# The risky business of drug development in neurology

**Long timelines and high attrition rates make drug development for disorders of the nervous system an expensive and risky business. Can the problems be overcome to speed up the delivery of effective, safe treatments to patients with neurological conditions? Rebecca Craven investigates.**

When GlaxoSmithKline (GSK) announced in February, 2010, that it was pulling out of drug discovery in some aspects of neuroscience, including psychiatric disorders and pain, many researchers in the field of neurology were deeply concerned. Among them was Jes Olesen, professor of neurology at the University of Copenhagen and chief of the Danish Headache Centre at Glostrup University Hospital, Copenhagen, Denmark. "GSK has been a world leader in the field of migraine for almost two decades", explains Olesen. "To back out of such a position of strength really illustrates the difficulties that we are encountering in drug discovery and development."

For more on **Tufts CSDD's report for the Institute of Medicine** see *Science* 2010; **329:** 502–04

Patent expirations, constrained health-care budgets, and increasingly stringent regulatory requirements, coupled with escalating costs of research and development (R&D), have put the pharmaceutical industry under growing pressure to overhaul its R&D practices to improve efficiency and productivity. "Pain has been an area, over the last 10 years or so, which has had a very high failure rate", says Patrick Vallance, GSK's head of medicines discovery and development. "The fundamental decision we made is to base our investments in drug discovery on where we see the biggest scientific opportunity to make the biggest difference to patients."

For more on **drug development for CNS disorders** see *Nat Rev Drug Discov* 2007; **6:** 521–32

For more on **R&D productivity** see *Nat Rev Drug Discov* 2010; **9:** 203–14

For **Tufts CSDD's most recent analysis** see *Clin Pharmacol Ther* 2010; published online Dec 29. DOI:10.1038/clpt.2010.286

And GSK is not the only company to be making difficult decisions about the allocation of its resources. Other major pharmaceutical companies are also stopping work on pain medication, their efforts to develop new, effective, and safe analgesics having been thwarted time and again. But what of other aspects of neurology? Are other programmes managing to find success where pain R&D has failed?

For more on **drug development for pain** see *Nat Med* 2010; **16:** 1241–47

For **PhRMA's reports on medicines in development** see http://www.phrma.org/medicines_in_development/

At a meeting convened in June, 2010, by the US Institute of Medicine's Forum on Neuroscience and Nervous System Disorders, to consider the challenges of drug development for CNS disorders—a response to GSK's cuts and the announcement in March, 2010, that AstraZeneca would also be pulling out of R&D for psychiatric disorders—Kenneth Kaitin, director of the Tufts Center for the Study of Drug Development (CSDD) at Tufts University (Boston, MA, USA) presented some sobering figures to leaders from industry, academia, and government.

> **"The industry's saying, we have to work together or nobody will have products for these diseases."**

Clinical programmes for CNS disorders tend to be larger, longer, and more complex than those for other indications, says Kaitin, and the inclusion criteria are often more rigorous, adding to the time, cost, and risk of drug development. "Based on the most recent analysis that we've done", he says, "it takes, on average, a decade to go from the start of clinical testing to approval by a regulatory agency." Making matters worse, says Kaitin, "is the fact that the success rates for CNS products are the lowest for any therapeutic area". Only 8% of the products that start clinical testing will eventually reach the market place, he says. Of the compounds that reach phase 3 testing, "less than half will move on to approval, and that's a worst case scenario for the industry".

A report released in 2008 by the Pharmaceutical Research and Manufacturers of America (PhRMA) boasted more than 500 drugs in development for neurological disorders, but Kaitin says that the figures are deceptive. "If you look at worldwide R&D activity, it looks as though there are a lot of projects going on in the CNS area. But when you look at what those projects are—what types of compounds are entering clinical trials—it's clear that there are very few new, innovative compounds entering R&D programmes around the world in CNS."

The pipeline contains a lot of "me too" drugs or old drugs being tested for new indications, says Kaitin. "This is industry's way of saying, we're looking for an easy hit here. We don't want to put all our money into the next Alzheimer's drug, because there have been some colossal pipeline failures lately." A recent casualty was semagacestat, a γ-secretase inhibitor in phase 3 trials for Alzheimer's disease. In August, 2010, Lilly announced that it would be halting development of the drug after an interim analysis showed that it did not slow disease progression and seemed to worsen some symptoms.

