Dizzying but scary: looking towards R&D in 2005

Alarm bells rang for the industry at the Pharma Directions '99 conference held in Barcelona (2–4 June 1999), organized by ECPI. Industry leaders and advisors gathered to identify the challenges for the industry with predictions of where we will be in 2005. The event ties in with the release late last year of the PriceWaterhouseCoopers report entitled *Pharma 2005: an industrial revolution in R&D* (see Ref. 1).

George Poste (SmithKline Beecham, Harlow, UK) stirred the audience with an opening presentation highlighting the challenges and opportunities for the pharmaceutical industry. He acknowledged that it has never been more exciting to be part of the industry, but reflected that the current prospects in economic, regulatory and technological terms are both dizzying and scary. The technological revolution of the past five to ten years has been truly phenomenal and changes in scale, miniaturization, automation and parallelism have impacted every aspect of drug discovery. Poste pointed out that before 1995, there were less than 500 biological targets available, whereas now, through genomics, there are in excess of 70,000 possible biological targets. No company can cover all the bases and so the growth of collaborative research will continue.

As the advances in discovery translate into new leads, the bottleneck is moving downstream. Drug testing and evaluation will present major challenges for the industry as more compounds enter the pipeline, especially into Phase I clinical trials. As a consequence of the recent focus on molecular biology and new technologies, too few *in vivo* pharmacologists and toxicologists have been trained for the industry to cope. As Poste points out, it is scarcely likely the cassette dosing in humans will be acceptable to regulatory authorities.

Adverse drug reaction burden

Poste highlighted the important role that molecular diagnostics will play in the future of healthcare, both in terms of reduced cost of drug development for targeted patient groups and through reduced adverse effects by exposing only the most appropriate patients to dangerous drugs. Remarkably, adverse drug reactions are now the fourth greatest killer in the US, even before taking clinical ineptitude into account. By focusing therapy through the use of pharmacogenetic profiling to identify polymorphisms and patient variability, it should be possible to substantially reduce this burden. By 2005, authorities might require the production of dossiers that include a pharmacogenetic element.

The industry already faces a crisis of low productivity (in terms of the number of new therapies being launched versus the spiraling cost of new drug discovery). Pharmacogenetic profiling will result in a reduction in patient populations eligible for a given drug, and hence, the revenue from these drugs can be expected to fall. However, companies might be able to compensate for this through smaller scale, well-focused human trials and premium pricing policies for exquisitely directed drugs.

Poste identified what he considered to be the two biggest threats to the health of the industry. One threat is cost controls, which are already having a major impact in Europe, and are expected to start to affect the US. Society must therefore find a way forward that will allow the industry to produce innovative but affordable products. Poste predicts that the current complacency within society regarding the wide availability of effective medicines will be punctured by a severe window of exposure to antibiotic-resistant bacteria between the year 2003 and 2008. The second threat, which has largely been unforeseen, is the Internet. Notably, transparency of pricing through the release of information on the Internet is likely to expose major disparities in discounting policy. Payers are then likely to become forceful in demanding the lowest available price.

Productivity deficit

Stuart Walker (CMR International, Carshalton, UK) illustrated the productivity crisis for the industry by looking at output of new therapeutic entities in recent years. Chief Executive Officers (CEOs) of the major players are promising two to three new molecular entity launches per annum from the year 2000 (which is almost upon us). The reality of recent years is that the average figure has been approximately 0.8 launches per company per year. At the same time, even though the duration for approval of regulatory submissions has reduced, overall drug development times are not yet falling substantially. In addition, the regulatory load can be expected to increase, possibly to the point of overload. More dossiers of increasing complexity will be reviewed by an increasing number of authorities as emerging markets

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develop. At the same time, much of this effort will be redundant as authorities, in parallel, review what is effectively the same dossier (because of standardization via the International Conference on Harmonisation process). The logical way to overcome this problem must be to prevent duplication through the increased use of standard operating procedures and joint review or adoption of mutual recognition procedures along the lines of those now in use in Europe.

Clinical trials remain an expensive process and represent approximately one-third of the research and development (R&D) budget. Walker predicts that outsourcing of clinical trials will continue to grow. A major challenge will be to source adequate numbers of patients and this will require the use of specialized organizations. It is, however, likely that there will be a much wider use of computer simulation of clinical trials, with trials in humans being increasingly used as a final proof-of-concept stage. We can also expect to see a new policy of conditional drug approval based on minimal data sets, with mandatory extensive follow-up for certain patient groups.

In general, there is now no part of the process of drug development that cannot be outsourced, and virtual companies are now feasible propositions. The value of effective project management of relationships with external partners was illustrated by Tony Kennedy (Roche Products, Welwyn, UK). He used, as an example, the clinical evaluation of Oseltamivir, Roche's anti-influenza neuraminidase inhibitor licensed from Gilead Sciences (Ro640796 or GS4104). Well-designed logistics for clinical trial management and supply, and disease tracking were essential given the epidemiology of influenza. Kennedy focussed on several reasons for entering into these collaborations:

- The partner company might have superior capabilities
- These companies might have poorer capabilities but might possess specific intellectual property (e.g. through luck)
- In-house capacity of the company might be at carrying capacity
- Synergy.

Managing people and cultures

By increasing the speed of drug discovery, and by overlapping the stages within discovery and development, it has been possible to expedite R&D. Several speakers highlighted the importance of efficient team structures that can transcend geographical boundaries effectively, both by employing the best technology for information retention and transfer, and by breaking culture barriers. Several speakers, such as Leandro Herrero (Allergan, High Wycombe, UK) and Frank Douglas (Hoechst Marion Roussel, Frankfurt-am-Main, Germany) highlighted how rewards are still often designed to stimulate individual endeavour, whereas the greatest advantages can only be achieved through team-based reward and a sharing culture.

