STATUTORY INSTRUMENTS

2012 No. 1916

The Human Medicines Regulations 2012

PART 11

Pharmacovigilance

Application of this Part and interpretation

177.—(1) This Part and Schedule 33 apply, except to the extent set out in paragraph (4)(b), in relation to medicinal products that are the subject of—

(a) a UK marketing authorisation;

(b) a traditional herbal registration; or

(c) an Article 126a authorisation.

(2) References in this Part to a "holder" are to the holder of—

(a) a UK marketing authorisation;

(b) a traditional herbal registration; or

(c) an Article 126a authorisation,

and, in relation to such references, "product" means the product to which the authorisation or registration relates.

(3) References to an "authorisation or registration" in this Part and in Schedule 33 are references to—

(a) a UK marketing authorisation;

(b) a traditional herbal registration; or

(c) an Article 126a authorisation

and "authorised or registered" is to be read accordingly.

(4) The following provisions of this Part and Schedule 33 apply in relation to medicinal products that are the subject of an EU marketing authorisation—

(a) regulation 206 (infringement notices); and

(b) regulation 210 (offences relating to pharmacovigilance obligations under Regulation (EC) No 726/2004), and paragraphs 2 and 4 of Schedule 33 (transitional arrangements: pharmacovigilance), but that regulation and those paragraphs do not apply in relation to the medicinal products specified in paragraph (1).

(5) In this Part and in Schedule 33—

"co-ordination group" means the group of that name established under Article 27 of the 2001 Directive;

"Eudravigilance database" means the database and data-processing network set up and maintained by the EMA under Article 24 of Regulation (EC) No 726/2004;

"infringement notice" has the meaning given to it in regulation 206 (infringement notices);

"relevant competent authorities" means the competent authority of each EEA state other than the United Kingdom which has granted in relation to a medicinal product—

(a) an authorisation in accordance with Chapter 1 of Title III to the 2001 Directive (marketing authorization);

(b) an authorisation in accordance with Chapter 4 of Title III to the 2001 Directive (mutual recognition and decentralised procedure);

(c) a registration in accordance with Chapter 2a of Title III to the 2001 Directive (traditional use registration for herbal medicinal products); or

(d) an authorisation in accordance with Article 126a of the 2001 Directive;

"relevant post-authorisation safety study" means a post-authorisation safety study which—

(a) is non-interventional;

(b) is initiated, managed or financed by the holder voluntarily or pursuant to conditions imposed under regulation 59 (conditions of a UK marketing authorisation: general) or 61 (conditions of a UK marketing authorisation: new obligations post-authorisation); and

(c) involves the collection of safety data from patients or health care professionals; and

"UK web-portal" has the meaning given in regulation 203 (obligations on licensing authority in relation to national medicines web-portal).

Obligations on licensing authority in relation to pharmacovigilance

General obligations of the licensing authority

178. The licensing authority must—

(a) take all appropriate measures to encourage the reporting to it of suspected adverse reactions;

(b) facilitate reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner, through publication on the UK web-portal, and through other means of publicly available information as necessary; and

(e) ensure that all appropriate measures are taken to identify any biological medicinal product (including name and batch number) prescribed, dispensed or sold in the United Kingdom which is the subject of a suspected adverse reaction report through—

(i) the methods for collecting data, and

(ii) where necessary, the follow up of suspected adverse reaction reports.

Obligation on licensing authority to operate pharmacovigilance system

179.—(1) The licensing authority must operate a pharmacovigilance system.

(2) The pharmacovigilance system must in particular enable the collection of information on the risks that medicinal products present to patients' health or public health, including information on—

(a) adverse reactions in humans arising from use of a medicinal product (irrespective of whether the use was within the terms of an authorisation or registration); and

(b) adverse reactions associated with occupational exposure.

(3) The licensing authority must on an ongoing basis—

(a) evaluate scientifically the information collected under the pharmacovigilance system;

(b) consider options for minimising and preventing risks presented by medicinal products; and

(c) take appropriate regulatory action, if any.

Obligation on licensing authority to audit pharmacovigilance system

180.—(1) The licensing authority must perform a regular audit of its pharmacovigilance system and report the results of that audit to the European Commission.

(2) The results of the audit referred to in paragraph (1) must be reported to the European Commission—

(a) on the first occasion no later than 21st September 2013; and

(b) every two years after the first occasion.

Delegation of obligations under this Part

181.—(1) The licensing authority may delegate any of its obligations under this Part to another EEA State where the conditions in paragraph (2) are met.

(2) The conditions in this paragraph are that the EEA State to whom the obligations are to be delegated—

(a) has given its written agreement to the delegation; and

(b) is not performing delegated obligations under this Part on behalf of another EEA State.

(3) Where the licensing authority has delegated any of its obligations under paragraph (1), it must—

(a) inform the European Commission, the EMA and all other EEA States in writing of the delegation as soon as is reasonably practicable; and

(b) make the delegation public as soon as is reasonably practicable.

(4) The licensing authority may agree to carry out any of the obligations of another EEA State under Title IX of the 2001 Directive on a delegated basis, but may carry out obligations under that Title only for one EEA State at any time.

Obligations on holders in relation to pharmacovigilance system

Obligation on holder to operate pharmacovigilance system

182.—(1) The holder must operate a pharmacovigilance system.

