US scientists urge overhaul of clinical trials to restore confidence

Michael Day *London*

The US government's top biomedical scientists have called for an overhaul of clinical trials to protect the public and to restore trust in medicine. After a summit at the National Institutes of Health (NIH), in Maryland, the institutes' director, Elias Zerhouni, warned that failure to spot serious side effects of drugs quickly enough was gradually eroding public trust. He announced an eight point plan designed to improve clinical trials and reduce the likelihood of side effects being swept under the carpet.

A key recommendation is for equal weight to be given to determining the safety as well as the efficacy of medicines. The NIH committee cited the scandal surrounding the painkiller Vioxx (rofecoxib) as evidence that safety needed to be stepped up. Merck withdrew the drug in 2004 after it emerged that users were at increased risk of heart disease and stroke. Earlier this month, a jury in New Jersey ordered the company to pay $13.5m (£7.6m; €10.9m) in damages to a 77 year old man after Vioxx was found to have contributed to his heart attack, and Merck had failed to warn about the dangers of taking the drug (*BMJ* 2006;332:927, 22 Apr). The company is facing thousands of other lawsuits in the United States.

The NIH committee called for longer term follow-up, increased powers for the Food and Drugs Administration to do postmarketing surveillance, and more effective dissemination of information relating to adverse events.

The committee's recommendations, published in *PLoS Medicine* (2006;3:e144), also call for researchers to treat prior observational evidence with greater scepticism, pointing to combined oestrogen-progestogen hormone replacement therapy. For years doctors were convinced that the treatment protected women from heart disease and stroke, on the basis of limited observational studies. But in 2002, the women's health initiative trial showed that it actually increases the risk of circulatory disease. Selection bias in the original observation studies was to blame, says the National Institutes of Health—women taking hormone replacement treatment were likely to be fitter and more educated and less likely to smoke.

The committee also singled out a tendency to mislead both patients and practitioners with statistics. In particular, the committee noted that presenting drug efficacy in terms of relative risk alone can be misleading. It cited publicity for an antiosteoporosis drug that simply said that in 12 months the treatment cut vertebral fractures by 68% compared with placebo. But this was the relative risk. In absolute terms, the proportion of vertebral factures was 0.738% for patients given placebo compared with 0.238% for patients given the drug—a difference of half a percentage point.

A British expert, Joe Collier, professor of medicines policy at St George's Hospital Medical School in London, told the *BMJ* that the proposals probably did not go far enough. "A lot of the things suggested are laudable. But we've known for years that they're needed." □

MARY GODLESKI/AP/EMPICS

Superior court judge Carol Higbee at the 2006 hearing which ruled that Merck had failed to warn of Vioxx's risks

Conflicts of interest are common at FDA

Jeanne Lenzer *New York*

Members of drug advisory committees at the US Food and Drug Administration often have financial conflicts of interest and those conflicts affect voting patterns, says a study in *JAMA* (2006; 295:1921).

In 73% of the 221 meetings analysed, at least one advisory member or consultant had one or more conflicts. On an individual level, 28% of advisory members and voting consultants had conflicts. The researchers found that if panellists with conflicts had been excluded, voting margins for the index drug would have been less favourable. In none of the instances studied would exclusions have changed the majority vote for or against approval.

The study, by Peter Lurie of the Public Citizen's Health Research Group in Washington, DC, and colleagues, analysed data from agency transcripts over a four year period, from 1 January 2001 to 31 December 2004. The most common conflicts of interest were consulting arrangements, contracts or grants, and investments. Nineteen per cent of consultancies involved payments over $10 000 (£5600; €8100); 23% of contracts or grants were over $100 000; 30% of investments were over $25 000; and 44% of lecturing honorariums were over $10 000. Despite the frequency of conflicts, only 1% of panellists with conflicts were "recused"—that is, disqualified because of their personal involvement.

The researchers studied three categories of conflicts of interests: "index conflicts" (those with financial interest in the drug under discussion); "competitor conflicts," and "any conflict." In all three categories, voting margins would have been less favourable to the index drug if panellists with conflicts had been excluded. Panellists with competitor conflicts sometimes exhibited the widest margin in favour of a drug, something the authors suggested might be due to a general "pro-industry" position among those with any industry ties.

The impact of the agency's January 2002 draft guidance on conflicts of interest was mixed, say the researchers. Compliance with provision of details about the types of conflicts and their monetary values approached 100% after the guidance. However, the guidance did not require the name of the competitor company, and disclosure of this information dropped from 54% to 1%.

In at least 32 cases, patient advocacy groups that were funded by a drug company provided speakers during the public sessions, and in 47 instances a public speaker was flown in by a drug sponsor. This, said the researchers, "amplifies the growing concern that pharmaceutical industry sponsorship is becoming more prominent in nonprofit, patient advocacy groups that were once viewed as grassroots organizations independent of industry influence."

The researchers found that both individual level and meeting level effects were created by conflicts of interest. Meeting level effects can arise when panellists are affected by the votes of others or by the presentation of public speakers—swaying the entire panel. The authors point out that the recent advisory panel's review of COX 2 (cyclo-oxygenase-2) inhibitors, which occurred outside of the time frame of the current analysis, would have had a different outcome in two of the votes taken if panellists with conflicts had been excluded.

Dr Lurie told the *BMJ*, "Our tolerance for undue influence at a committee as important as an FDA advisory committee should be zero." □