FDA fails to reduce accessibility of paracetamol despite 450 deaths a year

Confidential documents from the US Food and Drug Administration suggest that the agency has avoided a debate on tough new measures to reduce overdoses from painkillers—to avoid offending the pharmaceutical industry. **Ray Moynihan** reports from Washington, DC

Staff at the Food and Drug Administration's Office of Drug Safety wanted the United States to consider following the United Kingdom's policy of reducing the public's ease of access to paracetamol to try to reduce the number of deaths from overdose, a concern in both these countries.

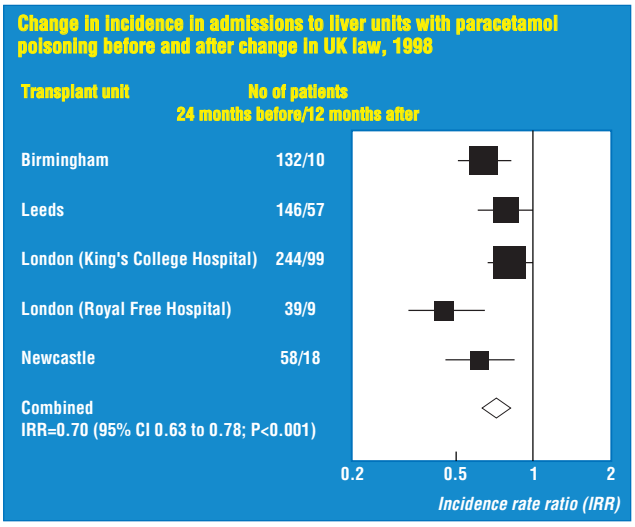
But the office's views never reached the FDA's non-prescription drugs advisory committee, which met last week to consider the drug's safety. The result was that the advisory committee recommended only that the drug, known as acetaminophen in the United States, carry expanded safety warnings. No change was recommended in how it is sold.

Drug company executives were delighted with the committee's decision. "I felt really very good," said Dr Anthony Temple, a vice president of the Johnson & Johnson company McNeil, which dominates the market in paracetamol products, taken by almost 50 million Americans a week. "I'm pleased the panel came up with the same concepts we've come up with already."

The advisory committee was looking at the drug, which is contained in many combination products, in an effort to reduce the accidental liver damage it can cause when taken in overdose. In the United States paracetamol is associated with more than 100 000 calls a year to poison control centres, as well as 56 000 visits to emergency departments, 26 000 hospitalisations, and 450 deaths.

The FDA appoints outside expert members to its advisory committees, and before meetings it provides them with background documents and lists of questions, in an effort to seek informed recommendations on important decisions about drug approval or regulation.

In the case of last week's hearing, after eight hours of what were at times confused, uncertain, and vague deliberations, the FDA advisory committee simply recommended changes to labelling and better consumer education about paracetamol (marketed in the United States as Tylenol). These are initiatives in which the manufacturer is already engaged. Asked whether the recommendations could have been worse, Dr Temple responded instantly: "Absolutely—it could have been a lot worse."



The FDA advisers did not seriously consider following the lead of the United Kingdom and some other countries, which have introduced measures to restrict the numbers of tablets per pack and replacing bottles full of loose pills with "blister packs." The option was not even suggested for consideration by FDA officers appearing before the advisory committee despite the fact that tentative evidence indicates that such reforms in the United Kingdom may have significantly reduced the number of drug related poisonings, liver transplantations, and deaths (*BMJ* 2001;322:1203-7).

The reforms in the United Kingdom have also led to a substantial reduction in annual sales of tablets containing paracetamol and paracetamol compounds, from 123 billion to 84 billion.

Behind the closed doors of the FDA, in the lead up to the meeting, staff from the Office of Drug Safety had suggested that the advisory committee should consider the measures that the United Kingdom took. A confidential draft document reveals that the Office of Drug Safety also wanted the advisory panel to discuss whether the "maximum tablet strength should be decreased," whether "combination products be reformulated without acetaminophen," and whether there was "a need to standardize the various paediatric formulations."

The advisers never saw that draft, however, and none of these key options ended up being clearly presented to the committee by the FDA in the final list of questions they were to consider.

Acknowledging an unusual level of confusion throughout the hearings, the advisory committee's chairman, Dr Lou Cantilena, said in an interview afterwards that the questions supplied by the FDA were too vague. "The committee would have preferred more focused questions," he said.

According to one FDA insider, the draft questions were dropped because senior FDA managers saw them as too offensive to Johnson & Johnson. Asked about this alleged corporate influence within the FDA, Dr Cantilena smiled and said he did not want to speculate.

In an interview last Friday, FDA spokesman Dr John Jenkins said he was not aware of the draft questions from the Office of Drug Safety but said that FDA managers had opted to give the advisory committee more open ended, rather than yes/no-type, questions.

At one point, when the committee's deliberations drifted towards consideration of the United Kingdom changes, another FDA manager, Dr Charles Ganley, effectively cut off debate by strongly cautioning advisers against such action. "It's very difficult to impose these things," he warned. Dr Ganley is understood to have been actively involved in rejecting the draft questions before they got to the advisory committee.

More than 200 people attended last week's two day hearing, which focused first on paracetamol and then on aspirin and non-steroidal anti-inflammatory drugs, said to be associated with more than 16 000 deaths in the United States every year as a result of gastrointestinal bleeding. As on day 1, the recommendations on day 2 were for minor changes to labels and more education.

Although liver damage from paracetamol is rare, its effects can be devastating. Ms Kate Trunk told the committee meeting that her healthy 23 year old son Marcus had died after an accidental overdose, because he had inadvertently taken several products containing the same drug. "Death is not an acceptable side effect," she said.

The FDA's apparent timidity over reforming the marketing of the multibillion dollar paracetamol will only add to concerns that the regulatory agency may be too close to the companies that by law now fund half of its drug review work. Rejecting those concerns, Dr Temple said the manufacturer had "shared data with the FDA, worked with them, and talked back and forth" in the lead up to last week's meeting, but the FDA had been "pretty arm's length on this."

The FDA refused a request by the *BMJ* for an interview with Dr Ganley. □