(2) The holder must (as part of its pharmacovigilance system)—

(a) have permanently and continuously at its disposal an appropriately qualified person responsible for pharmacovigilance who resides and operates in the EU and is responsible for the establishment and maintenance of the pharmacovigilance system;

(b) maintain and make available on the request of the licensing authority a pharmacovigilance system master file;

(c) operate a risk management system for the product in accordance with the risk management plan (if any) for the product (subject to regulation 183);

(d) monitor the outcome of the risk minimisation measures which are contained in the risk management plan (if any) for the product or which are laid down as conditions of the authorisation of the product under regulations 59 to 61 (conditions of UK marketing authorisation); and

(e) update the risk management system for the product and monitor pharmacovigilance data to determine whether in relation to the product—

(i) there are new risks,

(ii) risks have changed, or

(iii) there are changes to the risk-benefit balance.

(3) The holder must keep the licensing authority and the EMA informed of the name and contact details of the appropriately qualified person mentioned in paragraph (2)(a) at all times.

(4) The holder must use its pharmacovigilance system to—

(a) evaluate scientifically all information relevant to the product;

(b) consider options for minimising and preventing the risk presented by the use of the product; and

(c) take appropriate measures as soon as is reasonably practicable to—

(i) investigate the potential risks of the product,

(ii) communicate the risks, and

(iii) implement actions for minimising and preventing the risks, including updating the risk management system for the product.

(5) Where the licensing authority requests that the pharmacovigilance system master file is made available under paragraph (2)(b), the holder must submit a copy of the pharmacovigilance system master file to the licensing authority before the end of the period of 7 days beginning on the day after the day when the request was made.

(6) This regulation is subject to regulation 212 (transitional arrangements).

Exception to obligation to operate risk management system

183.—(1) The holder is not required to operate a risk management system under regulation 182(2)(c) in relation to a medicinal product which has an authorisation or registration that was granted before 21st July 2012.

(2) The licensing authority may impose an obligation on the holder to operate a risk management system in relation to a medicinal product referred to in paragraph (1) if there are concerns about new or changed risks affecting the risk-benefit balance of that product.

(3) Paragraphs (4) to (6) apply where the licensing authority imposes an obligation to operate a risk management system on the holder under paragraph (2).

(4) The licensing authority must without delay notify the holder in writing of—

(a) the imposition of the obligation;

(b) the justification for the obligation;

(c) the timeframe for submission of the detailed description of the risk management system required under paragraph (8)(a); and

(d) the opportunity to present written observations in accordance with paragraph (5).

(5) Where the holder so requests before the end of the period of thirty days beginning on the day after the receipt by the holder of the notice referred to in paragraph (4), the licensing authority must provide the holder with an opportunity to present written observations in response to the imposition of the obligation within such a time limit as the licensing authority may specify.

(6) Where a holder presents written observations under paragraph (5), the licensing authority must withdraw or confirm the imposition of the obligation under paragraph (2), having regard to the written observations, as soon as is reasonably practicable.

(7) Paragraphs (8) and (9) apply where the licensing authority—

(a) imposes an obligation under paragraph (2) and the holder does not present written obligations under paragraph (5); or

(b) confirms the imposition of the obligation under paragraph (2) pursuant to paragraph (6).

(8) The holder must—

(a) submit to the licensing authority in writing a detailed description of the risk management system which it intends to introduce for the product in accordance with the timeframe set out in the notification under paragraph (4); and

(b) comply with the obligation to operate a risk management system.

(9) Where the imposition relates to a product with a UK marketing authorisation, the licensing authority must vary the authorisation to include the measures to be taken as part of the risk management system as conditions of the authorisation as if they were conditions imposed under regulation 59 (conditions of UK marketing authorisations: general).

Obligation on holder to audit pharmacovigilance system

184.—(1) The holder must—

(a) perform a regular audit of its pharmacovigilance system;

(b) place a note concerning the main findings of each audit on the pharmacovigilance system master file on completion of each audit; and

(c) ensure that an appropriate corrective action plan is prepared and implemented as soon as is reasonably practicable after completion of each audit.

(2) The holder may remove the note placed on the pharmacovigilance system master file under paragraph (1)(b) when all the measures in the corrective action plan under paragraph (1)(c) have been fully implemented.

Recording, reporting and assessment of pharmacovigilance data

Recording obligations on the licensing authority

185. The licensing authority must record all suspected adverse reactions to medicinal products that—

(a) occur in the United Kingdom; and

(b) are reported to it by a patient or a patient's carer, a health care professional, a coroner or a procurator fiscal.

Reporting obligations on the licensing authority

186.—(1) The licensing authority must—

(a) when it receives a suspected adverse reaction report from a person mentioned in regulation 185(b), follow up the report with that person as appropriate;

(b) ensure that reports of suspected adverse reactions in the United Kingdom may be submitted to it, whether by the UK web-portal or by other means;

(c) collaborate with the EMA and the holders of authorisations or registrations in the detection of duplicates of suspected adverse reaction reports;

(d) submit reports of serious suspected adverse reactions that it has recorded under regulation 185 electronically to the Eudravigilance database before the end of the period of 15 days beginning on the day following the day on which the report was received; and

(e) submit reports of non-serious suspected adverse reactions it has recorded under regulation 185 electronically to the Eudravigilance database before the end of the period of 90 days beginning on the day following the day on which the report was received.

(2) Paragraph (3) applies where the licensing authority has received a report of a suspected adverse reaction arising from an error associated with the use of a medicinal product.

(3) The licensing authority must (in addition to meeting the requirements in paragraph (1) in respect of the report) ensure that the report is made available to any statutory body with functions in relation to patient safety within the United Kingdom.

