US drug regulation

Congress finds FDA wanting

Washington

Eli Lilly and Company has repeatedly failed to report adverse findings about drugs it was testing or marketing, according to Food and Drug Administration (FDA) documents made public last week. Sales of one of the drugs mentioned in the documents, Oraflex (benoxaprofen), were suspended last week in both Britain and the United States after a review of British data revealed 61 deaths associated with its use (see box).

The allegations against Lilly are spelled out in a series of internal FDA memoranda released by the House intergovernmental relations subcommittee, which was holding hearings on FDA's proposed streamlining of the new drug evaluation process.

One of the most serious charges is that "data for benoxaprofen appear to have been deliberately withheld, thus biasing the NDA (new drug application) in favour of approval". The investigator who reached that conclusion, Dr Michael Hensley, recommended last September that FDA "consider prosecution of appropriate Lilly employees".

Dr Hensley's investigation revealed in particular that 65 adverse effects that occurred during the clinical trials of Oraflex were not reported to FDA, even though they were apparently related to the drug, and were in Lilly's files when the application was made in December 1979. These effects were principally photosensitivity and onycholysis (loosening of the fingernails), and all occurred after the "cut-off date" of November 1978 that Lilly had set on data that were to go into their application. The cut-off is apparently a usual procedure.

But the Lilly employee in charge of the application, Dr H.A. Bartlett, did review the adverse effect reports from trials that continued after the "cut-off date", and included "serious" reactions in the application, according to a memorandum written by Dr Hensley on 16 September 1981. This memorandum then states that Dr Bartlett instructed an employee "not to report others (such as onycholysis and photosensitivity) which he allegedly felt were, because of their frequent occurrence, no longer alarming" (*sic*). In fact, the new data showed a sharp increase in the incidence of these side effects. A letter from Dr Marion Finkel, then associate director for new drug evaluation, to R.D. Wood, chairman of the board of Lilly, on 12 March this year charges that "the consequence was a biased presentation clearly more favourable to the drug than was warranted by the data".

Lilly's answer is that FDA regulations simply do not require applications to include data on all adverse reactions observed after the cut-off date. At the subcommittee hearings, Dr Robert Temple, acting director of the office of new drug evaluation, agreed. He called it a "defect in the regulations".

A similar mix-up occurred over the reporting of four deaths from jaundice associated with the drug. Attention was focused on this matter by reports (Goudie, E.M. *et al. Lancet* **i**, 959; 1982/Halsey, J.P. & Cardoe, N. *Br. med. J.* **284**, 1365; 1982.) of several jaundice deaths in Britain associated with Oraflex. On 23 June, FDA officials met Lilly officials to discuss the matter, and "expressed surprise that (American) cases of jaundice had not been submitted prominently to the NDA (new drug application) prior to its approval".

Lilly officials claimed that they had in fact submitted two reports to the IND file before approval. At the subcommittee hearings, FDA officials said they had had no way of checking that, since there was a six-month backlog in processing the IND files. They said they have since found that all four cases were reported to FDA by Lilly — but that FDA reviewers apparently approved the application without seeing the reports. FDA Commissioner Arthur Hayes Jr says that it "wouldn't have made any difference" in the approval, since the reviewers knew about the problem.

Dr Hensley's memorandum of 29 September 1981, in which he recommended possible prosecution of Lilly employees, referred to three other drugs about which he said "allegations . . . . that Lilly has repeatedly failed to make required reports of important adverse findings" had been "confirmed" by FDA investigators. About aprindine, an anti-arrhythmia drug, Dr Hensley found that "Lilly employees may have engaged in highly objectionable, perhaps ethically questionable practices in their handling of the aprindine clinical programme". Furthermore, Lilly apparently ignored findings from its own experiments with dogs of a possibly lethal side effect of the drug, fibrillation. It was not until January 1974, after four patients in the aprindine clinical trials had died, that the dog studies were reviewed and finally reported to FDA on 4 February 1974. An FDA memorandum dated 4 February 1982 recommends that Lilly be issued a "Notification of Adverse Findings" for failing to incorporate the data from the

Arthritis drug proscribed in Britain

A voluntary decision by Eli Lilly to withdraw the anti-arthritis drug benoxaprofen from sale in all countries came soon after the imposition of a 90-day ban on UK sale by the Committee on Safety of Medicines (CMS). The Department of Health withdrew the product licence for the drug (sold under the trade name Opren in the United Kingdom) to allow time to assess the alarming total of 3,500 reports of serious side effects, especially in the elderly.

