

# **MHRA Investigation into Glaxosmithkline/ Seroxat**

**6 March 2008**



## MHRA Investigation into Glaxosmithkline/ Seroxat

### Summary

This is a report produced by the Medicines and Healthcare products Regulatory Agency (MHRA) following the conclusion of an investigation concerning Glaxosmithkline (GSK) and the anti-depressant drug Seroxat. The investigation was carried out to determine whether a criminal prosecution should be pursued into alleged breaches of drug safety legislation.

The decision taken by Government Legal Prosecutors, on the basis of the investigation findings and legal advice, is that the case should not proceed to prosecution. The key factor behind this was that the law regarding companies' obligations to disclose safety-related information was not – at the time in question – sufficiently clear in applying to the use of a drug outside its licence (in this case, use in children when it was licensed only for adults). As a result of this, steps are now being taken to strengthen the law in this area.

The report is in four sections:

- Section 1 sets out the history behind the investigation, and details the events leading up to it. It includes the details of actions taken by the MHRA to respond to the public health issues (in particular, to take immediate steps to advise against use of Seroxat in under-18s);
- Section 2 gives a brief description of how the investigation was carried out.
- Section 3 is an account of the decision-making process as to whether a prosecution should be pursued. This decision is taken not by the MHRA but by Government Legal Prosecutors, and this section is written by them
- Section 4 gives an explanation of the law, how it stood at the time, and changes that have since taken place. It also covers the further changes to strengthen the law that will now be pursued.

Together with this report, the MHRA is releasing documents relating to the matters set out in the report. Legal constraints make it impossible to disclose any information or evidence gathered during the course of the investigation itself except to the extent that it is already in the public domain.

MHRA

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## Section 1 – Events Leading to the Investigation

1. Selective Serotonin Re-uptake Inhibitors (SSRIs) are a class of medicines that have been used in the treatment of depressive illness and anxiety disorders since the late 1980s. The general adoption of SSRIs into clinical practice reflected in particular their greater safety in overdose, an important advantage in comparison with risks associated with the previous generation of antidepressants, known as tricyclic antidepressants. SSRIs had been authorised in the late 1980's and early 1990's on the basis of data showing a positive balance of benefits and risks in the adult population. No antidepressants were specifically authorised at that time for the treatment of depression in children and adolescents, because until the mid-1990s clinical trials to investigate the safety and effectiveness of medicines in children were not encouraged.

### *Efficacy of Seroxat in children*

2. Between April 1994 and September 2002 SmithKline Beecham plc (SKB)<sup>1</sup> and subsequently GSK conducted a programme of 9 clinical trials in to the paediatric use of Seroxat<sup>2</sup>. The trials were conducted in a number of different countries, with one trial being partly conducted in the UK. The Summary of Product Characteristics (SPC)<sup>3</sup> for Seroxat at that time had the following statement in relation to use in children: “Children: The use of Seroxat in children is not recommended as safety and efficacy have not been established in this population”. This was a standard statement added to SPCs for products which had not been specifically studied in children.
3. The first trial conducted by SKB, trial number 329<sup>4</sup>, failed to show that Seroxat was effective in treating major depressive disorder in children. A second trial, number 377, was conducted and this also failed to show that Seroxat was effective. Both studies completed towards the end of 1998. SKB made no amendment to the SPC on the basis of these data. An internal GSK management document (which subsequently came into the public domain) dated October 1998 says that “it would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine”. During 1999, 32,000 Seroxat prescriptions were issued to children in the UK.
4. SKB, and its successor company GSK, continued to conduct clinical trials of Seroxat in children after the failure of the first two trials. The safety and efficacy of using Seroxat to treat MDD, obsessive compulsive disorder and “social anxiety disorder” in the paediatric population were examined in a further 7 clinical trials,

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<sup>1</sup> SmithKline Beecham merged in 2000 with Glaxo Wellcome to create Glaxosmithkline

<sup>2</sup> Seroxat is the brand name for the medicine, whilst paroxetine is its generic name. In the USA the brand name is Paxil. Seroxat is used throughout this report.

