Pharma's year of trouble and strife

Industry hit hard by safety and policy issues

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For many reasons, 2005 was a year that the pharmaceutical industry would rather forget. Public confidence in the industry is arguably at an all-time low, and safety and policy issues overshadowed scientific achievements.

Safety in the spotlight

The year began, much as 2004 had ended, with Vioxx (rofecoxib; Merck) and the other cyclooxygenase-2 (COX2) inhibitors dominating the headlines. In February, an FDA Advisory Committee narrowly voted 17–15 in favour of the overall risk–benefit profile for Vioxx supporting marketing in the US. The committee voted 17–13 with two abstentions that Bextra (valdecoxib; Pfizer) should continue to be marketed, and voted a more unanimous 31–1 in favour of continued marketing of Celebrex (celecoxib; Pfizer). Bextra was withdrawn in April, after another risk was highlighted — a severe skin reaction called Stevens–Johnson syndrome — and an injectable form of the drug (Dynastat) was rejected by the FDA in September.

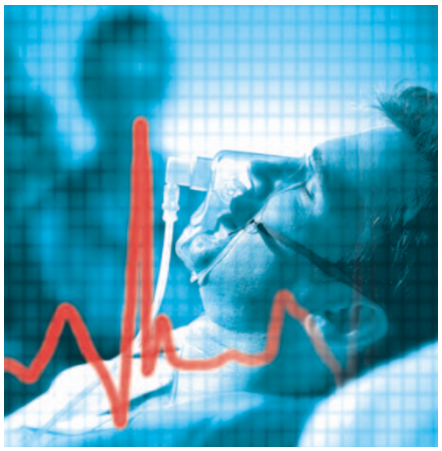
In the first of the lawsuit trials against Vioxx, a jury in Angleton, Texas, ordered Merck to pay a staggering US$253.4 million to Carol Ernst, whose husband died after taking the drug. The jury's decision seemed to be based more on how much Merck knew about the risks before it withdrew the drug than on whether the drug was responsible for Robert Ernst's death from an arrhythmia (heart attack being the only cardiovascular adverse event associated with Vioxx). Merck won the second case on its home turf in New Jersey, but the first of the federal cases was declared a mistrial (see page 10).

Merck is already feeling the effects of the Vioxx saga. CEO Raymond Gilmartin departed from his post in May, and was replaced by Richard Clark, the former head of the manufacturing division. With further pressure from the patent on Merck's best-selling drug, the statin Zocor (simvastatin), expiring in 2006 (see 'Six to watch in 2006') the company announced major cuts, with 7,000 jobs set to go.

The year ended with Pfizer saying it will spend up to $100 million for a trial run by Steven Nissen at the Cleveland Clinic which will compare Celebrex head-to-head with naproxen and ibuprofen in arthritis patients who are at a high risk of cardiovascular disease.

More safety woes

The COX2 inhibitors were not the only drugs hounded by safety problems. Elan and Biogen Idec's antibody treatment for multiple sclerosis Tysabri (natalizumab) was withdrawn in February after two patients developed the rare demyelinating disease progressive multifocal leukoencephalopathy (PML), with one case being fatal. It seemed that Tysabri's mode of action — inhibiting α4 integrin — could suppress the immune system so much it allowed the activation of the normally latent JC virus, which is associated with PML. A third case identified soon after increased fears of more cases and that this could be a class effect. But a safety evaluation of more than 1,000 patients failed to uncover any more cases, and Tysabri has been resubmitted for FDA approval. A decision is expected by mid-2006.



The first of the cases on cardiovascular-related deaths linked with Vioxx entered the courts.

Safety doubts also surrounded Johnson & Johnson's heart failure drug Natrecor (nesiritide). An analysis of pooled trial data showed that the drug might increase mortality or cause renal damage (Sackner–Bernstein, J. *et al. JAMA* 293, 1900–1905; 2005). J & J convened a panel headed by Harvard University's Eugene Braunwald, which concluded that Natrecor's use should be restricted to the most ill patients and that a large clinical trial should be conducted to prove that the drug is safe.

Natrecor was one of the five approved drugs that FDA whistleblower David Graham named in a Congress hearing in 2004 as posing a similar threat to the public's health as Vioxx. In November, the FDA requested that another of the named drugs, GlaxoSmithKline's asthma treatment Serevent (salmeterol xinafoate), should carry warnings that it might increase the risk and severity of asthma episodes (see page 11). Warnings were placed on other drugs ▸

TROUBLING YEAR IN FIGURES

New molecular entities approved by FDA in 2004: **31**
New molecular entities approved by FDA in 2005*: **14**

Black-box warnings given to drugs in Jan-Feb 2005: **37**
Black-box warnings given to drugs in 2004: **33**

Drugs approved in the 1980s that were subsequently withdrawn: **3.2%**
Drugs approved in the 1990s that were subsequently withdrawn: **3.5%**
Drugs approved from 2000 onwards that were subsequently withdrawn‡: **1.6%**

Lester Crawford served term as Permanent FDA Commissioner: **67 days**
Lester Crawford served term¶ as Acting FDA Commissioner: **477 days**
Percentage number of days since 2001 there's been an Acting FDA Commissioner: **49**

Blockbuster patents expiring in 2005: **3**
Blockbuster patents expiring in 2006: **6**

CEOs from top-ten pharmaceutical companies leaving in 2005: **2**

*As of 16 December 2005. ‡Tufts CSDD Impact Report September/October 2005.
¶After Mark McClellan's departure.

containing long-acting β-agonists — GSK's Advair (fluticasone propionate; salmeterol xinafoate) and Schering-Plough's Foradil (formoterol fumarate) — and the agency also recommended restricting their use to patients who failed to respond to other asthma treatments.