(4) This regulation is subject to regulation 212 (transitional arrangements).

Recording obligations on holders

187.—(1) Subject to paragraph (2), the holder must record all suspected adverse reactions to the product occurring in the EEA or in third countries which are brought to its attention irrespective of whether the reaction—

(a) is reported spontaneously by patients or health care professionals; or

(b) occurred in the context of a post-authorisation study.

(2) Paragraph (1) does not apply where the suspected adverse reaction occurred in the context of a clinical trial within the meaning of the Clinical Trials Regulations.

(3) The holder must not refuse to consider reports of suspected adverse reactions to the product received electronically or by any other appropriate means from patients or from health care professionals.

(4) The holder must ensure that reports recorded under paragraph (1) are accessible (electronically or physically) at a single point within the EEA.

Reporting obligations on holders

188.—(1) Subject to paragraph (2), the holder must in relation to the product—

(a) submit electronically to the Eudravigilance database a report on all serious suspected adverse reactions that occur in the EEA and third countries before the end of the period of 15 days beginning on the da*y* following the day on which the holder gained knowledge of the reaction;

(b) submit electronically to the Eudravigilance database a report on all non-serious suspected adverse reactions that occur in the EEA before the end of the period of 90 days beginning on the day following the day on which the holder gained knowledge of the reaction;

(c) establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) collect follow-up information on reports submitted under sub-paragraphs (a) or (b) and submit it electronically to the Eudravigilance database by way of an update to the original report within the specified time period; and

(e) collaborate with the EMA and the competent authorities of the EEA States in the detection of duplicates of suspected adverse reaction reports.

(2) The holder is not required to submit a report of a suspected adverse reaction to the product under paragraph (1)(a) or (b), or to provide follow-up information under paragraph (1)(d), where—

(a) the suspected adverse reaction relates to a medicinal product which contains a monitored active substance; and

(b) the suspected adverse reaction is recorded in a monitored publication.

(3) Paragraph (4) applies to medicinal products containing a monitored active substance.

(4) The holder must—

(a) monitor medical literature other than the monitored publications for reports of suspected adverse reactions to the product; and

(b) report suspected adverse reactions identified under sub-paragraph (a) in accordance with paragraph (1).

(5) In this regulation—

"monitored active substance" means an active substance on the list of active substances being monitored by the EMA published under Article 27 of Regulation (EC) No 726/2004;

"monitored publication" means a publication on the list of publications being monitored by the EMA published under Article 27 of Regulation (EC) No 726/2004; and

"the specified time period" means—

(a) in the case of serious adverse reactions, the period of 15 days beginning on the day following the day on which the follow up information became known to the holder; and

(b) in the case of non-serious adverse reactions, the period of 90 days beginning on the day following the day on which the follow up information became known to the holder.

(6) This regulation is subject to regulation 212 (transitional arrangements).

Signal detection

Signal detection: licensing authority obligations

189.—(1) The licensing authority must in relation to each medicinal product—

(a) monitor the data in the Eudravigilance database to determine whether there are any relevant changes;

(b) assess updates to the risk management system for the product;

(c) monitor the outcome of risk minimisation measures contained in the risk management plan (if any); and

(d) monitor the outcome of conditions imposed under regulations 59 to 61 (conditions of UK marketing authorisations) (if any).

(2) The licensing authority must collaborate with the EMA in carrying out its functions under paragraph (1).

(3) The licensing authority must inform the bodies specified in paragraph (4) without delay if it detects any relevant changes in relation to a medicinal product.

(4) The bodies specified in this paragraph are—

(a) the EMA; and

(b) the relevant competent authorities.

(5) In this regulation "relevant changes" in relation to a medicinal product means—

(a) new risks;

(b) risks that have changed; or

(c) changes to the risk-benefit balance.

Signal detection: holder obligation

190.—(1) The holder must inform the EMA and the licensing authority without delay if it detects any relevant changes in relation to the product.

(2) In this regulation, "relevant changes" has the meaning given in regulation 189(5).

Periodic Safety Update Reports

Obligation on holder to submit periodic safety update reports: general requirements

191.—(1) The holder must submit reports known as periodic safety update reports ("PSURs") in relation to the product to the EMA in accordance with this regulation, or in a case where paragraph (2) applies, in accordance with regulation 192.

(2) This paragraph applies to—

(a) a marketing authorisation granted pursuant to regulations 51 (applications for UK marketing authorisations relating to generic medicinal products) or 54 (application relating to products in well-established medicinal use); or

(b) a traditional herbal registration.

(3) In the following paragraphs of this regulation—

"authorisation" means a UK marketing authorisation or an Article 126a authorisation;

"the holder" means the holder of a UK marketing authorisation or an Article 126a authorisation; and

"product" means a product to which a UK marketing authorisation or Article 126a authorisation relates.

(4) Each PSUR must contain—

(a) summaries of data relevant to the benefits and risks of the product, including results of all studies, with a consideration of their potential impact on the authorisation for the product;

(b) a scientific evaluation of the risk-benefit balance of the product; and

(c) all data relating to the volume of sales of the product and any data the holder has relating to the volume of prescriptions, including an estimate of the population exposed to the product.

(5) For the purposes of paragraph (4)(b), the scientific evaluation must be based on all available data, including data from clinical trials conducted outside the terms of the authorisation for the product.

(6) Each PSUR must be submitted electronically.

(7) PSURs must be submitted to the EMA with the frequency and on the dates as set out in paragraphs (8) to (10).

