



Being Pharmacovigilant

Tim Worden of Taylor Wessing LLP discusses the MHRA's investigation into GSK's reporting of adverse events in Seroxat paediatric clinical trials

On 6th March 2008, the Medicines and Healthcare products Regulatory Agency (MHRA) published its report into GSK's alleged failure to report certain adverse event data from clinical trials in children of its anti-depressant, Seroxat (paroxetine), to the MHRA in a timely manner. Certain data from those trials – a pooled analysis from all paediatric trials of Seroxat – suggested a causal association between the anti-depressant and an increased risk of suicidal behaviour. The MHRA's report concluded that there was insufficient evidence to provide a realistic prospect of a criminal conviction for the alleged breach of pharmacovigilance legislation by GSK, and that there was, at the time of the alleged offences, a “significant gap in the law governing drug safety”. This article examines the MHRA report and its findings, as well as the MHRA's recommendations for changes in the law on drug safety.

GSK CLINICAL TRIALS AND THE REGULATORY BACKGROUND

According to the MHRA report, between April 1994 and January 2002, GSK carried out nine clinical trials on the use of Seroxat in children and adolescents, a patient population for which the medicine was not approved (1). Of those trials, only one was conducted (in part only) in the UK. The Summary of Product Characteristics at the time of the trials stated that: “The use of Seroxat in children is not recommended as safety and efficacy have not been established in this population”, although a substantial number of prescriptions of Seroxat were being issued to children in the UK in that time (2).

The first two clinical trials failed to show that Seroxat was effective in treating major depressive disorder (MDD) in children. The subsequent seven clinical trials were designed to assess the safety and efficacy of Seroxat in the treatment of MDD, obsessive compulsive disorder and social anxiety disorder in children. None of the trials showed efficacy in treating MDD in the paediatric population.

Seroxat is a selective serotonin re-uptake inhibitor (SSRI). A possible connection between the use of SSRIs and suicidal behaviour in patients became the subject of considerable scientific debate and public concern during the 1990s. The level of this concern was such that the opinion of the UK Government's Committee on Safety of Medicines was sought on the issue, and SSRI marketing authorisation holders were required to make regular submissions of data in relation to their products.

In May 2003, in a briefing document relating to GSK's proposed application to extend Seroxat's licensed indications to include use in children, GSK flagged up to the MHRA that the

data from their paediatric trials into depressive illnesses indicated an increased rate of events relating to suicidal behaviour among children with MDD being treated with Seroxat (compared to placebo). The evidence for this increased risk of suicidal behaviour was derived from a meta-analysis (pooled analysis) of all GSK's paediatric clinical trials data for the treatment of depressive illnesses with Seroxat.

MHRA INVESTIGATION

In October 2003, the MHRA commenced an investigation into whether GSK had breached pharmacovigilance regulations by: failing to provide adverse event information during its paediatric clinical trials; and delaying the provision of such information to the MHRA. The relevant provisions of UK legislation at the time stated that:

“Any person responsible for placing a relevant medicinal product on the market who fails to report to the licensing authority any suspected adverse reaction, or to submit to the licensing authority any records of suspected adverse reactions as required by [Directive 2001/83/EC]...shall be guilty of an offence” (3).

“Any [Qualified Person] who...fails to...provide to the licensing authority any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product...shall be guilty of an offence” (4).

The MHRA obtained an opinion from independent counsel as to whether or not it would be appropriate to prosecute GSK in the circumstances. In summary, the advice from counsel was that there was no “realistic prospect of conviction” because the GSK paediatric trials and alleged failure to provide information from those trials did not fall within the legislation set out above. On the basis of that advice, the MHRA decided not to prosecute.

RELEVANT PHARMACOVIGILANCE LEGISLATION

During the relevant period (April 1994 to May 2003), EU legislation required member states to have in place pharmacovigilance systems requiring notification of adverse reactions occurring under the “normal conditions of use” of a medicinal product.