<sup>3</sup> The Summary of Product Characteristics provides specific details about the medicinal product. The SPC forms an integral part of the Marketing Authorisation Application (MAA) and the content of the SPC must be approved by the Competent Authority. The SPC is the basis of information for health professionals on how to use the medicinal product safely and effectively.

<sup>4</sup> Clinical trial identification numbers are those used by GSK..

the last of which concluded on 16th September 2002. None of these trials demonstrated efficacy for Seroxat in treating paediatric MDD.

### *Safety of Seroxat*

5. The safety of SSRIs was kept under close scrutiny by the Agency since they were first marketed. During the 1990s the issue of whether there is an increased risk of suicidal behaviour associated with treatment with SSRIs became the subject of scientific debate and public concern. This signal was difficult to evaluate because of the known tendency of depression to worsen during the early stages of treatment and the increased risk of suicidal behaviour and self-harm associated with depressive illness. The concerns about suicidal behaviour took place in the context of an ongoing debate about the nature and incidence of withdrawal symptoms associated with SSRIs. Furthermore the available information related mainly to individual case reports which were not in themselves considered sufficiently robust evidence to confirm a causal association between SSRIs and suicidal behaviour.

### *Expert committee advice*

6. In the light of the public concern about the safety of Seroxat and other SSRIs, the advice of the Government's independent scientific advisory committee, the Committee on Safety of Medicines (CSM), was sought on a number of occasions. Throughout that time, the marketing authorisation holders for all SSRIs were asked to provide data to inform the ongoing expert review. Health professionals were kept informed through changes to product information (SPC and Patient Information Leaflet<sup>5</sup>) as new data emerged. Articles were published in the drug safety bulletin 'Current Problems in Pharmacovigilance' in 1993 and 2000.
7. In 2001-2 Seroxat and the extent to which the product information reflected evidence relating to withdrawal reactions and suicidal behaviour became the subject of particular public concern. On 13 October 2002 a "Panorama" documentary which examined the safety of Seroxat was broadcast. To address these continuing concerns the Agency convened an ad hoc meeting of relevant experts to consider the latest data relating to SSRIs in general and Seroxat in particular. In preparation for the ad hoc group, and to ensure a current understanding of all ongoing work, the Agency called a meeting with GSK. The meeting with GSK took place on 14 November 2002 and focused on changes that were required to the product information for Seroxat in relation to withdrawal reactions. The Agency also asked about the status of clinical trials in children and GSK provided an overview, indicating that they were planning to submit an application for paediatric indications for Seroxat. GSK did not raise any concern about lack of efficacy or adverse reactions in the clinical trials in the paediatric population at that meeting.

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<sup>5</sup> The Patient Information Leaflet accompanies the medicine and is consistent with the content of the SPC but is written in language more easily accessible to non-health professionals.

8. On 21 November 2002 the ad hoc group of experts met with MHRA representatives and independent experts to discuss issues relating to SSRIs. The meeting focused mainly on withdrawal reactions although suicidality (events possibly related to suicide, suicide attempt, suicidal thoughts etc) was also discussed. The ad hoc group made recommendations on these issues, based on consideration of the available safety data in the adult population. The considerations on SSRIs had up to this point focused on the risks and benefits in adults as there had not been a strong signal of a safety issue in children. MHRA presented recommendations to the CSM in January 2003 and CSM agreed that further work was required. In February the CSM agreed formally to establish an Expert Working Group to investigate the safety of SSRIs.

#### *Clinical trial data on Seroxat*

9. On 28 February 2003 GSK sent to MHRA an update on the clinical trial data GSK held in relation to suicidal behaviour. This was unprompted by any request from the Agency. The submission also enclosed two sets of analyses which GSK had carried out on these data; both were dated the 25 October 2002. The letter from GSK which accompanied the submission states there was no signal identified as regards suicidality revealed by these analyses. This submission contained adverse event data but failed to identify or differentiate between adult and paediatric trials. It only became clear later that this was the case and that events from paediatric studies had been merged together with the adult data. The number of studies and the number of people involved in each study were far greater for the adult than the paediatric population. Therefore any safety signal evident from the paediatric trials when they are considered separately, was lost when the two different trial populations were mixed together, as the relatively small number of adverse events in the paediatric trials is swamped by the large number of patients involved in the adult trials.