Although PhRMA reported more than 100 drugs in development for Alzheimer's disease in 2010, Lon Schneider, director of the California Alzheimer's Disease Center at the University of Southern California (Los Angeles, CA, USA), says that "the near pipeline is rather dull, rather non-innovative. It almost looks like all amyloid, all the time". If the concept is wrong, warns Schneider, a lot of the drugs will fail.

What needs to be done to improve the chances of bringing effective, safe medicines to market? Schneider says

that progress is needed on several levels. In the case of Alzheimer's disease, "we still don't have the core information needed to be able to identify a range of valid targets for drug development. So we need better knowledge—a better understanding of pathology and aetiology. That's easy to say and really hard to do".

Then we need to make progress in translational research, says Schneider. "For example, anti-amyloid drugs are currently tested in preclinical animal models to prevent amyloid accumulation and cognitive impairment", he says, "but they are given to humans who already have Alzheimer's disease instead of being tested in prevention trials." Developing better models of neurological conditions and better ways of translating preclinical findings into humans will be key to developing new, improved drugs for a range of disorders. From a research standpoint, adds Kaitin, "companies are looking for better biomarkers and validated endpoints". And from an operational standpoint, "industry is looking to make trials more efficient".

Having identified what needs to be done, companies are faced with the thorny question of how to do it. The therapeutic needs of patients with neurological disorders are "tremendously high", says Mary Baker, president of the European Brain Council and the European Federation of Neurological Associations. For many patients no truly effective treatment exists, "and yet we're not getting the delivery of products despite substantial investment by the pharmaceutical industry". In Baker's view, the process of bringing new drugs to market "is no longer fit for purpose".

"Industry is realising that the only way to conquer these difficult, complex disorders is perhaps to work together", says Kaitin. "In the past, drug companies would rather fail alone than share in the rewards of success with their competitors. Now that view is definitely changing. The industry's saying, we have to work together or nobody will have products for these diseases."

A new model of drug discovery and development seems to be emerging in which large drug companies form alliances with academia, and with smaller pharmaceutical and biotech companies, to boost early research capabilities and promote innovative R&D, while spreading the risks. "We have a world of great scientists out there", says Vallance. "We need to be part of that community rather than assume we can do it all ourselves."

Drug companies are realising that "there may be a pre-competitive area where we can share information on biomarkers, on patients, on early clinical trials that may have failed", says Schneider. Vallance adds that collaboration between companies is important, "but actually getting a lot of this stuff out into the public domain is in a sense more important in terms of stimulating the science base".

Public–private partnerships are one way in which the various stakeholders are trying to make progress. In June, 2010, the US Coalition Against Major Diseases—a public–private partnership formed to accelerate drug development for brain disorders, including Alzheimer's and Parkinson's diseases—launched the first database of combined clinical trials data on neurodegenerative diseases to be shared openly by pharmaceutical companies and made available to qualified researchers.

The US Institute of Medicine held a workshop in July, 2010, to look at ways in which the information and partnerships formed as part of the Alzheimer's Disease Neuroimaging Initiative could be used to facilitate the development of new treatments. The panellists from industry, academia, and government also discussed the possibility of developing similar international efforts to explore other CNS disorders.

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**The pharmaceutical industry is striving to improve R&D productivity**

In Europe, Olesen hopes that public–private partnerships such as the Innovative Medicines Initiative, which brings together industrial and academic experts, and supports collaborative research projects, will help to tackle some of the sticking points in drug discovery and development for neurological disorders. But he is "deeply worried" about the prospects of progress in specialties in which industry is reluctant to invest. Even "basic academic work is very dependent on an interaction with innovative pharmaceutical companies", he says.

"You can tell industry all you want that they should be in this area because there's a therapeutic need", says Kaitin, "but they're only partially responsive to market need. They also consider the economic challenges, and their response so far has been, I'm not sure we want to be in this area". Only time will tell whether the various stakeholders—industry, academia, patients, payers, and regulators—can pull together to meet the needs of a growing number of people with neurological disorders.

*Rebecca Craven*

For more on **new models of drug development** see *Clin Pharmacol Ther* 2010; **87:** 356–61

For more on the **Innovative Medicines Initiative** see http://www.imi.europa.eu/

For more on the **Critical Path Institute's Coalition Against Major Diseases** see http://www.c-path.org/CAMD.cfm/

For the **Institute of Medicine's report on the July workshop** see http://www.iom.edu/Reports/2010/Future-Opportunities-to-Leverage-Alzheimers-Disease-Neuroimaging-Initiative.aspx/

For more on the **Alzheimer's Disease Neuroimaging Initiative** see http://adni.loni.ucla.edu/