The merger of Pharmacia and Upjohn has presented the clearest example of how mismatched or misunderstood cultures from different regions can reduce the effectiveness of management. In a talk entitled *Working across borders*, André Laurent, Professor of Organizational Behaviour at the European Institute of Business Administration (Fontainebleu, France) characterized the behaviour of different geographical cultures as falling into two categories: low- and high-context cultures. The low-context culture is typified by the cut-to-the-chase approach common in North American and North European business cultures. In contrast, the business styles adopted in, for example, South European or Asian cultures rely strongly on relationship-building processes, and in these environments, direct approaches can even be perceived as rude. Laurent states that the 'global mindset' is still very rare, and what is more common is the perception among executives that the behaviour of their counterparts in other cultures is an unfortunate deviation from normal behaviour. He recommends that companies now become much more active in developing a positive appreciation of cultural differences. This drives a desire to learn from other cultures and acquire new ways of operating.

Coping with the big picture

Steve Arlington (PriceWaterhouse-Coopers, Uxbridge, UK) made it very clear that extensive changes are on the horizon for the industry and for healthcare as a whole, and that new ways of thinking will be necessary. The industry faces cost constraints, market growth has declined and, through competition, market exclusivity has declined from ten years to as little as 16 weeks. Companies also now face something of an identity crisis: with new technologies and technology partners they can all do the same things, and so where does the competitive advantage lie now? At the same time, the patient is better educated and informed about their disease and treatment requirements than ever before, with some 50% of Internet traffic being healthcare-related.

Arlington believes that, as a result of such pressures, the major companies will have to learn to live in a much lower margin business or make radical adaptations. There is a great need to move away from blockbuster mentality to careful husbandry of the portfolio as patient populations become more focused. PriceWaterhouseCoopers have applied their Value Builder™ model to drug development to evaluate total shareholder returns (TSR) in relation to productivity and R&D costs up to 2005. The results were not encouraging. They calculated that the industry can afford to launch 37 new chemical entities

(NCEs) at $350 million (total costs, including attrition of leads) per drug by 2005, but this will provide a TSR of less than 10%. Using R&D costs of $500 million per drug, only 26 NCEs could be launched and the TSR approaches zero. According to Arlington these estimates may be 'soft', as some experts now put R&D costs for drug development as high as $660 million. He concludes that the industry must transform itself in less time than it currently takes to develop a single new product by:

- Focusing – companies must understand very clearly what their business is and where it needs to be in 2005.
- Technology – innovations in technology must be used to reduce the costs in drug development and improve the quality of new products.
- Information technology – companies must use advances in informatics and knowledge management to harness the vastly expanding quantity of information generated in R&D and emerging in the public domain.
- Organization and team structure – companies must reinvent themselves as a new type of organization that facilitates the development and retention of new skills and enables people to work seamlessly and effectively across organizational and geographical boundaries.

Clearly, many new challenges face the industry and there is now realization that changes are coming very fast. The way forward lies in simpler, cheaper, streamlined drug development relying on the best use of informatics and knowledge management. As time passes, several of the traditional drug development steps can be expected to be performed *in silico*, with greater than ever reliance on research partners and the contract sector. Drugs will be more focused and patient groups smaller. Patient power will grow and the industry will have to respond through an increased focus on value with appropriate pricing, and middlemen (pharmacists and doctors) will feel the pressure. Competitive advantage will go to the smartest and fastest adapters.

The writing is on the wall for those companies that fail to adapt quickly enough to the pressures of cost containment, competition and technology.

The next Pharma Directions conference is to be held on 5–7 June 2000 in Cannes, France. For more information, contact Tracy Moring, ECPI conferences, tel: +44 171 242 1548, fax: +44 171 242 1508, e-mail: tracym@aic-uk.com

REFERENCE

1 Fenwick, S. (1999) *Drug Discovery Today* 4, 3

David Hughes

Researchers reveal ways to defeat 'superbugs'

For many years, the focus of antimicrobial development has shifted away from bacterial to viral pathogens. In addition, new antibiotics released onto the market were usually seen as 'me too' variations of existing therapies. With the advent of numerous resistant 'superbugs', such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP), an alarm has started to resound. Physicians have been faced with an ever-growing list of resistant bacteria threatening the lives of their critically ill patients as many time-honored drugs are not working against new, constantly mutating bacterial strains.

Fortunately, the pharmaceutical and biotechnology industries have risen to the challenge. With an array of new antimicrobial drugs, as well as new methods of preventing the development of bacterial infection with superpathogens, these superbugs are not now quite the 'doomsday' threat they were in the early 1990s.

With these issues in the forefront, a distinguished group of industry researchers gathered in London on 13–14 April 1999, for the conference, *Superbugs and superdrugs: innovations in anti-infectives*. The purpose of the meeting was to examine the latest advances in the treatment of life-threatening bacterial infections, as well as to present new methods of identifying and developing new antimicrobials. Chief among the presentations were those focusing on new therapies for pathogens resistant to multiple antibiotics, with an emphasis on resistant gram-positive organisms (Table 1).

George Miller (Microcide, Mountain View, CA, USA) outlined the company's strategic approach to targeting antibiotics and genomics. Microcide's targeted antibiotic program includes MC02479/RWJ54428, a cephalosporin antibiotic that is active against VRE and MRSA but not against ampicillin-resistant *Enterococcus faecium*. This product has been produced in partnership with Johnson & Johnson (Raritan, NJ, USA) and is in late-stage pre-clinical development, with clinical studies planned for later in the year.

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