#### *Data from trials on Seroxat in children*

10. The first meeting of the new CSM Expert Working Group was arranged for 23 May 2003. In advance of the first meeting of the Expert Working Group, on 21 May the Agency called a second meeting with GSK in order to ensure that all of the data that GSK held that was relevant to safety of Seroxat had been supplied and to discuss any proposed communication by GSK with the prescribing community following a second Panorama programme which had aired on 11 May 2003.
11. At the end of this meeting, GSK handed out copies of a briefing document relating to an application to extend indications for Seroxat to include use in children. GSK drew the Agency's attention to a safety issue which GSK had identified in their paediatric clinical trials in depressive illness. This safety concern was derived from their randomised, placebo controlled, double blind clinical trials and indicated an increased rate of events relating to suicidal behaviour among paediatric patients with major depressive disorder treated with Seroxat, compared with those given placebo. On pointing out these data GSK indicated that this safety signal was something the Agency might wish to bear in mind when

considering the application for use in children which GSK was proposing to submit in late June 2003.

12. The significance of the data provided in the GSK briefing document was that they represented robust evidence from controlled studies of a causal association between an SSRI and suicidal behaviour. It had previously been argued by some manufacturers that a causal link could not be drawn between suicidality and SSRIs because no link was evident from (adult) clinical trial data. On examination of the full clinical trial data in children submitted by GSK urgently on 27 May 2003 in response to requests from the Agency, it became clear that the evidence base for the safety concern of an increased risk of suicidal behaviour was derived from pooled analysis of all the trials (a meta-analysis). It was only when the trials were analysed together that the safety issue became apparent. These trials had been conducted over a number of years and some had been published in part, however the publications gave an incomplete and partial picture of the full data<sup>6</sup>. Importantly, the trials conducted in a range of conditions in children and adolescents failed to demonstrate that Seroxat was effective in the treatment of depressive illness.
13. The lack of evidence of efficacy, together with evidence of a causal association between Seroxat and suicidal behaviour, meant that the overall benefit-risk balance could not be positive for use in under-18s. At the time, there were an estimated 7-8,000 under-18s being treated with Seroxat in the UK.

#### *MHRA communications to patients and the public*

14. The importance of the data, in the context of significant usage of Seroxat in children in the UK was such that the CSM advised that there should be prompt communication to UK health professionals. A 'Dear Doctor' letter was issued on 10 June 2003 which advised that Seroxat should not be used in the treatment of depressive illness in children and adolescents under the age of 18 years. To support this communication the Agency asked GSK to submit a variation to the UK marketing authorisations for Seroxat contraindicating use in children and adolescents under the age of 18 years.
15. The data also triggered a review of the safety and effectiveness of all other SSRIs in the treatment of depressive illness in children, and then in all age groups. The report of this review was published on 6 December 2004 alongside clinical guidelines for the treatment of depression from the National Institute for health and Clinical Excellence (NICE).

#### *Referral of case to enforcement*

16. On review of the data provided by GSK in response to requests from the Agency, two factors raised concern within the Agency about the extent to which the issue of the increased risk of suicidal behaviour in the Seroxat paediatric clinical trials had been communicated and acted upon in a timely manner by GSK. The first

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<sup>6</sup> Whittington, C J et al (2004) Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data, *The Lancet* 363, 1341-1345.

area of concern was the length of time between completion of some of the trials included in the analysis which had raised the safety issue and the communication of this to the agency. The second was that this important safety concern had been communicated to MHRA in the form of a briefing about a proposed future application to extend the indication for use of Seroxat to children, rather than as a risk:benefit issue which required immediate attention. Applications to extend indications take some time to prepare, are not routinely reviewed by the pharmacovigilance group within the Agency and are not an appropriate mechanism for informing a regulatory authority of a new risk:benefit concern.

17. In light of these concerns, on 1 October 2003 the Pharmacovigilance Group of the Agency referred the matter to the Enforcement Group of the Agency for a criminal investigation to be commenced.

