EXPLANATORY MEMORANDUM TO

THE MEDICINES FOR HUMAN USE (MARKETING AUTHORISATIONS ETC.) AMENDMENT REGULATIONS 2008

2008 No. 3097

1. This explanatory memorandum has been prepared by the Medicines and Healthcare products Regulatory Agency, on behalf of the Department of Health, and is laid before Parliament by Command of Her Majesty.

2. Purpose of the instrument

2.1 This instrument amends the Medicines for Human Use (Marketing Authorisation) Regulations 2004, firstly in order to introduce measures in the UK to enforce the obligations set out in Regulation (EC) No. 1901/2006 as amended of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Paediatric Use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004.

2.2 The Paediatric Regulation (PR) was adopted on 12 December 2006 and came into force in the EU on 26 January 2007. It is directly applicable in Member States. The PR introduces a framework for providing incentives to companies to conduct research into the use of medicines by children in the EU.

2.3 By virtue of the fact that all EU Regulations have direct effect in Member States, the requirements are legally binding within the UK without any further implementing measures. However, Article 49 of the PR states that Member States shall determine the penalties to be applied for infringement of the provisions of the Regulation or the implementing measures adopted pursuant to it. The Article states that the penalties shall be effective, proportionate and dissuasive. It is these penalties that the amending regulations introduce.

2.4 This instrument also amends the Medicines for Human Use (Marketing Authorisations, Etc.) Regulations 1994 to state explicitly that marketing authorisation holders should report information from clinical trials outside the licensed indication, information arising from third countries and provides a timescale for the reporting of such information. The amending regulations are made using Section 2, (2) of the European Communities Act (1972) which provides a power for the making of regulations based on EU legislation. The 1994 Regulations implement Article 23 of the Directive (2001/83/EC as amended) which sets out reporting requirements of the pharmaceutical industry.

2.5 In March, the MHRA announced the outcome of an investigation into GlaxoSmithKline (GSK) and their failure promptly to supply important information relating to the safety of Seroxat in children. At that time, the Government committed the UK to playing an active part in the review of pharmacovigilance legislation at a European level. In addition, a commitment was made to strengthen UK legislation to make clear the requirements on marketing authorisation holders to supply information

impacting on risks and benefits, with a time frame for doing so. The commitment was to change the regulations by the end of 2008.

2.6 The instrument also corrects a typographical error in the Medicines for Human Use (Prescribing by EEA Practitioners) Regulations 2008.

3. Matters of special interest to the Joint Committee on Statutory Instruments

3.1 None.

4. Legislative Background

4.1 The Medicines for Human Use (Marketing Authorisations Etc.) Amendment Regulations 2008 (the amending regulations) make the amendments to the Medicines for Human Use (Marketing Authorisation) Regulations 2004 (the MA Regulations) necessary to enforce the obligations set out in the PR. In the following paragraphs references to paragraph numbers are to the paragraphs of Schedule 3 to the MA Regulations. Regulation 3 introduces the proposed offences in to Schedule 3 to the MA Regulations.

4.2 Regulation 3(2) of the amending regulations inserts a new offence into paragraph 6 of the MA Regulations, a paragraph which criminalises the breach of various obligations on Marketing Authorisation (MA) holders. The new provision inserted at 6(f) introduces an offence for an MA holder to fail to submit an annual report to the EMEA where a deferral has been granted. The corresponding obligation is in Article 34.4 of the PR.

4.3 Regulation 3(4) inserts two new offences by creating two new paragraphs: 6BA and 6BB of the MA Regulations.

4.4 The offence inserted at paragraph 6BA of the MA Regulations corresponds to the obligation in the first paragraph of Article 35 of the PR. This applies where a product is authorised for a paediatric indication, having benefited from the rewards offered in the PR, and the MA holder chooses to discontinue marketing of the product. MA holders must either transfer the marketing authorisation or enable another party to use the pharmaceutical, pre-clinical and clinical data. Given that a minimum of 6 months notice must be given of discontinuance (see below) an MA holder will have at least 6 months to meet this obligation. This is consistent with the Article taken as a whole. This is consistent with Recital 25 which aims to ensure that the paediatric population has continuous access to medicines marketed with paediatric indications.