(8) In the case of an authorisation granted on or after 21st July 2012, the holder must submit PSURs with the frequency as specified in the authorisation for the product, with the dates of submission being calculated from the date of authorisation.

(9) In the case of an authorisation granted before 21st July 2012 which specifies the frequency and dates of submission of PSURs, the holder must submit PSURs with the frequency and on the dates as specified in the authorisation for the product.

(10) In the case of an authorisation granted before 21st July 2012 which does not specify the frequency and dates of submission of PSURs, the holder must submit a PSUR—

(a) immediately upon the request of the licensing authority;

(b) where the product has not yet been placed on the market within the EEA, at least every six months following authorisation until the placing on the market within the EEA; and

(c) where the product has been placed on the market within the EEA—

(i) at least every six months during the first two years following the initial placing on the market,

(ii) once a year for the following two years, and

(iii) every three years after that.

(11) This regulation is subject to regulation 212 (transitional arrangements).

Obligation on holder to submit periodic safety update reports: derogation from general requirements

192.—(1) This regulation applies in relation to medicinal products granted—

(a) a marketing authorisation pursuant to regulations 51 (applications for UK marketing authorisations relating to generic medicinal products) or 54 (application relating to products in well-established medicinal use); or

(b) a traditional herbal registration.

(2) In the following paragraphs of this regulation—

"authorisation or registration" means a marketing authorisation to which paragraph (1)(a) applies or a traditional herbal registration;

"the holder" means the holder of a marketing authorisation to which paragraph (1)(a) applies or of a traditional herbal registration; and

"product" means a product to which a marketing authorisation referred to in paragraph (1)(a) or a traditional herbal registration relates.

(3) The holder must submit PSURs in relation to the product to the EMA in accordance with paragraph (5)—

(a) where requested to do so by the licensing authority in accordance with paragraph (4); or

(b) in the case of a product to which paragraph (1)(a) applies, where it is a condition to which the marketing authorisation for the product is subject by virtue of regulations 59 (conditions of UK marketing authorisation: general) or 60 (conditions of UK marketing authorisation: exceptional circumstances) to do so.

(4) The licensing authority may request the holder to submit PSURs where—

(a) it has concerns relating to the product's pharmacovigilance data; or

(b) it considers there is a lack of PSUR data relating to an active substance of the product after the authorisation or registration is granted.

(5) The submission of PSURs under paragraph (3) must be in accordance with—

(a) where the PSUR is submitted pursuant to a request under paragraph (3)(a), the terms of the request; and

(b) where the PSUR is submitted pursuant to a condition under paragraph (3)(b), the terms of the condition.

(6) Each PSUR must contain—

(a) summaries of data relevant to the benefits and risks of the product, including results of all studies, with a consideration of their potential impact on the authorisation or registration for the product;

(b) a scientific evaluation of the risk-benefit balance of the product; and

(c) all data relating to the volume of sales of the product and any data the holder has relating to the volume of prescriptions, including an estimate of the population exposed to the product.

(7) For the purposes of paragraph (6)(b), the scientific evaluation must be based on all available data, including data from clinical trials conducted outside the terms of the authorisation or registration for the product.

(8) Each PSUR must be submitted electronically.

(9) Where the licensing authority requests submission of PSURs under paragraph (3)(a), it must communicate a PSUR assessment report to the EMA as soon as is reasonably practicable after each report is received.

(10) In this regulation "PSUR assessment report" means a report which evaluates the information provided in a PSUR.

(11) This regulation is subject to regulation 212 (transitional arrangements).

Harmonisation of PSUR frequency or date of submission

193.—(1) Where products that are subject to different authorisations or registrations contain the same active substance or the same combination of active substances, the frequency and dates of submission may be amended and harmonised in accordance with—

(a) Article 107c(4) of the 2001 Directive; or

(b) paragraphs (2) to (4).

(2) The holder may, where one or more of the grounds in paragraph (3) is met, submit a request in relation to the product to the EMA—

(a) to determine an EU reference date; or

(b) to change the frequency of submission of the PSUR.

(3) The grounds in this paragraph are—

(a) reasons relating to public health;

(b) in order to avoid duplication of the assessment; or

(c) in order to achieve international harmonisation.

(4) The second paragraph of Article 107c(6) of the 2001 Directive has effect in relation to the submission and determination of a request under paragraph (2).

(5) Where the frequency or dates of submission of a PSUR are changed in accordance with Article 107c(4) or Article 107c(6) of the 2001 Directive, the holder must apply to vary the product's authorisation or registration to reflect the new frequency or date of submission before the end of the period of six months beginning on the day after the change is made public by the EMA.

(6) In this regulation, "EU reference date" in relation to a product means—

(a) the date of the first marketing authorisation in the EEA of a medicinal product containing the same active substance or the same combination of active substances as that product; or

(b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations in the EEA for a medicinal product containing the same active substance or the same combination of active substances as that product.

Responding to a single assessment of PSUR under Article 107e of the 2001 Directive

194.—(1) This regulation applies where PSURs relating to a medicinal product have been assessed under the EU single assessment procedure.

(2) The licensing authority must implement—

(a) the necessary measures that are consequent upon any agreement reached under Article 107g(2) of the 2001 Directive as part of the EU single assessment process, in accordance with the implementation timetable determined in the agreement; or

(b) any decision adopted under Article 107g(4)(a) of the 2001 Directive before the end of the period of 30 days beginning on the day after the day on which the licensing authority received notification of the decision.

