Predicting the future for R&D – science or art?

On page 491 of this issue, Jurgen Drews, former Head of R&D at Hoffmann-La Roche, examines recent productivity in the pharmaceutical industry and gauges the extent of the 'innovation deficit'. The Tufts Center for the Study of Drug Development, based in Boston, is one of very few organizations dedicated to the study of the drug development process itself, and it monitors key indicators of productivity in R&D. On a strictly confidential basis, the center is allowed access to proprietary information from most major companies in order to research issues such as R&D management, productivity and project management.

In September 1998, Kenneth Kaitin took over as Director of the Tufts Center, a position formerly held by Louis Lasagna. Ken is also the immediate past President of the 20,000-member Drug Information Association. In his new role, Ken is responsible for setting strategic direction and overseeing the research activities of the Center. His research interests include regulatory and legislative affairs, public policy and the speed of pharmaceutical innovation. Colleague Joseph Di Masi, Director of Economic Analysis at the Center, focuses his research program on pharmaco-economics and its impact on company structure and processes, and cost and productivity issues in drug development. I recently took the opportunity to present Drs Kaitin and Di Masi with some questions regarding the current direction of the industry and how progress can be monitored and evaluated.

To survive, the industry must ensure that it can generate sufficient payback from products. What tools can be used to measure productivity?

JD: The metrics that we use and have extensive experience in are development costs, development times and technical success rates for new drugs. The confidential information gained in surveying the pharmaceutical industry regarding investigational and approved new drugs includes a lot of development history data that allows us to estimate development and approval times and success rates. We have also looked at individual projects and obtained drug development costs for specific products. No-one of these measures fully defines productivity in drug development but they are all indicators of some aspect of productivity.

Kenneth Kaitin, Director (left) and Joseph Di Masi, Director of Economic Analysis at the Tufts Center for the Study of Drug Development.

Do you feel that the current levels of productivity will be adequate to sustain the industry?

JD: This is certainly a concern. On the other hand, what we don't know is what the biomedical advances of coming years will be – these may well feed the drug development pipeline. Recent advances in drug discovery technology provide much hope.

KK: From recent FDA data, the number of IND filings has increased dramatically, which would suggest that we are beginning to see the fruits of these new technologies. However, my sense is that the industry still relies to a great extent on the tried-and-tested methods of traditional drug discovery.

You hear a lot of people talking about the contribution of the new technologies, but although the companies are focusing their efforts on increasing productivity, I've yet to hear firms come out and say that they are capable of handling a tremendous increase in the number of products that might suddenly enter their pipelines. Firms are trying to cut R&D costs and they're trying to make go/no-go decisions earlier in the process. Many of the new technologies run counter to that. We're still not going to see the real impact of those technologies until a few years down the road.

Published estimates of the overall cost of drug development range between $200 million and $600 million. What is your current appraisal of this figure?

JD: We're currently updating our past work in this area. Our last study put the figure at more than $300 million in today's dollars. Depending on what interest rate one uses to capitalize costs, that figure could also be in the region of $450 million. So the figure would be in the range $300–450 million for products that reached the market in the 1980s and early 1990s. If one looks at a range of aggregate statistics, there is every reason to believe that the cost is higher for drugs coming onto the market now or in the near future – $500 or $600 million or more is not an unreasonable estimate for the costs of drug development.

The changing economics of this industry means that companies have become increasingly interested in development of breakthrough products.

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Recent years have seen lengthening development times, now in the region of 12 years. How do you expect this to change in future?

JD: I don't see them increasing substantially now and there is a good chance that they will decline. A lot of effort is being made to make the process more efficient in all phases and at a micro level. These efforts should pay off in the near future. FDA reform may also help. Legislation passed by Congress encourages the FDA to work more closely with companies throughout the development process and as early in the process as possible, which should lead to improved efficiencies.

KK: The Tufts Center played a significant role in these discussions. With the Prescription Drug User Fee Act of 1992, the emphasis was on review times, and the question within the industry was whether the FDA would be able to meet its statutory requirements under the act in reviewing drugs – 12 months for standard drugs, six months for priority drugs. The agency showed that it could approve drugs on schedule. Review times have now essentially become a non-issue. What we highlighted, through our congressional testimony, was that this misdirected the emphasis.

The emphasis should now be on development time – not only is this the lengthiest period of time to bring a new product to market, but it is also the area where there is most room for improvement. There was clear intent in Congress in the most recent debate that medicines should be brought to the market more quickly, and in order to do this, the industry must speed up development and the FDA must become an active partner in this process. Quite a few initiatives in the new piece of legislation (FDA Modernization Act of 1997) deal with such issues. The industry itself, for the purpose of its own survival, must reduce development times and costs, increase success rates and market blockbuster drugs. The likelihood of achieving all of these, all at once, is very small; so it will be a while before we see significant improvements in development times.

There are reasons for longer development times beyond inefficiencies in the system. For example, the increase in pharmacoeconomic and other market-oriented studies and the global marketing plans of some firms all impact on development times. Nevertheless, there are some positive signs – the International Conference on Harmonisation (ICH) initiatives for example; if one document can suffice for Europe, the USA and Japan, then that will make it easier for the industry. But there are factors acting in both directions. My feeling is that we will see a slow change in the direction of faster development times.

