

MHRA gives industry a morality check

Legislative changes will force pharmaceutical companies to report promptly the side effects of all medicines after an attempt by the Medicines and Healthcare products Regulatory Agency to prosecute GlaxoSmithKline for allegedly withholding safety data on Seroxat failed. Dawn Connelly reports

Most people would agree that pharmaceutical companies have a moral obligation to report information about the adverse effects of drugs to the regulatory authorities as they arise. However, it seems that this obligation cannot be relied upon and new legislation will now be passed to insist that companies disclose any information that could affect patient safety, regardless of its source.

The move follows a four-year criminal investigation into whether GlaxoSmithKline failed to inform the Medicines and Healthcare products Regulatory Agency of information it had on the safety of Seroxat in under 18-year-olds in a timely manner (see p297).

The MHRA's investigation is the largest of its kind in the UK, with 103 requests for documentation resulting in scrutiny of over one million pages of evidence.

The allegations against GSK were that it failed to comply with legislation requiring it to report adverse events occurring in clinical trials in which Seroxat was given to children, and that it failed to report a safety issue promptly once it was aware of its existence (see Panel 1).

After reviewing the investigation, Government lawyers have decided that there is no realistic prospect of a conviction in the case and that it should not proceed to criminal prosecution. "The legislation in force at the time was not sufficiently strong or comprehensive as to require companies to inform the regulator of safety information when the drug was being used, or tested outside its licensed indications," said the MHRA in a press release.

Although GSK has been spared prosecution, the MHRA believes that it should have disclosed vital safety data earlier. Commenting on the investigation, Kent Woods, the agency's chief executive, said: "I



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remain concerned that GSK could and should have reported this information earlier than they did. All companies have a responsibility to patients, and should report any adverse data signals to us as soon as they discover them."

GSK rejects any suggestion that it withheld information saying that it was only when a meta-analysis was conducted in late 2002 and further analyses in early 2003 that the increased risk of suicidal behaviour with Seroxat became evident. Alastair Benbow, medical director for GSK Europe, said: "We firmly believe we acted properly and responsibly in first carrying out this important clinical trials programme and then informing the regulatory agencies when we identified a potential increased risk of suicidal thinking and behaviour in patients under 18."

The MHRA acknowledges that the investigation has revealed significant weaknesses in the drug safety legislation in force at the time. "Subsequent legislation [see Panel 2] has partially addressed the problem, but we will take immediate steps to ensure the law is strength-

ened further, so that there can be no doubt as to companies' obligations to report safety issues," he promised.

The MHRA has written to the Association of the British Pharmaceutical Industry to ask it to remind its members of their responsibilities in advance of any changes to the legislation: "The public would undoubtedly expect that any information shedding new light on the risk:benefit relationship of a marketed medicine would be promptly communicated to the regulatory authority so that, if necessary, further advice could be provided to prescribers and users. This would apply equally whether or not that information emerged from use in a licensed indication."

The MHRA will be recommending that amendments to legislation are included in the forthcoming EU pharmacovigilance regulations. However, given the time it may take for EU legislation to be negotiated and come into force, proposals to amend UK law will shortly be put out for consultation.

The agency wants to see absolute clarity in the legislation as to the information that must be supplied to the regulator, regardless of its source (arising from inside or outside the UK, as a result of any use, eg, licensed, unlicensed or within clinical trials) and clear timescales within which such information must be supplied as well as sanctions for failing to comply.

The ABPI said that it welcomes the introduction of any new legislation that provides further genuine protection for the patient, without simply adding unnecessary bureaucracy. It added that, since 2005, the international pharmaceutical industry has committed to the registration and publication of its clinical trials involving patients whether the outcomes are positive or negative (see www.ifpma.org).

A spokeswoman for the MHRA told *The Journal* that the investigation has by no means been wasted. "The investigation scrutinised questionable actions by one pharmaceutical company, but there are much wider lessons for the whole pharmaceutical industry about the importance of working within the spirit as well as the letter of the law," she said.

Panel 1: The data in question

1998 — GSK completed two trials involving the use of Seroxat in children, which failed to demonstrate that it was effective at treating major depression in children.

September 2002 — In a further seven trials, the last of which ended in September 2002, Seroxat's efficacy for treating children with major depression was not demonstrated.

November 2002 — The MHRA asked GSK about the status of clinical trials in children and the company indicated that it intended to submit an application for paediatric indications. It did not raise any concerns about a lack of efficacy or adverse reactions during clinical trials.

February 2003 — Unprompted, GSK sent an update to the MHRA on clinical trial data it held in relation to suicidal behaviour. However, adult and paediatric data were not differentiated and any safety signal from the paediatric studies was lost when the two populations were mixed since the adult population was much larger.

May 2003 — At the end of a meeting with the MHRA to discuss the safety of Seroxat, GSK handed out a briefing document relating to an application to extend indications for Seroxat to include children. In it a safety concern related to suicidal behaviour among depressed children taking Seroxat was highlighted. The MHRA subsequently requested full clinical trial data from GSK, which showed that the safety concern became apparent after a meta-analysis of the trials was conducted.

June 2003 — The lack of efficacy together with evidence of a causal association between Seroxat and suicidal behaviour in children led the MHRA to advise that it should not be used in the treatment of depressive illness in the under 18s.

Panel 2: Recent legislation

Since 2003, an EU directive governing the conduct of clinical trials has been passed that introduced a criminal offence for failure to report adverse events. However, the directive does not apply to trials conducted outside the EEA. In addition, amendments to EU medicines legislation has clarified the obligation to report safety information from clinical trials using products outside their licensed indications, including an obligation to report the information promptly.