4.5 The offence inserted at paragraph 6BB of the MA Regulations corresponds to the second paragraph of Article 35 of the PR. This places an obligation on MA holders to give the EMEA 6 months notice when he chooses to discontinue marketing a product.

4.6 Regulation 3(5) of the amending regulations inserts a new offence as new paragraph 6G of the MA Regulations. This offence corresponds to Article 33 of the PR, which obliges an MA holder to market a paediatric indication (description of the illness for which the product is licensed to treat) on an already marketed product within 2 years of the authorisation of the paediatric indication.

4.7 Regulations 3(7) & (8) extend the two current offences regarding labelling to cover the labelling requirements of Articles 28 and 32 of the PR. Hence if the labelling requirements of Articles 28 & 32 are not satisfied, either by the MA holder (regulation 3(7)) or in the knowledge of specified third parties in certain circumstances (regulation 3(8)), an offence will have been committed.

4.8 Regulation 3(9) inserts new paragraph 13B of the MA Regulations, which contains 8 new offences each in a separate sub-paragraph. The text of each of these new offences is set out in full in regulation 3(9). The 8 offences relate to the provision of information relating to trials (either results or trial outline) to either the EMEA or the licensing authority. These reporting obligations arise under Articles 41.1, 41.2, 45.1 and 46.1 of the PR. The 8 offences are outlined below:

(a) New paragraph 13B(1) combines two obligations into one offence. Both offences relate to obligations placed on the addressee of the PIP decision. The first obligation comes from Article 41.1 of the PR and relates to submission of trial information to the EU-wide clinical trials database. This is captured at 13B(1)(a). The second obligation comes from Article 41.2 and relates to submission of results (13B(1)(b)). In summary, when it comes to reporting results of a trial in a PIP the obligation is on the addressee to report to the EMEA. The PR does not explicitly state where the Article 41.2 obligations falls (it refers to "the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan or by the MA holder, as appropriate"). Based on our understanding of the aims of the legislation and our public consultation, the regulations place the obligation as follows:

(a)(i) All results from a trial in a paediatric investigation plan (PIP), to be submitted to EMEA by the addressee of the EMEA's decision on the PIP (see 13B(1)(b));

(a)(ii) All results from a non-PIP trial, to be submitted to EMEA by MA holder if involved (see 13B(2)/(3)). If no MA holder is involved, or there is no MA, then sponsor has to submit the results to the EMEA (see 13B(4)/(5)).

(b) New paragraph 13B(2) of the MA Regulations makes it a criminal offence for a MA holder not to submit the results of new trials in which he is involved and where the trial is not in a PIP.

(c) The new offence at paragraph 13B(3) of the MA Regulations is the same offence as 13B(2); but whereas 13B(2) applies to new trials, 13B(3) applies to trials started after the PR came into force on 26 January 2007 but concluded before these regulations come in to force.

(d) The new offence at 13B(4) of the MA Regulations makes sponsors responsible for reporting trial results where (i) the trial is not in a PIP, and (ii) there is no MA or the MA holder is not involved with the trial; and creates an offence in these terms.

(e) 13B(5) of the MA Regulations applies the offence in 13B(4) to trials started after the PR came into force but concluded before these MA Regulations came in to force.

(f) The new offences at 13B(6), (7) & (8) relate to submission of paediatric studies to the licensing authority (as opposed the EMEA) by MA holders. The new offence inserted as 13B(6) of the MA Regulations enforces Article 45.1 of the PR. It makes it an offence for an MA holder to fail to submit the results of pre-PR trials of which he has knowledge to the licensing authority.

(g) 13B(7) of the MA Regulations enforces Article 46.1 and requires an MAH to submit the results of new trials he sponsors on the authorised product to the licensing authority or be guilty of an offence.

(h) 13B(8) of the MA Regulations is the same basic offence as 13B(7) but covers 'new' trials which are excluded by 13B(7) because they begin and end between the PR coming into force (26 January 2007) and implementation of these Regulations.

4.9 With respect to offences contained in paragraph 13B of the MA Regulations (paragraph. 4.8 above), the requirements to submit trial results that flow from Article 41.2 must be satisfied "without delay". The regulations interpret "without delay" in this context as within 6 months.

