

## Safety first

We'll never be able to trust the drugs we take until they are developed according to proper safety guidelines, say **Paula J. Caplan** and **Emily H. Cohen**

TO AN American public weary of being told that the drugs they are taking are dangerous, the recent controversy over the diabetes drug Avandia will have come as little surprise. Health experts want the medicine withdrawn after various studies suggested it increased the risk of heart failure and other illnesses.

Last week a Food and Drug Administration (FDA) committee voted to keep Avandia on the market, though it demanded stronger warnings on the label (*New Scientist*, 4 August, p 7). This is hardly reassuring, especially since there is considerable disagreement within the FDA over the significance of the safety concerns.

This is the latest in a string of drug safety controversies in the US. Why do they keep happening? Congress voted last month to give the FDA more powers and funding to police drugs that are already on the market, but this is just a sticking-plaster approach. Safety concerns should be flagged long before a drug is approved.

A major reason they aren't is that the FDA's guidelines for research into new medicines contain serious flaws. There is little chance of substantially improving the US's safety record on medicines unless these guidelines are rewritten. Alarming, few physicians and even fewer consumers appear to be aware of the problem.

Our concerns apply to the guidelines for all drug groups, but to illustrate the dangers and how they might be rectified we will focus here on antidepressants. These are the top-selling drugs, and the pharmaceutical industry has regularly concealed their negative effects. It is 30 years since the FDA published the current guidelines for research into antidepressants. They were scheduled for review every 18 to 24 months, but the 1977 version is still all there is. We have found more than a dozen major problems with them.

One of the most serious is the failure to list any essential symptoms of depression for participants in



clinical trials, requiring loosely that they show four or five "associated symptoms". This introduces the risk that non-depressed individuals will be recruited and genuinely depressed patients with, say, three severe symptoms will be left out.

Equally problematic is that the guidelines say subjects whose clinical condition worsens or fails to improve "in a reasonable period of time" are to be removed from the study, but drug companies need not include data about them in their statistical analyses. The drug's effectiveness is thus inflated and its negative effects minimised.

There's more. The guidelines state that clinical trials should last for around four to six weeks, yet drugs may take longer than six weeks to achieve maximum effectiveness or indeed produce noticeable negative effects. Trials of this length will also likely fail to pick up the many people for whom psychotropic drugs are initially helpful but later ineffective. Similarly, the FDA recommends that drug companies monitor trial participants for at least

one week after they stop taking the drug, yet it may take longer than that for withdrawal symptoms to emerge.

Then there's the astonishingly vague guideline that "evidence for safety and efficacy is acquired over the course of many studies carried out over considerable periods of time and at different geographical locations" – hardly a recipe for the efficient collection of robust safety data. Furthermore, the guidelines require neither that all the findings are pooled together nor that the research be overseen by an independent regulator.

Finally, there's the advice that "women of childbearing potential, children and individuals with serious diseases" be excluded from the research. How can we know about the effects of drugs on these groups, many of whom are regularly prescribed antidepressants? Indeed, some women take antidepressants throughout pregnancy, even though the FDA says that long-term safety studies need last no more than three to six months.

Equally glaring and alarming flaws plague the FDA's standards for pre-approval research on other categories of drugs. It's time for a full review of FDA research guidelines for all categories of drugs.

There are plenty of indications that all is not well. For example, the FDA failed to act on Avandia despite the fact that the main European medical regulator, the European Medicines Agency (EMA), strengthened its warning about the risks the drug carries. That wasn't the first time it had drawn better conclusions than the FDA. The FDA approved Prozac to treat premenstrual dysphoric disorder even though, as EMA noted, the evidence showed that PMDD was not a real entity.

Revising the research guidelines is a far safer way to uncover negative effects than the existing system of monitoring a drug after it is licensed for use. Besides, the FDA leaves it to the drug companies to conduct the research. If the guidelines are faulty, what reason has the public to trust the drugs they produce? ●

**"The guidelines were scheduled for review every two years, but the 1977 version is still all there is"**

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