## Section 2 - Investigation Methodology and Resources

18. The allegation referred to the Enforcement Group of the Agency on 1st October 2003 related to whether GSK had breached pharmacovigilance regulations
  - by failing to provide information relating to adverse reactions among the paediatric population during its programme of paediatric clinical trials; and
  - delaying the provision of that information to the Agency;
19. At a later stage the investigation looked at whether GSK's communications with health professionals breached advertising legislation.
20. To investigate these allegations it was therefore necessary to obtain the totality of the information generated by GSK and its agents in connection with the relevant clinical trials and to review it to ascertain if any information had not been supplied or had been supplied late. The relevant information included, inter alia: the raw clinical trial data, all subsequent analyses of it performed by GSK and all records of management decision making in connection with the provision of information to the Agency. The intention was that once this information had been reviewed witnesses could be interviewed and finally, if appropriate, the company would be invited to attend an interview under caution. A file could then be passed to prosecutors in the Department for Work and Pensions for a decision to be made in accordance with the Code for Crown Prosecutors as to whether a prosecution of GSK and/or individual officers of GSK should be commenced for pharmacovigilance offences.
21. Section 112(3) of the Medicines Act 1968 provides the MHRA with a right to require pharmaceutical companies to provide it with documentation relating to their business. During the investigation the MHRA exercised these rights on 103 separate occasions. A vast amount of information was received in response. The Agency's own records were also reviewed during the investigation including, inter alia: records of pharmacovigilance information that was provided by GSK, all correspondence with GSK related to the safety of Seroxat and variations to the



licence for Seroxat, and the Agency's minutes of meetings with GSK management where the safety of Seroxat was discussed. In total it is estimated that approximately 1,000,000 pages of documentation were reviewed during the conduct of the investigation.

22. Enquiries were also made with the Food and Drug Administration in the United States of America and with individual patients who had been treated with Seroxat in the UK. Shelley Jofre, the BBC journalist who made the Panorama programmes, was also interviewed by investigation staff and kindly provided copies of documentation she had obtained whilst preparing the programmes.
23. GSK and individual members of GSK staff declined invitations to attend interviews under caution, but three written witness statements were received, two on behalf of GSK and one on behalf of an individual member of GSK staff.

#### *Investigation staff*

24. The composition of the team of investigators assembled by the Enforcement group to conduct the investigation varied over time depending upon the particular stage that the investigation had reached and the particular investigatory task being undertaken. At various times the team included the following staff:

- Three senior Enforcement Group investigating officers
- Two independent consultants
- One expert inspector (a medic from the Inspection and Standards Division)
- Two inspectors (also from the Inspection and Standards Division)
- One assessor (from the Post Licensing Division)
- One pharmacovigilance investigator (recruited to the Enforcement Group from the Post Licensing Division)
- Two statisticians
- One clinical trial assessor (from the clinical trials unit)
- One office manager
- One administrative assistant

25. On 5th January 2005 the leadership of the investigation passed from one of the senior investigating officers to an investigating solicitor who had been seconded from the Prosecution Division of the Government Legal Services for that purpose.
26. In line with the Agency's standard arrangements for preventing conflict of interest, no member of the investigation team had any links or financial or other interests in GSK. All counsel instructed by the Agency were also asked if they had any financial or other interest in GSK and reported that they did not.

#### Section 3 – The Decision not to Prosecute

27. The Prosecution Division is responsible for legal services connected with prosecutions in magistrates' and crown courts for the Department for Work and Pensions and the Department for Health and their respective agencies. It has

responsibility for deciding whether cases investigated by the MHRA should proceed to prosecution.