4.10 Paragraph 17 of Schedule 3 (which creates a due diligence defence for certain other obligations in the MA Regulations) is extended to cover the following PR obligations:

- 6BA - transferring MA or making available data at least 6 months before the marketing of a product is discontinued (paragraph 4.4 above)
- 6BB - giving 6 months notice of discontinuance (paragraph 4.5 above)
- 6G - mandatory placing on market of a product for which a paediatric indication has been granted within 2 years of the granting of the indication (paragraph 4.6)
- 13B(1) to (8) - obligations to provide information/data (paragraph 4.8)

4.11 Any person guilty of committing an offence will be liable to a fine not exceeding the statutory maximum or imprisonment for up to two years or both. The Secretary of State for Health's powers to introduce these new offences derives from section 2(2) of the European Communities Act, which provides powers to implement Community legislation.

4.12 The amending regulations also make the amendments to Schedule 3 of the Medicine for Human Use (Marketing Authorisations Etc.) Regulations 1994 necessary to strengthen UK law to ensure that MA holders provide MHRA with information arising from clinical trials outside the licensed indication, information arising from third countries and address the issue of the lack of a timescale for the reporting of such information.

4.13 In the following paragraphs references to paragraph numbers are to the paragraphs of Schedule 3 to the 1994 Regulations.

4.14 New paragraph 6AA includes the new provisions that clarify what data MAHs must provide to MHRA. These are information arising from use of the product:

(a) in a country which is not an EEA state;
(b) outside the terms of the marketing authorisation, including use in clinical trials.

4.15 The requirement on the Qualified Persons for Pharmacovigilance to provide to the licensing authority any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post authorisation safety studies to be supplied "as soon as is reasonably practicable" is clarified in the amendment to 10(d), reflecting the changes in paragraph 4.14 above.

5. Territorial Extent and Application

5.1 This instrument applies to all of the United Kingdom.

6. European Convention on Human Rights

6.1 The Minister of State for Public Health has made the following statement regarding Human Rights:

In my view the provisions of the Medicines for Human Use (Marketing Authorisations Etc.) Amendment Regulations 2008 are compatible with the Convention rights.

7. Policy background

What is being done and why

7.1 The PR introduces a framework for providing incentives to companies to conduct research into the use of medicines by children in the EU. It has the following high level objectives:

- Increase the availability of medicines specifically adapted and authorised for use by children
- Increase the information available to the patient/carer and prescriber about the use of medicines in children, including clinical trial data
- Increase the levels of high quality research into medicines for children

7.2 The UK played a major role in developing the PR, working with the European Commission in developing the proposals and with other Member States and the European Parliament in the negotiation process. This was a key part of the UK's strategy on developing new medicines for use on the paediatric population.

7.3 Until relatively recently there was a relative reluctance to conduct studies of medicines used in the treatment of children. This was due to a number of factors including ethical concerns about, and the practical difficulties of, conducting trials in children, together with commercial considerations. As a result, most medicines have only been tested for safe and effective use in the adult population and there are comparatively few medicines on the market which are specifically licensed for the treatment of children. This led to prescribers having no option but to prescribe unlicensed and off-label medications, sometimes in unsuitable formulations. This may result in reluctance to use newly introduced drugs, medication errors, inappropriate

dosing (both too high and too low), inadequate efficacy and unforeseen adverse events.

7.4 There has been a significant shift in opinion in recent years about conducting clinical trials in the paediatric population. For example, the number of clinical trials carried out the US has increased in the US over the last few years. The lack of such trials is now seen as the chief ethical concern.

7.5 The US has introduced legislation that provides financial incentives to industry to undertake clinical trials on products used in the treatment of children whilst they are still "patent protected". This has succeeded to a point but has not encouraged trials of products for some important children's diseases, where the commercial incentive is still considered insufficient. For this reason the US has also introduced a legal obligation for companies to conduct trials on the paediatric use of medicines where there is a therapeutic need.

7.6 The PR establishes a system of requirements and incentives aimed at satisfying the need for medicines that are appropriately formulated and labelled for paediatric use. The PR improves the quality of information available on the use of medicines in children enables publication of paediatric clinical trial information.