What is your view on the impact of creation of the EMEA in this context?

KK: We have done some work in this area. We compared drugs that have been assessed by EMEA (European Authority Evaluation of Medicines) and the FDA. There are many caveats to this work: the EMEA is a new organization and they are still working out some of the kinks in the system. At the same time, the FDA is going through a period of rapid approval of compounds, especially priority products. What we see is that the FDA is approving some products faster than the EMEA, but in the long haul there will be great benefits in the new European system.

How can companies predict market values of their drugs in order to budget R&D effectively and direct their research efforts? Pfizer, for example, talks in terms of being 'overwhelmed' by the response of the market to Viagra.

JD: If you're far enough along in the drug development process, you can get a reasonable idea of what the market value will be. There will always be exceptions – Viagra was certainly one of those, but once a company is clear what the indications for use will be, it is possible to estimate future market value. There is one major complication – the development and timing of competitors.

KK: There's probably more art than science here, but this doesn't stop companies from trying to make such assessments earlier and earlier in the process. There are now marketing people involved in drug development even at the preclinical phase trying to establish net present value. This seems an impossible task, but the goal is to obtain a sense of what the value of a drug might be if it were marketed today, but on the basis of limited data.

JD: Such processes may be imprecise, but they do help companies to make rational choices. Basically, they are better off with such analyses than without them.

What are your expectations of consolidation within the industry?

KK: There is no evidence of this trend declining – largely due to development cost issues. One solution that industry has found to optimize its product development and marketing and to increase its pipelines is to merge. I think the near merger of Glaxo Wellcome with SmithKline Beecham (who are both already merged companies) is an indication of things to come. Even though there remain many unmet medical needs and opportunities for niche providers, such as biotech firms, to address some specific areas, my view is that within 10 years we will see only a few

companies with a great share of the market – maybe 5–10 companies controlling 70–80% of the market.

We see increasing interactions between different players in R&D such as academia, major companies, biotechs and the contract sector. What sort of dynamics will characterize the next five years?

JD: My expectation is for a continued increase in outsourcing – especially early in the process. We will continue to see a lot more strategic alliances between big pharmaceutical firms and biotechs and also between biotechs.

KK: The contract market is not close to being saturated at this point. To cut costs and improve efficiency there will be further reliance on outsourcing. The changes in the contract sector alone will be interesting to observe – i.e. the integration of the site management organizations (SMOs) and the CROs. Large full-service CROs are becoming more global as they move into China and developing countries, but there will always also exist the niche provider CROs, specializing in, say, pediatric trials or Phase IV trials.

How would you summarize the challenges and opportunities for the industry?

KK: The major challenge is to take advantage of the current environment worldwide (but particularly in the USA) where there exists a spirit of cooperation between regulatory authorities and the industry. There is no reason to assume that this level of cooperation will last forever, and there is currently a unique opportunity for the industry to work as a partner with the FDA. For example, it should be possible to improve the process of drug development – making it more efficient and obtaining more feedback earlier in the process on clinical development and trial design. A major challenge is for companies to operate effectively on a truly global basis. However, global initiatives such as ICH provide more direction and assistance to the industry to market products in this changing environment. It is definitely a time of change for the industry but also a time of opportunity.

JD: An important challenge in the current environment is for firms to discover more breakthrough products than they have in the past. Alongside that is the opportunity to take advantage of exciting scientific opportunities, which requires improved networking with academic research in the drug discovery area.

Information about research programmes, publications, workshops and other issues associated with the Tufts Center for the Study of Drug Development can be found on the Center's website (http://www.tufts.edu/med/research/csdd).

David Hughes

Natural extracts – a new perspective on assessing diversity

A revolutionary new technique for assessing molecular diversity in natural extracts has been developed by scientists at Eli Lilly's research laboratories in Indianapolis, IN, USA. The algorithmic technique based on chromatography and mass spectrometry assesses natural extracts using relevant information directly related to the drug-like compounds being searched for, rather than to any biological classifications of the source. The method will help researchers decide whether to pursue particular leads in different extracts without having to carry out isolation and assaying of individual compounds that could be dead-ends.

High-throughput screening is an everyday technique for screening huge libraries of known compounds, often generated by combinatorial techniques. Drug researchers, however, are still in hot pursuit of novel molecules in natural products that might display interesting biological activity.

Comparing extract diversity

Randall K. Julian Jr of Lilly's Natural Products R&D and his colleagues believe that it is possible to reduce the technical demands of natural extract screening. 'If two extracts are overly similar, the likelihood of them containing the same compounds is high,' says Julian. It would be like reinventing the wheel to isolate and screen such extracts, but assessing similarity is not trivial. Julian's technique allows the team to assess molecular diversity among paired extracts in a simple way without recourse to taxonomy, which acts only as an indirect predictor of chemical diversity. They can then decide in which extracts to invest limited resources. 'This investment takes the form of

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