28. In order to reach their decision the Prosecution Division instructed independent counsel to advise on whether a prosecution would be appropriate and advice was provided by Mr Robert O'Sullivan and Mrs Miranda Moore QC.
29. Advice provided by counsel to the Prosecution Division is confidential and may not be published. Further, in this particular case a decision has also been taken that the suspect/s should not face prosecution, and it would, therefore, be particularly inappropriate to publish advice which examines their alleged conduct.
30. The decision not to prosecute was taken in strict accordance with the Code for Crown Prosecutors which sets out a framework within which the CPS and all Government Prosecutors reach their decisions.
31. The Code for Crown Prosecutors sets out a two part test that must be passed by any case before a prosecution may be commenced. The first part of this test is known as the "evidential test". This requires that consideration must be given to whether there is a "realistic prospect of conviction". If it is decided that a realistic prospect of conviction exists, consideration must then be given to the second part of the test which is whether a prosecution would be in the public interest ("the public interest test"). It should be noted that if a case does not pass the evidential test the question of whether a prosecution would be in the public interest does not fall to be considered.
32. The evidential test is set out in paragraph 5 of the Code for Crown prosecutors. Paragraphs 5.2 and 5.3 were particularly relevant to the decision not to prosecute made in this case and they provide as follows:-
  - 5.2 *Crown Prosecutors must be satisfied that there is enough evidence to provide a "realistic prospect of conviction" against each defendant on each charge. They must consider what the defence case may be, and how that is likely to affect the prosecution case.*
  - 5.3 *A realistic prospect of conviction is an objective test. It means that a jury or bench of magistrates or judge hearing a case alone, properly directed in accordance with the law, is more likely than not to convict the defendant of the charge alleged. This is a separate test from the one that the criminal courts themselves must apply. A court should only convict if satisfied so that it is sure of a defendant's guilt.*
33. The offences that GSK were suspected of committing are set out in schedule 3 to the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 SI 3144/1994 ("the 1994 Regulations"). The 1994 Regulations implement European Union Directives in UK law and were amended several times during the period of the alleged offending, the most important amendments being implemented on 28th February 2002. At this date paragraphs 8 and 10(d) of schedule 3 to the 1994 Regulations provided as follows:

8 *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 ...Title 9 of the 2001 Directive, shall be guilty of an offence.*

10 *Any person who, while employed or engaged as an appropriately qualified person responsible for pharmacovigilance for the purposes of ...Title 9 of the 2001 Directive fails to*

*(d) provide to the licensing authority any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product...*

*...as required by any provision of any...Title...shall be guilty of an offence.*

34. These offences are punishable with up to two years imprisonment and/or an unlimited fine.
35. Having considered the advice provided by counsel the Prosecution Division reached the conclusion that no offence has been committed contrary to the 1994 Regulations because the clinical trials conducted by GSK on the paediatric use of Seroxat, and GSK's alleged failure to provide information from those trials, most likely did not fall within the regime implemented by those Regulations.
36. Moreover in criminal law it is only possible to obtain a conviction against a defendant for regulatory offences if the relevant regulations were clear enough in their meaning for the defendant to have known what was required of them. In light of counsel's advice the Prosecution Division reached the view that even if the 1994 Regulations did apply to GSK's paediatric clinical trials the relevant provisions were not sufficiently clear so as to permit a criminal sanction for their breach.
37. Consideration was also given by the Prosecution Division to whether any other offences, either from medicines regulatory law or from the general criminal law, may have been committed by GSK in connection with their programme of paediatric clinical trials. Again the assistance of counsel was sought in considering this question and the Prosecution Division have concluded that there is insufficient evidence to support the prosecution of any such offence.
38. In light of the matters discussed above and the advice received from counsel it was decided that there was no realistic prospect of obtaining a conviction for any offences and a decision was accordingly taken by the Prosecution Division in accordance with the Code for Crown prosecutors that there should no prosecution.

#### Section 4 – The Legal Position

39. Clinical trials of Seroxat in children were conducted by or on behalf of GSK between April 1994 and January 2002. The trials were conducted primarily in the

USA, although one trial was conducted partly in the UK. The allegation against GSK was that they failed to comply with legislation requiring them to report adverse events occurring in clinical trials in which Seroxat was given to children, and failed to report a safety issue promptly once they were aware of its existence.

### *Medicines legislation*

40. The legislation governing the regulation of medicines, including the reporting of adverse reactions to medicines, is laid down in EU Directives. EU Directives are given force of law in the UK through regulations<sup>7</sup>. The UK regulations are amended when the EU Directives are amended, or new Directives introduced. In many cases the UK regulations repeat or cross-refer to the EU Directive provisions, rather than re-interpreting them. In the latter case they do this by specifying that the Marketing Authorisation Holder – MAH (a company with a medicinal product on the market) must comply with all obligations which apply to him by virtue of the “relevant Community provisions”.