Benoxaprofen had rapidly become one of the most prescribed of anti-rheumatic drugs since the UK product licence was issued in 1980, and the CMS review cites 61 deaths associated with its use. In the United States the drug (sold as Oraflex) was given FDA approval only in April of this year, but already at least 11 deaths have been linked with benoxaprofen, again mostly in elderly patients and mostly involving liver or kidney damage.

In withdrawing the drug, Eli Lilly was at pains to explain that it still believed benoxaprofen to be safe and effective if used as directed. But after seven years of development before being allowed on the market, the question of why possible contraindications seem to be emerging only at this stage will be taxing regulatory authorities and Lilly's medical teams on both sides of the Atlantic.

Benoxaprofen is undoubtedly effective in many cases of rheumatoid arthritis and osteoarthritis but it is probably not irreplaceable — other non-steroid anti-inflammatory agents with similar activity include aspirin, naproxen, ibuprofen and fenoprofen. For Eli Lilly, though, the whole episode is a major setback. Even if benoxaprofen is allowed back onto the market, the damage will have been done and doctors will be reluctant to prescribe it and patients to take it.

The latest events surrounding benoxaprofen provide another reminder of the high risks involved for companies attempting to reap the high rewards that accompany a successful new drug launch. Only two weeks ago the London Stock Market witnessed extraordinary fluctuations in the price of shares in the pharmaceuticals company Glaxo. High hopes of massive profits from sales of the new anti-ulcer drug Zantac (ranitidine) were dampened when a few reports of possible side effects were publicized with little analysis in the financial press. Share prices recovered when Glaxo and others pointed out the relatively minor nature of the reported effects, but predictably the price has not matched the high levels seen before the fracas. **Charles Wenz**

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animal studies into the clinical protocols and failing to report properly to FDA.

Dr Hensley's memorandum of 29 September 1981 concludes that for a third drug, drobuline, proper case report records were not maintained, and protocols were not followed. In the case of the fourth drug, monensin, the FDA documents charge that Lilly failed to report adverse effects in animals and humans exposed to the drug, or delayed reporting these effects by as much as 23 months. Lilly was issued a notice of adverse findings on monensin on 6 July 1981.

At the subcommittee hearings, Lilly issued a statement to reporters denying the charges. "Eli Lilly and Company takes vigorous exception to any implication that it withheld data, maintained inadequate records, or failed to comply with the requirements of the FDA".

Stephen Budiansky

FDA regulations

Saving time, but carefully

Washington

The Food and Drug Administration (FDA)'s plans to relax some of its requirements for new drug applications came under congressional scrutiny last week during two days of hearings that also raised serious questions about Eli Lilly and Company's reporting of adverse effects of its drugs (see p.597).

FDA Commissioner Arthur Hull Hayes Jr, testified that the proposed changes in FDA procedures should shorten the approval process for the average application by six months. It now takes nearly two years. An FDA spokesman said, however, that the new procedures would probably have little effect on applications for drugs deemed important, since they are already given expedited treatment.

Representative L. H. Fountain (Democrat, North Carolina), chairman of the House subcommittee that conducted the hearings, focused strongly on two of FDA's proposed changes. One would drop the requirement that drug companies submit the detailed "case report forms" from clinical trials of the drug; the other would allow FDA to approve a new drug application on the basis of foreign studies.

At present, applicants are required to turn over to FDA all case report forms. These are the reports made by the clinical investigators on each patient; according to FDA, they make up 70 per cent of the applications now, often running into hundreds of volumes. FDA is proposing that, instead, the drug companies should be allowed to submit tabulations of the raw data, and only submit the case reports for cases that raise significant safety questions, such as patients who died, or dropped out of the study because of an adverse effect. The companies would still have to supply the case reports if requested by FDA.