(3) Paragraph (4) applies where—

(a) an agreement reached under Article 107g(2) of the 2001 Directive requires a variation to be made to an authorisation or registration; and

(b) the terms of the agreement are known to the holder of that authorisation or registration.

(4) A holder of an authorisation or registration referred to in paragraph (3)(a) must submit to the licensing authority in accordance with the implementation timetable determined in the agreement an appropriate application for a variation, including—

(a) an updated summary of the product characteristics; and

(b) an updated package leaflet.

(5) In this regulation, "EU single assessment procedure" means the single assessment procedure laid down in Article 107e of the 2001 Directive, which covers—

(a) medicinal products that are authorised in more than one member State; and

(b) medicinal products that contain the same active substance or the same combination of active substances and for which a harmonised EU reference date and frequency of submission of PSURs have been established under Article 107c of the 2001 Directive.

Obligation on licensing authority to assess PSURs where EU single assessment procedure does not apply

195.—(1) This regulation applies where PSURs relating to a medicinal product have not been assessed under the EU single assessment procedure because—

(a) the medicinal product to which the PSUR relates has not been authorised to be placed on the market in accordance with the 2001 Directive in an EEA State other than the United Kingdom; and

(b) a harmonised EU reference date and frequency of submission of PSURs have not been established for that product under Article 107c of the 2001 Directive.

(2) The licensing authority must assess the PSURs to determine whether there are any relevant changes.

(3) Where the licensing authority has assessed a PSUR under paragraph (2) it must—

(a) consider whether any action concerning the authorisation or registration of the product to which the PSUR relates is necessary; and

(b) vary, suspend, or revoke the authorisation or registration as appropriate.

(4) In this regulation—

"EU reference date" has the meaning given in regulation 193(6);

"EU single assessment procedure" has the meaning given in regulation 194(5); and

"relevant changes" in relation to a medicinal product means—

(a) new risks,

(b) risks that have changed, or

(c) changes to the risk-benefit balance.

Urgent action

Urgent action

196.—(1) This regulation applies where the licensing authority forms the view that as a result of the evaluation of data resulting from pharmacovigilance activities urgent action is necessary in connection with—

(a) suspending or revoking an authorisation or registration of a medicinal product or class of medicinal products;

(b) prohibiting the supply of a medicinal product or class of medicinal products;

(c) refusing the renewal of an authorisation or registration of a medicinal product;

(d) receiving information from the holder that, on the basis of safety concerns, the holder has interrupted the sale or supply, or offer for sale or supply, of the product or that the holder has taken action to have the product's authorisation or registration cancelled or that the holder intends to do so; or

(e) considering whether the terms of the authorisation or registration of a medicinal product or class of medicinal products should be varied to include a new contra-indication, an alteration of a recommended dose or a restriction to the therapeutic indications.

(2) The licensing authority must provide information about the urgent action it considers necessary by the end of the day following the day on which the view under paragraph (1) was formed to—

(a) the competent authorities of the EEA States other than the United Kingdom;

(b) the EMA; and

(c) the European Commission.

(3) When informing the EMA under paragraph (2), the licensing authority must make available to the EMA in relation to the medicinal product or class of medicinal products—

(a) all relevant scientific information at its disposal; and

(b) any assessment it has carried out.

(4) Where the EU urgent action procedure does not apply in relation to the medicinal product or class of medicinal products referred to in paragraph (1), the licensing authority—

(a) must inform the holder that it has taken action under paragraph (2); and

(b) may take such steps as it sees fit to address the safety concerns.

(5) Where the EU urgent action procedure does apply in relation to the medicinal product or class of medicinal products referred to in paragraph (1), the licensing authority may where the conditions in paragraph (6) are met—

(a) suspend the authorisation or registration of the medicinal product or the authorisations and registrations for the class of medicinal products referred to in paragraph (1) (as the case may be); or

(b) prohibit its or their use within the United Kingdom.

(6) The conditions in this paragraph are that—

(a) urgent action is necessary to protect public health; and

(b) an agreement under Article 107k of the 2001 Directive in respect of the medicinal product or class of medicinal products has not been reached.

(7) Where the licensing authority takes action under paragraph (5), it must by the end of the next working day after the day on which the action is taken inform of the reasons for the action the following—

(a) the European Commission;

(b) the EMA; and

(c) the competent authority of each EEA State other than the United Kingdom.

(8) In this regulation "the EU urgent action procedure" means the procedure under Articles 107j and 107k of the 2001 Directive.

EU urgent action procedure

197.—(1) Where the EU urgent action procedure is initiated in relation to a medicinal product or class of medicinal products, the licensing authority—

(a) may publicly announce the initiation of the EU urgent action procedure on the UK web-portal; and

(b) must implement the measures set out in any agreement reached under Article 107k of the 2001 Directive in relation to the medicinal product or class of medicinal products in accordance with the implementation timetable determined in the agreement.

(2) Paragraph (3) applies where an agreement under Article 107k of the 2001 Directive in relation to a medicinal product or class of medicinal products requires a variation to be made to one or more authorisation or registration.

(3) Each holder of an authorisation or registration covered by the agreement referred to in paragraph (2) must submit to the licensing authority in accordance with the terms of the agreement (including its implementation timetable) an application for a variation in respect of the authorisation or registration including—

(a) an updated summary of the product characteristics; and

(b) an updated package leaflet.

(4) In this regulation, "EU urgent action procedure" has the same meaning as it is given in regulation 196(8).