Under EU legislation introduced in 2000, a marketing authorisation holder's qualified person was required to inform the relevant regulator about information relevant to a product's risks and benefits, including information on “post authorisation studies”. Such studies are defined as studies being conducted in

accordance with the product's authorised use (within its licensed indications).

Furthermore, the GSK trials took place before the implementation of the Clinical Trials Directive (2001/20/EC). This Directive introduced a criminal offence for failing to report adverse reactions in clinical trials in the European Economic Area. Relevant UK legislation at the time – the Medicines Act 1968 – did require the reporting of adverse events during clinical trials, but a failure to do so was not a criminal offence; the reporting obligation applied only to trials carried out wholly or partly in the UK.

WHY DIDN'T THE MHRA PROSECUTE?

The MHRA report gives a number of reasons for its decision not to prosecute:

- ◆ Relevant EU legislation requires the reporting of adverse reactions occurring in the normal conditions of use. A clinical trial in relation to an unlicensed indication did not fall within "normal conditions of use"
- ◆ Although EU legislation also required adverse events to be reported in 'post authorisation studies', such studies did not include studies on a product outside of its licensed indications
- ◆ UK legislation did require the reporting of adverse events during clinical trials, but it applied only to clinical trials in the UK and a failure to do so was not a criminal offence
- ◆ Although UK legislation from 2002 required a marketing authorisation holder's qualified person to report any information relevant to the risk/benefit evaluation of a product, the MRHA received legal advice stating that the legislation was not sufficiently clear in showing that this obligation applied to clinical trials outside a product's licensed indications

LEGISLATIVE CHANGES AFTER MAY 2003

Since May 2003, UK legislation has been amended to implement Directive 2004/27/EC, and one of the amendments clarifies the obligation to report adverse reactions in clinical trials of products outside their normal conditions of use. Furthermore, as mentioned above, the Clinical Trials Directive has come into force, making failure to report adverse reactions in clinical trials in the European Economic Area a criminal offence. In addition, the EU consulted between December 2007 and February 2008 on a strengthening of drug safety monitoring, although no new provisions are yet in effect.

WHAT NEXT?

The MHRA report concludes that the legislation should be clarified further to ensure that:

- ◆ There is an obligation to report regardless of where the clinical trial takes place
- ◆ The timescale for reporting is clear

Although the EU has consulted on changes to the pharmacovigilance system, the MHRA recommended in its

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report that UK legislation should be amended in the interim. To date, no additional UK legislation has been published.

In its response to the MHRA report, GSK pointed out that none of the nine clinical trials, when reviewed individually, showed a clinically meaningful increase in suicidal behaviour (5). It was only when the data was pooled, in late 2002, that a signal became apparent. This raises a question as to whether the signal would have been picked up any sooner if the adverse events from each trial had been reported to the MHRA, or any other regulatory body at the time that they occurred. Furthermore, when the UK and EU legislation is amended – as it no doubt will be – to require a broader reporting obligation, the question will arise as to whether regulatory bodies are required to carry out fuller analyses, such as meta-analyses, to assess whether the pooled adverse event data shows a significant risk signal.

The changes proposed by the MHRA to pharmacovigilance reporting would ensure that the legislation is comprehensive, and therefore they are to be welcomed. It is anticipated that the proposed changes to UK legislation will be made available in the near future, so the pharmaceutical industry should ensure that they keep abreast of the proposals and are able to comment on them. ◆

References

1. <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON014153>
2. The MHRA report states that 32,000 such prescriptions were issued in 1999
3. Paragraph 8, Schedule 3, the Medicines for Human Use (Marketing Authorisation etc) Regulations 1994 (SI 3144/1994)
4. Paragraph 10(d), Schedule 3, the Medicines for Human Use (Marketing Authorisation etc) Regulations 1994 (SI 3144/1994)
5. <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON014153>