Dr Robert Temple, acting director of the office of new drug evaluation, assured the subcommittee that FDA would not lose anything in the change. But detailed reports "will still be asked for as they're needed", he said; and Commissioner Hayes argued that tabulation of the raw data is "more consistent with current scientific practices".

Subcommittee staff members, however, noted that two in-house reviews at FDA found tabulations which did not agree with the case reports they were supposedly drawn for. They were also concerned that FDA reviewers might be intimidated by the prospect of having to make a special request for the case reports, if for no other reason than the time it would take.

On the issue of foreign data, FDA officials similarly tried to be reassuring that the proposed changes would not undermine FDA's ability to make a thorough evaluation. FDA rules now allow foreign studies to be accepted if the investigators are "well-qualified" and if they make background data available to FDA. But in almost all cases, at least one domestic study is also required.

That would change under the new rules. A drug could be approved solely on the basis of foreign data; Hayes suggested that this would be especially important when requiring domestic trials would "cause an unjustifiable delay in the drug's availability to the public", would result in "unnecessary or duplicative testing", or would present an "unnecessary burden on the drug sponsor".

Foreign data would still have to meet US standards and be the product of "investigators of recognized competence". Critics worry that standards will nonetheless be lowered. Dr Sidney Wolfe of Ralph Nader's Health Research Group, said, "The main problem with the use of foreign data is that the drug laws and the protection of human subjects are weaker everywhere in the world" than they are in the United States. And according to Dr John Nestor, a retired FDA employee who worked for many years reviewing drug applications in the agency's cardio-renal drug division, the main effect of the change will be that "the drug companies will be getting their studies done in Mexico and Canada and everywhere else because it's easier to escape surveillance by FDA". At the subcommittee hearing, Representative Fountain released evidence that FDA had encountered just such problems when it attempted to investigate studies done in Mexico and Canada.

The changes FDA is planning appear to enjoy support in Congress. But there are some reservations. Representative Elliot Levitas (Democrat, Georgia) enthused about the benefits of deregulation, and then implied that the only weapon against the drug companies is vigilance.

Stephen Budiansky

Venture capital investment

Now Monsanto

Britain now has one of the best environments in Europe for innovation, a director of the US chemicals company Monsanto said last week. And Mr Richard A. Onians has put Monsanto's money where its mouth is, investing £4.75 million in a new £9.7 million venture capital fund launched last week in London (see *Nature* 5 August, p.505).

Onians describes Monsanto's investment as a window on European technology, but what the company will see through it is mostly British work. The fund is to be managed by Advent Management, which already controls another £10 million fund, Advent Technology, now 15 months old and with ten British investments already under its belt. Monsanto will have no control over the new fund, but Advent Management will use Monsanto for technology assessment.

Monsanto itself seems to have been tempted to Britain for its "window" because of government willingness to allow foreign investment (France would not let Monsanto invest there, in spite of a desperate need to rebuild the French chemical industry), low capital gains taxes and because of what Onians called British inventiveness. There are probably plenty of potential British entrepreneurs as well, he thinks, if only the money is made available.

Sir Kenneth Cork, the accountant and ex-Lord Mayor of London who is chairman of the new fund, believes Britain could make good use of £500 million of venture capital, ten times the total probably now on offer. "But the Trades Union Council plan of £1,000 million from government and £1,000 million from industry just wouldn't work", he said; venture money needs to be hard to get.

Advent Management has certainly found it harder to raise the money for Advent Eurofund than it was two years ago to raise it for Advent Technology, an essentially similar fund. The fashion among finance houses and insurance companies for investing in such funds seems to have been short-lived, says Advent director David Cooksey.

University investment in high technology venture funds seems, however, to be new — new certainly for Cambridge (£500,000) and Oxford (£100,000). St Andrews, Imperial College London, the Nuffield Foundation and Boston University (Massachusetts) have also invested, reaching a total academic interest of £1.5 million. Some 20 other British universities were interested, said Cooksey, but they had not got the cash.

From the universities' point of view, these investments are dealt with like any other but offer a chance of protecting assets against inflation. Cooksey, however, clearly sees them as a window on potential invention, and this is bound to be

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