Post-authorisation safety studies

Post-authorisation safety studies: general provisions

198.—(1) A relevant post-authorisation safety study—

(a) may not be conducted where the act of conducting the study promotes the use of a medicinal product; and

(b) may not provide for payments to health care professionals for participating in the study except in compensation for time and expenses incurred.

(2) The licensing authority may require the holder for the product which is the subject of a relevant post-authorisation safety study to submit the protocol and progress reports for the study to the competent authorities of the EEA States in which the study is conducted.

(3) The holder for the product which is the subject of a relevant post-authorisation safety study must—

(a) comply with a requirement imposed by the licensing authority under paragraph (2) (if any);

(b) while the study is being conducted—

(i) monitor the data generated, and

(ii) consider its implications for the risk-benefit balance of the product which is the subject of the study;

(c) communicate to the relevant competent authorities any new information that arises at any point during the study which might influence the evaluation of the risk-benefit balance for that product as soon as is reasonably practicable after it becomes known to the holder; and

(d) send the final report on the study to the competent authorities of the EEA States in which the study was conducted before the end of the period of 12 months beginning on the day after the day on which data collection for the study ended.

(4) This regulation is subject to regulation 212 (transitional arrangements).

Submission of draft study protocols for required studies

199.—(1) This regulation applies to a relevant post-authorisation safety study that is to be conducted pursuant to a condition of a UK marketing authorisation imposed under regulation 59 (conditions of a UK marketing authorisation: general) or 61 (conditions of a UK marketing authorisation: new obligations post-authorisation).

(2) The holder for the product which is the intended subject of the study must submit a draft protocol for the study to the body specified in paragraph (3) before the study is commenced.

(3) The body specified in this paragraph is—

(a) where the study is to be conducted in the United Kingdom only, the licensing authority; or

(b) in all other cases, the Pharmacovigilance Risk Assessment Committee.

(4) Paragraph (5) applies where a draft protocol is submitted to the licensing authority under paragraphs (2) and (3)(a).

(5) Where this paragraph applies, the licensing authority, before the end of the period of 60 days beginning on the day after the day on which the draft protocol is submitted, must issue—

(a) a letter endorsing the draft protocol;

(b) a letter objecting to the draft protocol on the grounds that—

(i) it considers that the conduct of the study promotes the use of a medicinal product, or

(ii) it considers that the design of the study does not fulfil the study objectives; or

(c) a letter notifying the holder for the product which is the intended subject of the study that the study is a clinical trial within the meaning of the Clinical Trials Regulations.

(6) A study may not commence unless a letter endorsing the draft protocol has been issued by—

(a) the licensing authority under paragraph (5)(a); or

(b) the Pharmacovigilance Risk Assessment Committee under Article 107n(2) of the 2001 Directive.

(7) Paragraph (8) applies where a letter endorsing the draft protocol has been issued by the Pharmacovigilance Risk Assessment Committee under Article 107n(2) of the 2001 Directive.

(8) Where this paragraph applies, the holder for the product which is the intended subject of the study must forward the protocol to the competent authorities of the EEA States in which the study is to be conducted before commencing the study.

(9) In this regulation, "a letter" includes email correspondence.

(10) This regulation is subject to regulation 212 (transitional arrangements).

Amendment to study protocols for required studies

200.—(1) This regulation applies where a study to which regulation 199 applies has been commenced.

(2) The holder for the product which is the subject of the study must submit any substantial amendments to the study protocol to the body specified in paragraph (3) before their implementation.

(3) The body specified in this paragraph is—

(a) where the study is being conducted in the United Kingdom only, the licensing authority; or

(b) in all other cases, the Pharmacovigilance Risk Assessment Committee.

(4) Paragraph (5) applies where a proposed amendment to a study protocol is submitted to the licensing authority under paragraphs (2) and (3)(a).

(5) Where this paragraph applies, the licensing authority must as soon as is reasonably practicable—

(a) assess the amendment; and

(b) inform the holder of its endorsement of, or objection to, the proposed amendment.

(6) Paragraph (7) applies where the proposed amendment to a study protocol is submitted to the Pharmacovigilance Risk Assessment Committee under paragraphs (2) and (3)(b).

(7) Where this paragraph applies, the holder who submitted the amendment must inform the competent authorities of the EEA States in which the study is being conducted of any amendment to the study protocol approved by the Pharmacovigilance Risk Assessment Committee as soon as is reasonably practicable.

(8) This regulation is subject to regulation 212 (transitional arrangements).

Submission and evaluation of final study reports for required studies

201.—(1) This regulation applies where a study to which regulation 199 applies has been completed.

(2) Subject to paragraph (4), the holder for the product which is the subject of the study must submit electronically, before the end of the period of 12 months beginning on the day after the day on which data collection for the study ended, to the body specified in paragraph (3)—

(a) a final study report; and

(b) an abstract of the study results.

(3) The body specified in this paragraph is—

(a) where the study was conducted in the United Kingdom only, the licensing authority; or

(b) in all other cases, the Pharmacovigilance Risk Assessment Committee.

(4) Paragraph (2) does not apply where a written waiver has been granted by the licensing authority for reports falling under paragraph (3)(a), or by the Pharmacovigilance Risk Assessment Committee for reports falling under paragraph (3)(b).

(5) The holder must without delay—

(a) evaluate whether the results of a final study report submitted under paragraph (2) have an impact on the authorisation or registration of the medicinal product to which the report relates; and

(b) if necessary, submit an application to vary the authorisation or registration for the product.

(6) This regulation is subject to regulation 212 (transitional arrangements).