Race discrimination

The highly controversial subject of 'race-based medicine' came to the fore in June when the FDA approved NitroMed's BiDil for heart failure in African-American patients only. BiDil is a combination of two generic drugs — isosorbide dinitrate and hydralazine — that increase nitric oxide levels which relaxes the smooth muscle cells that line arteries.

It's generally agreed that race is a crude surrogate maker for disease, and many feared that approving BiDil would set a worrying ethical precedent. But given that middle-aged African-Americans are more than twice as likely to die from heart failure as Caucasians of similar age, there is a major clinical need for an effective treatment. And studies showed that BiDil, at least in part, met that need. Self-described black patients taking BiDil had a 43% reduction in death and a 39% decrease in hospitalization for heart failure compared with placebo (Taylor, A. L. *et al. NEJM* **351**, 2049-2057; 2005).

Although much more needs to be understood about the ethnic variation in drug response, BiDil's approval highlighted the need to identify markers to explain and predict such clinical observations to develop better drugs. Another study from deCODE Genetics showed that a particular variant of a gene that boosts inflammation called *LTA4H* raises the risk of heart attack in African-Americans by more than 250% (Helgadottir, A. *et al. Nature Genet.* Published online: 10 Nov 2005; doi:10.1038/ng1692). The company is currently developing a drug candidate, called DG031, which inhibits the inflammation pathway that *LTA4H* functions through, and is creating a diagnostic test for the gene.

Flu fears grow

The growing fear of an avian flu pandemic was arguably the biggest health story of the year. As isolated cases of infection with the deadly H5N1 avian flu virus strain slowly spread across the globe from South East Asia, it became clear what little we can do to protect against a pandemic.

With current vaccine technologies unable to deal with a potential pandemic (despite, for example, the US government's pledge to increase funding for vaccine development, including a long-overdue boost for research on cell-culture-based methods), Roche and Gilead's antiviral drug Tamiflu (oseltamivir) emerged as the best available treatment against the H5N1 strain. Demand for Tamiflu bordered on the hysterical: governments and states fought to stockpile the yellow and white

SIX TO WATCH IN 2006

1. ***Patent expiries.*** With an unprecedented six blockbusters coming off patent in 2006, how will Bristol-Myers Squibb, GlaxoSmithKline, Merck, Novartis, Pfizer and Sanofi-Aventis cope with the loss of their big sellers, and how soon can they plug the void with drugs from their pipelines?

2. ***Rimonabant.*** If all goes to plan, Sanofi-Aventis's much-anticipated cannabinoid receptor antagonist for obesity and smoking cessation could be approved by FDA.

3. ***Cervical cancer vaccines.*** Merck has already filed its vaccine against the human papilloma virus for approval, and GlaxoSmithKline will soon follow suit. The vaccines protect against a sexually transmitted virus, so will a fear that the vaccines might encourage promiscuity hamper chances of approval?

4. ***RNA-interference-based therapies.*** The first of the Phase I trials (in age-related macular degeneration) are due to be completed soon, providing the first clinical evidence of whether small RNAs can successfully make the step from scientific to medical revolution.

5. ***User fees.*** The authority for PDUFA expires in September 2007, but many issues will be thrashed out in 2006. Of particular interest to the pharmaceutical industry will be whether fess will increase to cover preliminary discussions and/or post-market surveillance.

6. ***Biogenerics.*** After several attempts, will 2006 finally be the year that Sandoz's generic form of the human growth hormone Somatropin is approved?

Public health concerns: BiDil, the first race-based drug to be approved, and fears of an avian flu pandemic dominated the headlines in 2005.

capsules, and doses of Tamiflu even found themselves put up for sale on the online auction site eBay.

For a drug that hadn't been selling well, Tamiflu's instant fame was good news for its manufacturers, but it also brought several problems. With the current supply thought to cover just 2% of the world population, production of the drug needed to be ramped up way above Roche's current capabilities to make enough doses for a potential pandemic. Generics companies succeeded in forcing Roche to allow other manufacturers to produce the antiviral drug as well. Companies such as Cipla claimed that they could make Tamiflu within months, despite Roche's claims that it would take a newcomer 2–3 years to start from scratch and produce significant amounts of the drug through the complex ten-step synthetic process.

But a bigger problem seemed to be that the starting material, shikimic acid, comes from a limited source — the Chinese cooking spice star anise. Ironically, one solution to the problem of manufacturing the antiviral could lie within bacteria. One-third of Roche's Tamiflu supplies is currently made by engineering bacteria to produce shikimic acid; whether this technology can be scaled up to cope with the increased demand remains to be seen.

