go elsewhere. Ground-breaking drug discovery processes will quickly become outdated and the company will be left without internal resources to maintain a research advantage over the competition.

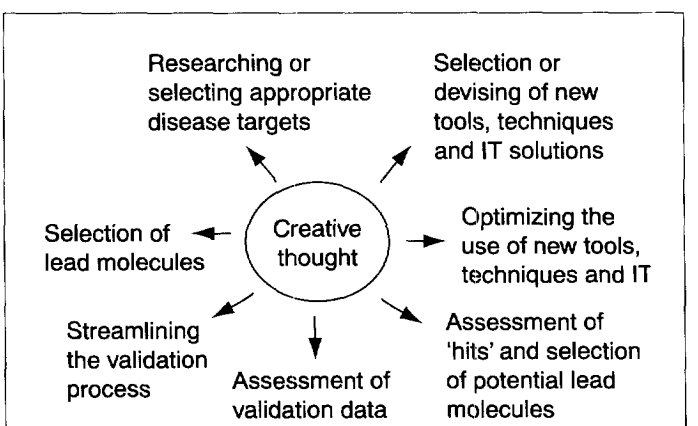

Figure 2. *Importance of creativity in pharmaceutical R&D.*

Stimulating innovation

Good laboratory scientists are essential for the construction, operation and maintenance of research systems. However, high-quality research scientists are the lifeblood of any R&D organization. Such individuals represent a company's primary source of product innovation because they are able to think beyond existing boundaries. Many large companies have made the mistake of trying to 'control' research and research scientists using standard management techniques. This has failed, resulting in reduced creativity and the loss of these key people to small, innovative R&D organizations, such as biotechnology companies. To gain a competitive edge, it is essential to attract and retain high-calibre researchers – a major challenge to the human resources policies currently in place in many major pharmaceutical companies.

The loss of highly innovative staff to small companies is unlikely to stop until large companies take a look at the attractions that these companies hold for scientists. Foremost is the freedom to carry out independent research in an environment that promotes personal academic/scientific growth and the promise of sharing directly in the 'prize'. With R&D departments of large companies under pressure to perform, providing this research freedom and linking this to adequate rewards is not without its problems for management.

To recruit and keep high-quality scientists, the industry must promote a climate of innovation in which scientists can work to full efficiency, thus increasing the likelihood of new advances and innovative products. Companies need to concentrate on providing a working environment tailored to maximize creativity and be willing to act quickly on scientific success and to learn from scientific failure. This type of commitment to innovation is a long-term investment. It also requires a shift in thinking and resourcing. Traditionally, research has received about 30% of the R&D budget, but if innovation and creativity is to be maximized this needs to increase to about 50%[8].

These same principles apply when working with other companies. When striking up strategic alliances it is important that the larger company does not place such heavy legal, commercial and procedural restrictions on the activity of the smaller partner that they stifle the very innovation that they are trying to obtain[18,19].

Understanding the process of innovative discovery

Top scientists begin life in universities. Here, the process of discovery includes benchwork, reading, thinking, formal and informal discussions with colleagues and attendance at scientific and medical conferences. It is this mix of intellectual and practical disciplines that provides the environment for leaps of imagination. Status for a scientist is dependent on the quality of their published work and their profile at meetings and among their peers. It is that individual's contribution to scientific understanding – the quality, not the quantity, of discoveries – that brings acknowledgement. Often the failure of an experiment or hypothesis is seen as a positive addition to knowledge.

When a scientist joins a pharmaceutical company these working practices and belief systems do not change and are often in conflict with corporate culture. For companies, the objective is fast throughput of large numbers of new therapeutic entities. Management often fails to see the need for scientists to maintain their academic networks, and does not encourage spontaneous informal discussion or diversions away from the perceived primary research tasks. Systems are in place to limit 'off-track' experimentation and failure of a research idea is often viewed as wasted time and resource.

Encouraging the maverick

People who think and act in a highly innovative and often unconventional manner are likely to be perceived as mavericks. If they can go beyond the boundaries of scientific thought, they probably also tend to ignore the boundaries of management practice and corporate structure. Instead of attempting to force mavericks into a mould, companies should strive to create an environment with a built-in acceptance of maverick behaviour and intrinsic strategies for working with such individuals. Indeed, would yesterday's Nobel prize winners fit into today's pharmaceutical industry environment?

How important is the environment?

Companies wanting to recruit and keep good scientists must provide a good physical environment and a management structure designed to maximize innovation (Box 4). Excellent research facilities, realistic budgets and motivational reward structures will prove good attractions, but to keep good people and to maintain their creativity, it is essential to provide a lively, supportive environment that combines scientific challenges, freedom and debate with corporate openness and risk taking (Figure 3). In addition, perhaps companies should challenge the general tenet that money and managerial status are not major drivers for researchers.

Box 4. The dimensions of the creative environment

Increases creativity	Decreases creativity
• Enjoyable, energetic	• Alienated, indifferent
• Independent, initiatives taken	• Passive, rule bound
• Excitedly busy	• Boringly slow
• Trusting, failure accepted	• Suspicious, failure punished
• Off-task pay	• Little off-task pay
• High performance incentives	• Few performance incentives
• Happy, humorous	• Serious, dull
• High status within the company	• Low status within the company
• Handled with insight	• Warfare
• People listen helpfully	• Negative, critical
• Contentious ideas voiced	• Little questioning
• Job security	• Job insecurity
• Fast decision, risk acting on new ideas	• Cautious, safe decisions, detail and committee bound

Towards more effective decision making

Companies must handle huge quantities of information, both internal and external, on all aspects of new drug discovery – automated new drug discovery technology, strategic alliances, the published literature and the Internet. Consequently, companies are drowning in data. To rise to the information challenge, companies must recognize that the key to effective decision making lies not merely with the quantity or quality of data acquired but with the effective management of those data to deliver the knowledge upon which informed decisions can be made. At present, in many companies the quality of data management, and as a consequence the quality of acquired knowledge upon which decision making is based, is woefully inadequate.