### *The legislation governing reporting of adverse reactions*

41. During the period in question (April 1994 to 21st May 2003) there were various EU Directives in force that included provisions requiring Member States to establish a pharmacovigilance system, having regard to “information obtained about adverse reactions to medicinal products under normal conditions of use”<sup>8</sup>. Until June 2000 they required the MAH to notify suspected serious adverse reactions to their product to the regulator<sup>9</sup> within 15 days, and to maintain records of other suspected adverse reactions and provide those to the regulator at specified intervals, together with a scientific evaluation.
42. On 30 June 2000 the EU legislation was amended and additional provisions were introduced. In particular, the new provisions included a requirement that placed a specific obligation on the “Qualified Person” (a person companies are obliged to employ whose responsibility it is to ensure completion of records and provision of information concerning suspected adverse reactions to, and monitoring of the risks and benefits of, their authorised products). The new provision required the Qualified Person to inform the regulator about any information relevant to the risks and benefits of the product, including appropriate information on “post authorisation studies”. “Post authorisation studies” are defined in EU legislation as studies or trials being conducted in accordance with the product’s authorised use, in other words, not studies into potential new, unauthorised uses of the product.
43. Another new provision was introduced that required the MAH to report all suspected serious unexpected adverse reactions occurring in a third country (that is, occurring anywhere outside the EU) to the regulators of the EU country in which the product is authorised within 15 days. Records of all adverse reactions

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<sup>7</sup> The Medicines for Human Use (Marketing Authorisations etc) Regulations 1994.

<sup>8</sup> Directive 75/319/EEC as amended (inter alia) by Directive 93/39/EEC and Directive 2000/83/EC and consolidated and replaced by Directive 2001/83/EC

<sup>9</sup> The EU legislation refers to the “competent authorities” which in the UK is the Medicines and Healthcare products Regulatory Agency - MHRA

are to be submitted to the regulator at specified periods, together with a scientific evaluation of the risks and benefits of the product.

44. On 19 December 2001 the EU legislation was repealed and for the most part the provisions were brought together in a single consolidating Directive<sup>10</sup>. The UK regulations were amended to implement the new EU legislation with effect from 28 February 2002.

*The legislation governing the conduct of clinical trials*

45. During the period when the clinical trials were conducted (April 1994 – January 2002) there was no specific EU legislation governing the conduct of clinical trials, or of the reporting of adverse reactions occurring during such trials. The conduct of clinical trials undertaken in the UK was governed by the Medicines Act and orders made under the Act.<sup>11</sup> Under these orders a person conducting a trial was required to report adverse reactions occurring during a trial, but failure to do so was not a criminal offence. The legislation only applied to trials conducted wholly or partly in the UK.

*The legal position in respect of reporting adverse reactions from 1994 onwards*

46. The UK regulations<sup>12</sup> include various criminal offences for breaching medicines legislation. During the period up to 27 February 2002 there were offences in place for failure by the MAH to report suspected adverse reactions, or to submit records of suspected adverse reactions to the regulator as required by the EU legislation, and for failure by the Qualified Person to prepare for the regulator a report on any suspected adverse reactions required under the EU legislation.
47. The UK regulations were amended from 28 February 2002 to take account of the new EU Directive<sup>13</sup>, as above, and to introduce a further offence for failure by the Qualified Person to provide the regulator with information relevant to the evaluation of the risks and benefits of the product, including information on post authorisation safety studies.

*Assessment of the strength and clarity of legislation in place at the relevant time*

48. As part of its investigation into GSK, and preparation for a possible criminal prosecution, the MHRA sought independent Counsel advice on whether these criminal offences covered the circumstances in this case. The advice received stated that the law as it stood at the relevant time did not cover the circumstances in this case, and that failure to provide the regulator with the safety-related information was not covered by a criminal offence. Even if there were doubt on

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<sup>10</sup> Directive 2001/83EC

<sup>11</sup> Section 31 of the Medicines Act 1968

The Medicines for Human use (Exemptions from Licenses) (Clinical Trials) Order 1981  
Medicines for Human use (Exemptions from Licenses) Clinical trials) order 1995

<sup>12</sup> The Medicines for Human Use (Marketing Authorisations Etc) regulations 1994. Regulation 7(4) and Schedule 3

<sup>13</sup> Directive 2001/83/EC

the interpretation, the legislation was sufficiently unclear as to make a criminal prosecution impossible.