7.7 The main elements of the PR are as follows:

(i) The establishment of a new body, the Paediatric Committee, comprising representatives from Member States and representatives of healthcare professionals and patient groups, appointed by the European Commission

(ii) For new products and certain changes to the marketing authorisation for products still covered by patent protection:

- a requirement for paediatric data based on a paediatric investigation plan (PIP) unless the MA holder has been granted a waiver or deferral;
- a six-month extension of the supplementary protection certificate (SPC) if information arising from a completed PIP is incorporated into the Summary of Product Characteristics

(iii) For off-patent products a new category of marketing authorisation called the paediatric use marketing authorisation which will be associated with a ten-year period of data and market protection.

(iv) A European database of paediatric clinical trials, part of which will be publicly accessible

(v) An identifying symbol on the package of all products authorised for use in children

7.8 The PR was adopted on 12 December 2006 and came into force in the EU on 26 January 2007. Since January 2007 the UK and other Member States have been working together to manage the implementation of the various activities described above. Member States have also been required to formulate and implement measures to enforce the obligations of the PR on a national level. It is this narrow aspect of the initiative that the attached amending regulation covers.

7.9 On 6 March 2008, the MHRA issued a report on the outcome of an investigation into GlaxoSmithKline and its antidepressant drug Seroxat. The investigation focused on whether GSK had failed to inform the MHRA of information it had on the safety of Seroxat in under 18's in a timely manner.

7.10 The decision taken by Government Prosecutors, based on the investigation findings and legal advice, was that there was no realistic prospect of a conviction in this case, and that the case should not proceed to criminal prosecution. The legislation in force at the time was not sufficiently clear or comprehensive as to require companies to inform the regulator of safety information when the drug was being used for, or tested outside its licensed indications.

7.11 Several changes to the legislation governing the reporting of new information which might influence the evaluation of the benefits and risks for a medicine have already been made since the time of these events.

7.12 There is now an EU Directive governing the conduct of clinical trials that came into force in the UK on 1 May 2004. This introduced a criminal offence for the failure to report adverse reactions occurring in clinical trials. Articles 10(b) and 18 of the Directive have been interpreted in guidance to require reporting of certain events from clinical trials and other sources outside the EEA. The reporting rules are set out in Section 6 and Tables 1-3 of the "Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module) April 2004" and Section 5.1.1. of "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use" April 2006

7.13 Changes were introduced to the EU medicines legislation from October 2005 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 fully.

7.14 The European Commission is also 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 the above 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.

7.15 Given the length of time that it may take for EU legislation to be negotiated and come into force, the MHRA also gave a commitment to take steps to change UK legislation in the interim to clarify the requirement to report adverse reactions. The amending regulation meets this commitment.

Consolidation

7.16 There are no plans to consolidate the MA Regulations at this time.

8. Consultation outcome

8.1 The Government conducted a full 12-week public consultation on the proposals for enforcing the PR. This was circulated to over 2000 stakeholders including all MA holders in the UK, NHS Trusts and a range of research organisations. We received 10 responses of which 8 provided specific comments. The comments were received from research organisations, the pharmaceutical industry and NHS bodies. The issues on which consultees commented were:

- Consultees suggested that the 6 months timeframe to submit the results of clinical trials should either be extended or that defence of due diligence should be taken into account when enforcing this obligation
- There was general (but not absolute) support for defence of due diligence
- There were questions about some of the definitions used in the amending regulations, including whether a definition of 'paediatric study' was necessary

8.2 We propose to include a due diligence provision in the MA Regulations for the majority of reporting obligations (see paragraph 4.10) including the requirement to report the results of clinical trials within 6 months. With respect to definitions, the amending regulations rely on the definitions used in the 'parent' Regulation – in this case the PR. We do not believe a definition of 'paediatric study' is necessary. We will shortly publish a full summary of responses, responding to these issues.

8.3 The Government conducted a full 12-week public consultation on the proposals for strengthening pharmacovigilance provisions. This was circulated to all MA holders and a range of industry, professional, voluntary, and patient organisations. We received 31 responses of which 13 provided specific comments. The comments were received from the pharmaceutical industry, professional bodies, voluntary sector, a research organisation and a patient. The main issues on which consultees commented are:

- the need for further guidance on what to report within what timeframe.
- there should be further elaboration of the word "promptly".
- we should mirror the changes we consulted on in the obligations for the "qualified person" employed by the MA holder as well as for the MA holder.