Stem-cell pioneer under fire

Stem-cell therapies took a huge step towards fulfilling their long-hyped potential, yet within months took a bigger step backwards.

The leading group in the field, a South Korean team headed by Woo Suk Hwang, stunned the research community by showing that they could make embryonic stem-cell lines tailored to individual patients much more efficiently than was thought possible (Hwang, W. S. *et al.* Science 308, 1777–1783; 2005). Months later, it was announced that a World Stem Cell Foundation would be launched, where Hwang's group would use their know-how to create custom stem-cell lines for scientists worldwide.

But just a few weeks after the announcement came the bombshell that the South Korean team obtained human egg cells unethically from two junior researchers in an early study, and Hwang resigned from the new foundation. The dust has yet to settle on this saga, but at the time of going to press Hwang was also facing allegations over the validity of the scientific data presented in the *Science* paper (see page 10).

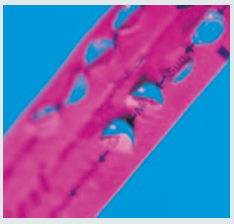
It was a good year for...

Vaccines. Long neglected by big pharmaceutical companies for cost and risk reasons, fears of bioterrorism and a flu pandemic, not to mention weak R&D pipelines and looming patent expiries on blockbusters, are forcing companies to rethink their philosophy on vaccines. GlaxoSmithKline expanded its development capabilities and said it intends to launch five major vaccines over the next five years. Novartis bought the remaining shares in Chiron, taking the company firmly into the vaccines business. Cervical cancer vaccines could soon be on the market (see 'Six to watch in 2006'), and positive Phase II results on a vaccine being developed by GSK and the Malaria Vaccine Initiative called RTS,S showed that protection against malaria could be possible.

Scientific persistence. For years, Barry Marshall and Robin Warren faced ridicule and hostility from the academic and industrial scientific communities for claiming that ulcers could be caused by a bacterial infection. After years of dogged pursuit, even to the point of swallowing a culture of *Helicobacter pylori* to show that it could infect the stomach lining, the researchers proved their case, changed medical thinking radically, and were awarded the Nobel Prize for Medicine or Physiology this year for their endeavours. Achieving science's highest accolade shows how the attitude of the scientific community can switch from ridicule to reward if a idea that bucks current wisdom can be backed up by hard evidence.

Public–private partnerships. Only 13 new drugs were developed for neglected diseases between 1975 and 1999. But by the end of 2004, there were 63 neglected-disease drug projects in progress, three-quarters of which are being carried out under the auspices of PPPs, according to a study published by a group at the London School of Economics, UK. The boost in the number of drugs in development is occurring despite the absence of new government incentives for industry, shattering the illusion that large companies need commercial incentives to commit to neglected diseases. Although this experiment is succeeding, thanks largely to funds from the Bill and Melinda Gates Foundation, it needs to be taken to the next level and made sustainable.

... but a year to forget for...



FDA. The agency came under fire from all quarters this year. The continued delay in approval of the over-the-counter emergency contraceptive Plan B (levonorgestrel; Barr Laboratories) fuelled the wrath of critics who say the decision puts politics ahead of science. The Government Accountability Office, an independent investigative agency of the US Congress, said the refusal to approve Plan B was not standard FDA procedure. Two FDA officials resigned in protest over the furore. Lester Crawford, whose approval as the full-time FDA's commissioner was delayed until the agency proposed a decision date, resigned shortly after taking up the post for allegedly failing to disclose potentially sensitive stock holdings owned by himself or a family member.

His acting successor, Andrew von Eschenbach, instantly drew criticism over wanting to continue his role as the head of the National Cancer Institute, which helps to develop dozens of experimental cancer drugs. The outcry led von Eschenbach to announce that he was shelving his day-to-day duties running the cancer institute and excusing himself from most involvement with FDA matters involving the NCI.

In the post-Vioxx environment it is hardly surprising to hear that regulatory agencies are considering a more cautious approach to approving drugs. Some of the FDA's approval decisions during 2005, such as for Exubera (inhaled insulin; Nektar/Pfizer/Sanofi–Aventis) and Pargluva (muraglitazar; Bristol-Myers Squibb/Merck), suggest that more safety data and longer trials might increasingly become an approval requirement. A new Drug Safety & Oversight Board will have responsibility for providing consumers with safety information on marketed drugs through a Drug Watch website.

The accelerated approval process also found itself under the spotlight. When a trial showed that the lung cancer drug Iressa (gefitinib; AstraZeneca) provided no clinical benefit despite being OK'd through the accelerated approval process, critics immediately accused FDA of being in the pocket of the industry that it is supposed to regulate. However, in order to get innovative drugs for life-saving drugs to patients as quickly as possible treatments going through the accelerated approval process are approved on the basis of surrogate data, but under the stipulation that the company continues with confirmatory trials to establish clinical effect. In November, members of FDA's Oncologic Drugs Advisory Committee said that 'accelerated approval' should be renamed 'conditional approval' to better convey the nature of the approval pathway.