Letter from America

by Howard Larkin

Is the FDA losing its lustre?

Funding, political and leadership questions persist in wake of Vioxx debacle

Physicians and surgeons across the globe have long looked upon approval by the US Food and Drug Administration (FDA) as the gold standard in evaluating drugs and medical devices. FDA approval has long opened doors for manufacturers to enter countries with weaker regulatory structures in South America, Africa and Asia. Even in Europe, with its many proud and effective review agencies, some wait for the FDA before prescribing new treatments.

Over the past two years, though, scandal has repeatedly tarnished the FDA's shining reputation. And even as the agency attempts to burnish its image with a series of self-examinations, new monitoring guidelines and reorganisations, questions persist as to whether the root causes of its recent problems are truly being addressed.

The FDA's image problems began in 2004. That year, word leaked out that the agency had suppressed a study by one of its own researchers suggesting that selective serotonin reuptake inhibitors increased suicidal ideation and behaviour in adolescents. Soon afterwards reports surfaced that COX-2 inhibitors Vioxx, Celebrex and Bextra increased the risk of heart attacks and other cardiovascular diseases, along with revelations that the FDA had ignored evidence of these risks dating back as far as 2001.

Criticism of the agency reached a crescendo after September when Merck voluntarily withdrew Vioxx from the market, raising questions about why the agency didn't act sooner. The subsequent storm of criticism from physicians, the press and the US Congress prompted a series of unprecedented changes at the FDA. A drug-safety review panel was formed to review incoming data after drugs are approved. Perhaps just as significant, the agency's bias toward suppressing preliminary findings in its review process was loosened, allowing internal reviewers to go public with their concerns. The agency has also secured new agreements from major pharmaceutical manufacturers to share data during drug trials.

Despite the changes, the FDA's troubles were far from over. In 2005, the agency took flack for failing to detect life-threatening defects in defibrillators manufactured by Guidant Corporation; defects which the company declined to disclose to physicians and patients implanted with potentially defective devices. That problem, too, has prompted the regulator to recommend expansion of advisory committees to oversee devices after they are approved and on the market.

Will these changes be enough? Many critics think not; even some within the FDA itself. For example, Peter Gross MD, who chairs the FDA's external advisory committee, recommended in February, that the agency add outside reviewers to its drug safety oversight board, which currently consists entirely of government officials from the FDA, the National Institutes of Health and the Department of Veterans Affairs. Earlier this year an FDA report recommended that the agency include outside representatives in developing oversight for medical devices. An industry group went a step further, recommending device manufacturers set up their own independent review boards. Other observers call for a complete reorganisation of the FDA to insulate it from what some believe is an inordinate and growing influence from drug manufacturers.

And how have drug manufacturers gained such influence? Part of the answer may lie in how the FDA funds its activities. Increasingly, this funding comes directly from the manufacturers the agency is charged with regulating in the form of user fees – payments drug makers make to offset the cost of reviewing new drug submissions.

The genesis of user fees is easy enough to understand. In 1992, at a time when the US government operated under strict budgeting policies, the drug industry agreed to contribute money to the FDA to help clear up a growing backlog of new drug reviews. To ensure drug company user fees went to hire more drug reviewers, and not simply to offset funding reductions from the US Treasury, the deal required the FDA to maintain drug review funding at current levels.

But government funding for the agency as a whole has not kept up with inflation. As a result, to meet the terms of the deal, the FDA has shifted an increasing portion of its budget to new drug reviews and away from, among other things, programmes to monitor the safety of drugs already on the market. In 1992, the agency's drug centre spent 53% of its budget on new drug reviews. In 2003, that number had increased to 79%. Over the years, the average fee paid by drug manufacturers has also risen from about $350,000 in 1999 to $800,000 last year.

The average time to review a new drug did fall after the FDA adopted user fees, from 27 months in 1993 to 14 months in 2001. As a result, many patient advocacy groups have favoured the approach, along with new rules designed to speed test drugs for rare and fatal conditions. However, agency doctors also report cannibalising laboratories and other activities to fund side-effect reporting programmes. Because of these kinds of problems, and the potential for conflicts of interest, even some patient advocacy groups have questioned user fees – food for thought as the European Union looks to user fees to fund the European Medicines Evaluation Agency.

Nonetheless, the FDA is looking for even more funding from manufacturers. Device manufacturers already pay user fees to expedite reviews. The FDA is also considering charging generic drug manufacturers. The agency is also looking to charge fees for re-inspecting manufacturing facilities cited for deficiencies. Finally, one policy analyst has called for expanding user fees to fund monitoring programmes for drugs after they reach the market.

Manufacturers aren't the only ones exercising influence over the agency. The FDA's stalling on approving over-the-counter status for levonorgesterel, the so-called "morning-after" contraceptive that prevents implantation of a fertilised egg, has become a political football. Abortion advocates charge that the Bush administration is holding up the approval to appease religious conservatives. Some are calling for liberal senators to block approval of a new FDA commissioner until the contraceptive is approved.

The fact that the top job at the FDA is vacant – and has been since September – raises other concerns about the agency. The previous commissioner, Lester M Crawford PhD, resigned suddenly after 16 months in the job amid questions about his wife's financial ties to the drug industry. Her family sold a chain of drug stores to a drug wholesaler. Dr Crawford, who served many years in various government positions, denies any financial conflicts, and says he resigned because he was tired of 20-hour days. He was also hounded politically over the morning-after pill approval and questions about the safety of the RU-486 abortion pill.

The current nominee, Andrew von Eschenbach MD, serves as both acting FDA commissioner and head of the National Cancer Institute. He will presumably resign as NCI director if confirmed, but so far he continues to hold both positions.

Despite these multiplying questions, the FDA manages to keep itself going and even make progress on improving its regulatory mission. The need for transparency in agency actions and, above all, in reporting of potentially dangerous findings about drugs and devices, is emerging as the paramount value.

Perhaps it's only to be expected that a government agency in a free society goes through such periodic soul-searching. Any such agency must juggle many competing priorities. Pressure will always exist to approve drugs faster to treat sick patients, and to slow down to avoid dangerous side effects. Politics will always intervene and budget pressures are unlikely to abate. Watchful waiting will tell the tale.