8.4 Further guidance on reporting requirements, including timescales, is provided in the MHRA's Good Pharmacovigilance Practice Guide, published in November 2008. The UK will also ensure these issues are addressed when the relevant European guidance is next updated. This, in turn, will be informed by an initiative through the Ministerial Industry Strategy Group where the MHRA has been working with industry on a pilot on early sharing of potential safety issues (signals).

8.5 On balance, use of "as soon as reasonably practicable" can be argued to give those required to comply a clearer understanding than the insertion of the word promptly. There is more case law around use of this phrase and it is more commonly used in offence-creating legislation.

8.6 Following consultation we have mirrored the changes on the obligations for the MA holder to apply to the "qualified person" employed by the MA holder as well.

We have published a full summary of responses, responding to issues raised in the consultation.

Parliamentary scrutiny

8.7 The parliamentary scrutiny committees were kept fully informed of progress when the PR was under negotiation and scrutiny clearance was granted before final agreement.

9. Guidance

9.1 The Co-ordination Group for Mutual Recognition and Decentralised Procedures – on which representatives from all Member States and the European Commission sit – and EMEA have developed comprehensive guidance on the requirements of the Paediatric Regulation. On 27 October 2008 the Commission published a guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies

9.2 In the UK the Medicines and Healthcare products Regulatory Agency has published guidance on the handling of the requirement to undertake a 'compliance check' of applications to ensure that trial data was collected in accordance with an agreed paediatric investigation plan. Further guidance is in preparation. It will provide further clarification on the issues raised in the consultation responses and will provide procedural guidance to MA holders and research organisations conducting trials.

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9.3 As we have said in paragraph 8.4 above, we have developed and published further guidance for the pharmaceutical industry on reporting requirements clarified in the amending regulations.

10. Impact

10.1 The impact on business, charities or voluntary bodies is nil as regards the PR as the amending regulations introduce no new obligations as the requirements set out in the PR are directly applicable in Member States. The amending regulations on strengthening pharmaceutical reporting requirements will have a negligible financial impact on businesses since it provides clarity to existing requirements under European legislation. These data should already be provided to MHRA.

10.2 The impact on the public sector is negligible.

10.3 An Impact Assessment has not been prepared for this instrument.

11. Regulating small business

11.1 The legislation applies to small business.

11.2 To minimise the impact of the requirements on firms employing up to 20 people, we have include a due diligence provision in the MA Regulations with respect to the obligations in the PR to report information. A person will not be guilty of

committing an offence if it can be demonstrated that he or she took all reasonable steps and precautions to avoid committing the offence. For clarifying the pharmacovigilance reporting requirements, the good practice guide in pharmacovigilance set out what is expected of all marketing authorisation holders, including small businesses.

11.3 The basis for the final decision on what action to take to assist small business was the support for the introduction of a due diligence provision in the public consultation on proposals to enforce the PR. For the pharmacovigilance reporting requirements for small businesses would not be appropriate, given the need to identify potential safety issues from even a small amount of data.

12. Monitoring & review

12.1 For the amendments that relate to enforcing the requirements of the PR, success can be judged by the levels overall compliance with the obligations set out in the PR. We would expect at least 95% compliance over 3 years.

12.2 For the amendments that strengthen pharmaceutical reporting requirements, success can be judged in monitoring the impact of the guidance on good practice in pharmacovigilance on the identification of safety issues.

12.3 The requirements will be subject to internal review within 3 years of implementation. The good practice guide in pharmacovigilance will be kept under review.

13. Contact

13.1 Michael Darbyshire at the Medicines and Healthcare products Regulatory Agency can answer any queries on the amendments related to the Paediatric Regulation (paragraphs 2.2 to 2.3 - Tel. 020 7084 2928 and e-mail michael.darbyshire@mhra.gsi.gov.uk). Jeremy Mean can respond to queries regarding the requirements to report information (paragraphs 2.4 to 2.5 – tel. 020 7084 2494 and e-mail jeremy.mean@mhra.gsi.gov.uk).