49. In summary, this is because:

- The EU legislation (and the regulations transposing it into UK law) in force at the relevant time only require notification of adverse reactions occurring in the normal conditions of use of the product. It did not therefore apply to products being used in trials outside the terms of the MA;<sup>14</sup>
- Although a requirement to report adverse reactions occurring in “post authorisation studies” was added to the EU legislation in June 2000<sup>15</sup>, legal advice confirms that this still only applied, because of the way the legislation was written, to studies on products within their normal conditions of use, such as safety studies;
- The UK’s own legislation on the conduct of clinical trials did impose an obligation to report adverse reactions occurring in clinical trials. However, this only applied to trials conducted in the UK (and would therefore only have applied to one of the GSK trials) and breach of this obligation was not a criminal offence;
- From 28 February 2002 the UK legislation places an obligation on the Qualified Person to report appropriate information arising from post authorisation studies, but again it is doubtful whether this includes information from studies undertaken outside the normal conditions of use of the product;
- From 28 February 2002 the UK legislation also required the Qualified Person to report to the regulator any information relevant to the evaluation of the risks and benefits of the product. The information that was eventually provided to the MHRA about adverse reactions experienced in the trials of Seroxat in children was clearly, in MHRA’s view, relevant to the risks and benefits of the product. However, the legal advice is that it is, insufficiently clear that there is a requirement to report this information when it is generated from studies undertaken outside the normal conditions of use for the product;
- The legislation also fails to provide a time limit within which such information must be provided by the Qualified Person to the MHRA. GSK did submit the information to the MHRA in May 2003.

50. This advice – which was at odds with what the Agency believed to be the scope of the legislation – meant not only that a prosecution was impossible in this case, but that there was a significant gap in the law governing drug safety. It is not

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<sup>14</sup> Since the trials all involved use in children - and Seroxat had never been licensed for use in children - the adverse reactions all related to use outside the terms of the MA.

<sup>15</sup> Directive 2000/38/EC

uncommon for medicines to be used outside the terms of their marketing authorisation for various reasons, and safety-related information related to such use should be subject to reporting obligations in the same way as for use within the MA.

*What has changed in the legislation since 21 May 2003?*

51. There is now an EU Directive governing the conduct of clinical trials<sup>16</sup> that came into force in the UK on 1 May 2004<sup>17</sup>. This introduced a criminal offence for the failure to report adverse reactions occurring in clinical trials. However, neither the UK regulations nor the Directive itself apply to trials conducted outside the European Economic Area.
52. Changes were introduced to the EU medicines legislation from October 2005<sup>18</sup> that clarify the obligation to report relevant safety information arising from clinical trials using products outside their normal conditions of use. These were implemented in the UK from 30 October 2005, and include an obligation to provide the necessary information promptly. Therefore, the law has been strengthened to an extent, but not yet fully.

*What still needs to be addressed and how?*

53. The European Commission is currently consulting on proposals to strengthen the EU system for monitoring the safety of medicines. The MHRA has proposed that the EU should take this opportunity to introduce a number of additional changes in the light of this investigation. The aim will be to ensure that as a result of this exercise there remains no room for doubt in industry's and regulators' minds about the obligations of Marketing Authorisation Holders under EU and UK legislation to report information of relevance to the risk and benefit of medicines on the market. In particular, we want to see absolute clarity in the legislation as to the information that must be supplied to the regulator, regardless of its source (eg inside and outside the EU, arising as a result of any use including use outside the terms of the marketing authorisation, use in any clinical trials, as well as use as defined in the marketing authorisation) and clear time scales within which such information must be supplied and sanctions for failing to comply with the legislation.
54. Given the length of time that it may take for EU legislation to be negotiated and come into force, steps will be taken to change UK legislation in the interim.

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<sup>16</sup> Directive 2001/20/EC

<sup>17</sup> Medicines for Human Use (Clinical Trials) Regulations 2004

<sup>18</sup> Directive 2004/27/EC which amended Directive 2001/83/EC