Follow-up of final study reports

202.—(1) This regulation applies where—

(a) the Pharmacovigilance Risk Assessment Committee has made recommendations concerning an authorisation or registration or a class of authorisations or registrations based on a final study report under Article 107q(1) of the 2001 Directive; and

(b) an agreement on the action to be taken in respect of the authorisation or registration or the class of authorisations or registrations has been reached by the co-ordination group under the procedure laid out in Article 107q(2) of the 2001 Directive ("the agreement").

(2) The licensing authority must implement the measures set out in the agreement in accordance with the implementation timetable determined in the agreement.

(3) Paragraph (4) applies where—

(a) the agreement requires a variation to be made to one or more authorisation or registration; and

(b) the terms of the agreement are known to the holder or holders for the product or products which is, or which are, the subject of the agreement.

(4) Where this paragraph applies, each holder must submit to the licensing authority in accordance with the terms of the agreement (including its implementation timetable) an application for a variation including—

(a) an updated summary of the product characteristics; and

(b) an updated package leaflet.

(5) This regulation is subject to regulation 212 (transitional arrangements).

Transparency and communications

Obligations on licensing authority in relation to national medicines web-portal

203.—(1) The licensing authority must set up and maintain a national medicines web-portal ("the UK web-portal") linked to the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004 ("the EU web-portal").

(2) The licensing authority must make available publicly by means of the UK web-portal the following (at a minimum)—

(a) the assessment reports prepared or revised by the licensing authority under regulation 64(5) and (6) (duties of licensing authority in connection with determination), each with a summary;

(b) the summary of the product characteristics for the medicinal products concerned;

(c) the package leaflet for the medicinal products concerned;

(d) a summary of the risk management plan (if any) for the medicinal products concerned;

(e) the list of medicinal products that are subject to additional monitoring referred to in Article 23 of Regulation (EC) No 726/2004; and

(f) information on the different ways of reporting suspected adverse reactions to medicinal products to the licensing authority by patients or their carers, health care professionals, coroners or procurators fiscal (including by way of the web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004).

Obligation on licensing authority in relation to public announcements

204.—(1) This regulation applies where the licensing authority intends to make a public announcement relating to information on pharmacovigilance concerns.

(2) Subject to paragraph (4), the licensing authority must inform the bodies specified in paragraph (3) not less than 24 hours prior to making the public announcement.

(3) The bodies specified in this paragraph are—

(a) the EMA;

(b) the European Commission; and

(c) the competent authority of each EEA State other than the United Kingdom.

(4) Paragraph (2) does not apply if the information in the announcement needs to be made public urgently for the protection of public health.

Obligations on holders in relation to public announcements

205.—(1) This regulation applies where the holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product.

(2) The holder must inform the bodies listed in paragraph (3) of its intention to make the public announcement—

(a) as soon as is practicable once it forms that intention; and

(b) in any event no later than at the same time as, or before, the public announcement is made.

(3) The bodies listed in this paragraph are—

(a) the licensing authority;

(b) the EMA; and

(c) the European Commission.

(4) The holder must ensure that the information in the public announcement—

(a) is presented objectively; and

(b) is not misleading.

Enforcement

Infringement notices

206.—(1) If an enforcement authority has objective grounds for considering that any person ("P") has contravened any provision of this Part, or of Chapter 3 of Title II of Regulation (EC) No 726/2004, it may serve upon P a notice in writing (referred to in this Part as an "infringement notice")—

(a) informing P of the authority's grounds for considering that P has contravened one or more provision of this Part or of that Chapter;

(b) specifying the relevant provision of this Part or of that Chapter;

(c) specifying the measures which P must take in order to ensure that the contravention does not continue or, as the case may be, does not recur;

(d) requiring P to take those measures, within such period as may be specified in the notice;

(e) specifying the further action (if any) that the enforcement authority may take.

(2) An infringement notice may include directions as to the measures to be taken by P to ensure that the contravention does not continue or, as the case may be, does not recur, including the different ways of securing compliance.

(3) If an enforcement authority serves an infringement notice in accordance with paragraph (1), it shall as soon as is reasonably practicable inform—

(a) the EMA; and

(b) the European Commission.

Offences

207.—(1) A person is guilty of an offence if the person commits a breach of a provision in this Part, other than regulation 199(2) or (6) (submission of draft study protocols for required studies).

(2) A breach of a provision in this Part includes any—

(a) failure by a holder to comply with any requirement or obligation in this Part; or

(b) contravention by any person of any prohibition in this Part.

False and misleading information

208. A person is guilty of an offence if the person provides information to the licensing authority or the EMA, pursuant to an obligation in this Part, but that information is false or misleading in a material particular.

Penalties

209.—(1) Subject to paragraph (2), a person guilty of an offence under regulation 207 or 208 is liable—

(a) on summary conviction to a fine not exceeding the statutory maximum; or

(b) on conviction on indictment to a fine, to imprisonment for a term not exceeding two years or to both.

(2) A person guilty of an offence under regulation 207 which relates to a breach of a provision listed in paragraph (3) is liable—

(a) on summary conviction to a fine not exceeding the statutory maximum; or

(b) on conviction on indictment to a fine.

(3) Those provisions are regulations—

(a) 182(2)(a) and (b), (3) and (5);

(b) 183(8)(a);

(c) 184(1)(a) and (b);

(d) 187(4);

(e) 188(1)(c) and (e);

(f) 193(5);

(g) 198(1) and (3)(a) and (d);

(h) 199(8); and

(i) 200(7).

