

Redesigning drug discovery

Glaxo Wellcome has set itself the objective of introducing three significant new medicines a year, every year, by 2000. Before they merged in March 1995, Glaxo and Wellcome together averaged one drug a year; if it succeeds, the re-engineered research and development process could thus become a role model for the industry.

This target and the restructuring of R&D needed to achieve it have profound implications for the drug discovery process. Assuming an improved success rate in Development of 20 per cent, 15 strong candidates a year must enter the development process by 2000. In 1995, 13 candidates made the grade. But that was, in fact, exceptional. On average there are fewer than 10, of which only one (taking an industry average) will reach the market.

The aim is therefore to produce drug candidates more quickly, while reducing the number that fall out during development and holding down expenditure on R&D. To achieve this, Glaxo Wellcome has adopted an approach based on the concurrent engineering techniques of manufacturing industries.

Drug discovery is now carried out by focused, multidisciplinary teams whose members work in parallel. Even some of the company's newest laboratories at Stevenage are being revamped to accommodate chemists and biologists working side by side. In addition, each disease area is now considered a horizontal business, with separate therapeutic directors for the research, clinical and commercial aspects. Team members study the big picture for each disease collectively, while individually directing strategy within their discipline.

For Glaxo Wellcome, this has been a radical change. Previously, output was determined mainly by scientific opportunity: if there was a good idea in Research it was exploited. Then, as Development revealed the qualities of the new drug candidates and their therapeutic potential was examined commercially, attrition at an unacceptably high rate set in.

A cultural change within drug discovery has been taking place over the past 18 months. Glaxo Wellcome values its high-quality scientists, but recognizes the motivation that comes from the prospect of a drug that will improve people's lives, rather than simply doing science for science's sake. So research must focus on disease processes that are clinically relevant and commercially viable. Even now, few people within Glaxo Wellcome (or, for that matter, anywhere else), have had the

privilege of discovering a drug that has gone on to play a valued role in treating patients. The new approach should dramatically increase the number within the company who will enjoy that satisfaction.

Commercial relevance is achieved in a number of ways. One of the simplest is by having senior commercial staff on all key decision-making bodies in R&D, together with R&D representatives on commercial committees. This leads to dialogue, not only about "What is possible?", but also about questions such as "Does it make sense?"; "Do we want to be in this area?"; "Do we see a medical need?"; "Can we prove the value of this new medicine?"; and "Does the company want it?"

Another key change, which should improve the success rate of compounds entering Development, comes from involving developmental disciplines earlier in the overall process. Some years ago, drug metabolism, pharmacy, toxicology and process chemistry were the sole remit of Development and were often distant from Research. Drug discovery teams thus produced compounds with potency and selectivity for particular receptor classes that were considered appropriate for further development, only to be dropped when pharmacokinetics and toxicity were assessed. It is now accepted that potency may have to be compromised in order to achieve a balance of potency, pharmacokinetics, safety, cost and selectivity.

But the major improvements in productivity needed will come through the use of new technologies, including combinatorial chemistry, robotic high-throughput screening, advances in medical genetics, and the application of bioinformatics. Target identification, in particular, is an area of unprecedented opportunity. This is not only because of the vast numbers of gene sequences in public and private databases, but because of the recognition that these gene sequences can be grouped in families which can be exploited efficiently and systematically, so the effort invested in one family member yields insights into others. To take an example, cloning many sodium channels, rather than one, can uncover targets not just for epilepsy, but also for stroke and pain.

Another hard truth of modern drug discovery is that no company can hope to stay at the forefront of all the scientific disciplines needed to remain competitive. Although Glaxo Wellcome has the world's largest pharmaceutical research resources, it remains a very small part of the international biomedical research community,

and it is well aware that most significant discoveries will occur outside its walls. Hence it is constantly seeking opportunities to form partnerships, collaborations and alliances with others who share its objective to understand disease.

Glaxo Wellcome now invests about 20 per cent of its £200 million budget allocated directly for research projects on external collaborations. The aim is to find people doing ground-breaking research who can benefit from the company's therapeutic expertise. It now has research alliances with biotechnology companies, university groups and even other major pharmaceutical companies. Glaxo Wellcome's new, systematic approach to drug discovery has also provoked a reappraisal of academic sponsorship, dictating a more strategic approach directed towards centres of excellence.

To maintain a thriving drug discovery process, Glaxo Wellcome needs input from a broad range of partners. But to attract and capitalize on this external research, the company must undertake credible in-house research, so as to bring something to the partnership. By participating fully in the international scientific dialogue, Glaxo Wellcome is much better placed to understand trends in research and exploit any therapeutic opportunities they present.

In addition to the work at its large sites in the UK and US, Glaxo Wellcome promotes this participation through its Geneva Biomedical Research Institute. The 140-strong institute has a growing reputation for doing world-class research, with well over 100 papers published in 1995. The work at Geneva is complemented by three further European research centres: Verona, which specializes in antibiotics and the central nervous system; Madrid, which specializes in antifungals; and Paris, which specializes in cardiovascular disease. Although these sites are relatively small, they are very effective in discovering new therapies, providing significant flexibility and dynamism together with access to a large population of highly educated researchers. Glaxo Wellcome also conducts research in Japan and funds a centre for screening natural products in Singapore.

Glaxo Wellcome's new drug discovery strategy is founded on the recognition that there must be change. The pharmaceutical industry has always known it must spend billions on R&D. But in the past it has run R&D as if it were a cottage industry — a series of small one-off projects with no attempt to look for economies of scale. □