Need for data management

IT should be exploited for the efficient storage of data, and the effective analysis, retrieval and dissemination of that

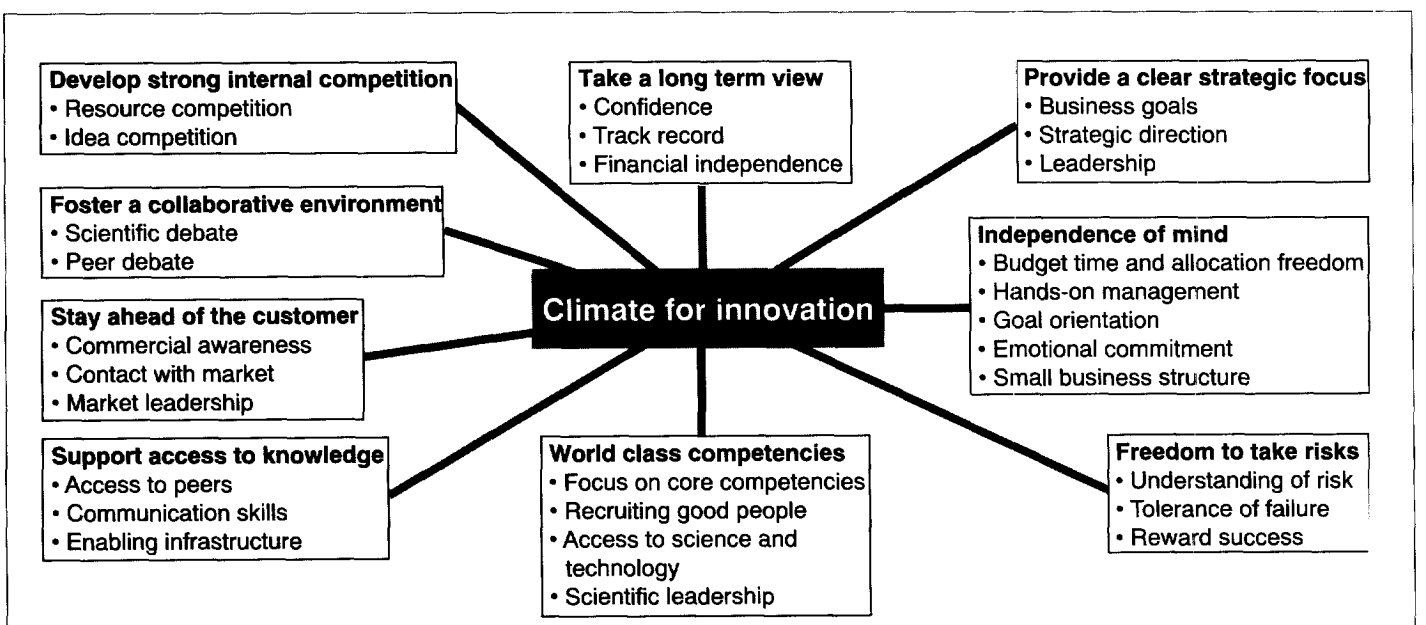

Figure 3. *Fostering a climate of innovation.*

data, in a format that will inform decision making at all levels within pharmaceutical companies[20]. To stay ahead, pharmaceutical companies must invest in the best IT systems that they can afford. However, all IT systems rapidly become outdated and require upgrades and further investment. For this reason it is often best to use existing technology effectively and to buy in updates and training as required, rather than developing new or bespoke technology[20,21].

Turning data into knowledge

Common access and ease of data retrieval throughout the organization are critical to the application of IT as a tool to inform decision making. Many companies do not have fully integrated systems, although this situation is changing rapidly. Each department, at least, probably has a computer system, but this is unlikely to be accessible (or readily understandable) by people from other disciplines. Consequently, isolated data analysis in one area of the business without access to data from other areas may deliver incomplete knowledge – leading to less effective decision making.

When linked to internal communication practices that facilitate effective information exchange between colleagues from different disciplines, integration of IT systems will ensure the delivery of higher-quality knowledge to decision makers. Investment in corporate and divisional infrastructure (LANs, data centres, intranet, WAN, e-mail, Internet, etc.) should be considered an integral component of the complete IT platform.

Re-engineering for creativity and efficiency in drug discovery

For a modern pharmaceutical company to remain competitive, it must:

- maximize the efficiency and quality of internal research output;
- construct alliances and joint ventures to maximize the spread of capabilities and knowledge;
- use information technology to facilitate effective research activity and to create a transparent decision-making environment.

Business process re-engineering has been applied successfully to many aspects of pharmaceutical development, but until now, research has not been tackled. The challenge facing companies today is how to re-work the research environment to promote creativity alongside speed and quality of output. Companies that invest in automation and IT alone, without undertaking a fundamental realignment of working practices or recognizing the need to foster creativity, risk becoming 'also rans' in the race to be first to market with innovative blockbusters.

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From the Anderson Consulting drug discovery study...

Between 1990 and 1994 the top 20 companies brought to market an average of only 0.45 new products each year. And, historically, only 8% of products in the market have ever achieved annual sales of more than £350 million (defined by the study as the minimum revenue target for truly successful products).

Companies vary greatly in the size of their discovery teams, but the study found no correlation between team size and NCE productivity. Rather, productivity appears to be more dependent on team structure.

Copies of the executive briefing on the study (released 15 October 1997) are available from David Martin at Anderson Consulting (tel +44 171 304 8748).