Offences relating to pharmacovigilance obligations under Regulation (EC) No 726/2004

210.—(1) A person is guilty of an offence if the person—

(a) commits a breach of a provision of Regulation (EC) No 726/2004 listed in paragraph (3); or

(b) provides information which is false or misleading in a material particular to the licensing authority or the EMA pursuant to an obligation in Chapter 3 of Title II of Regulation (EC) No 726/2004.

(2) A breach of a provision listed in paragraph (3) includes any—

(a) failure to comply with any requirement or obligation contained in any of those provisions;

(b) contravention of any prohibition contained in any of those provisions; or

(c) failure to comply with any requirement imposed by the licensing authority or the EMA pursuant to any of those provisions.

(3) Those provisions are—

(a) Article 16(4), second paragraph(**1**);

(b) Article 20(8)(**2**);

(c) Article 21(1) and (2)(**3**);

(d) Article 22(**4**);

(e) Article 28(1), (2) and (5)(**5**);

(f) Article 28a(3)(**6**); and

(g) Article 28b(1)(**7**), except insofar as it imposes an obligation under Article 107n(1), or the first paragraph of Article 107n(3), of the 2001 Directive.

(4) Subject to paragraph (5), a person guilty of an offence under this regulation is liable—

(a) on summary conviction to a fine not exceeding the statutory maximum; or

(b) on conviction on indictment to a fine, to imprisonment for a term not exceeding two years or to both.

(5) A person guilty of an offence under this regulation in relation to a provision of Regulation (EC) No 726/2004 listed in paragraph (6) is liable—

(a) on summary conviction to a fine not exceeding the statutory maximum; or

(b) on conviction on indictment to a fine.

(6) Those provisions are—

(a) Article 16(4), second paragraph;

(**1**) Article 16(4), second paragraph, of Regulation (EC) No 726/2004 ("the Regulation") imposes an obligation identical to that set out in Article 23(4), second paragraph, of the 2001 Directive; Article 23(4), second paragraph, of the 2001 Directive is transposed at regulation 182(5).

(**2**) Article 20(8) of the Regulation applies Article 107i of the 2001 Directive, which in turn applies Articles 107j and 107k of the 2001 Directive; Article 107k(2) second paragraph is implemented in regulation 197(3).

(**3**) Article 21(1) of the Regulation, first paragraph, cross-refers to obligations set out in Article 104 of the 2001 Directive, implemented in regulation 182 and 185; Article 21(1), second paragraph, and 21(2) of the Regulation are similar in effect to Article 104a of the 2001 Directive, implemented in regulation 183.

(**4**) Article 22 of the Regulation cross-refers to obligations set out in Article 106a(1) of the 2001 Directive; Article 106a(1) is implemented in regulation 205.

(**5**) Article 28(1) and (2) of the Regulation cross-refers to obligations set out in Articles 107, 107a, 107b and 107c of the 2001 Directive; those Articles are implemented in regulations 185, 186, 187, 188, 191, 192 and 193; Article 28(5) of the Regulation applies Articles 107e to 107g of the 2001 Directive; Article 107g of the 2001 Directive is implemented in regulation 194.

(**6**) Article 28a(3) of the Regulation imposes an obligation identical to that set out in the first sentence of Article 107h(3) of the 2001 Directive; Article 107h(3) first sentence is implemented in regulation 190.

(**7**) Article 28b(1) of the Regulation cross-refers to prohibitions and obligations set out in Articles 107m, 107n, 107o, 107p and 107q of the 2001 Directive; those Articles are implemented in regulations 198, 199, 200, 201 and 202; Article 107n(1) and the first paragraph of Article 107n(3), implemented in regulation 199(2) and (6), are excluded as they are enforced otherwise than by way of criminal offence.

(b) Article 21(1) insofar as it relates to obligations set out in—

(i) the second paragraph of Article 104(2) of the 2001 Directive save the obligation regarding preparing and implementing a corrective action plan,

(ii) Article 104(3)(a) of the 2001 Directive,

(iii) Article 104(3)(b) of the 2001 Directive, or

(iv) the second paragraph of Article 104(3) of the 2001 Directive;

(c) Article 21(2) insofar as it relates to the obligation to submit a detailed description of a risk management system;

(d) Article 28(1) insofar as it relates to obligations set out in—

(i) the second paragraph of Article 107(1) of the 2001 Directive,

(ii) the first sentence of Article 107(4) of the 2001 Directive, or

(iii) Article 107(5) of the 2001 Directive;

(e) Article 28(2) insofar as it relates to the obligation set out in the third paragraph of Article 107c(4) of the 2001 Directive; and

(f) Article 28b(1) insofar as it relates to prohibitions or obligations set out in—

(i) Article 107m(3) to (6) of the 2001 Directive,

(ii) the second paragraph of Article 107n(3) of the 2001 Directive, or

(iii) the last sentence of Article 107o of the 2001 Directive.

(7) This regulation is subject to regulation 212 (transitional arrangements).

Persons liable

211. If an offence under regulation 207(1) (offences) or regulation 210(1)(a) (offences relating to pharmacovigilance obligations under Regulation (EC) No 726/2004) is committed by a person acting as employee or agent, the employer or principal of that person is guilty of the same offence and is liable to be proceeded against and punished accordingly.

Transitional arrangements

Transitional arrangements

212. Regulations 182, 186, 188, 191, 192, 198, 199, 200, 201, 202 and 210 are subject to the transitional provisions set out in Schedule 33 (transitional arrangements: pharmacovigilance).